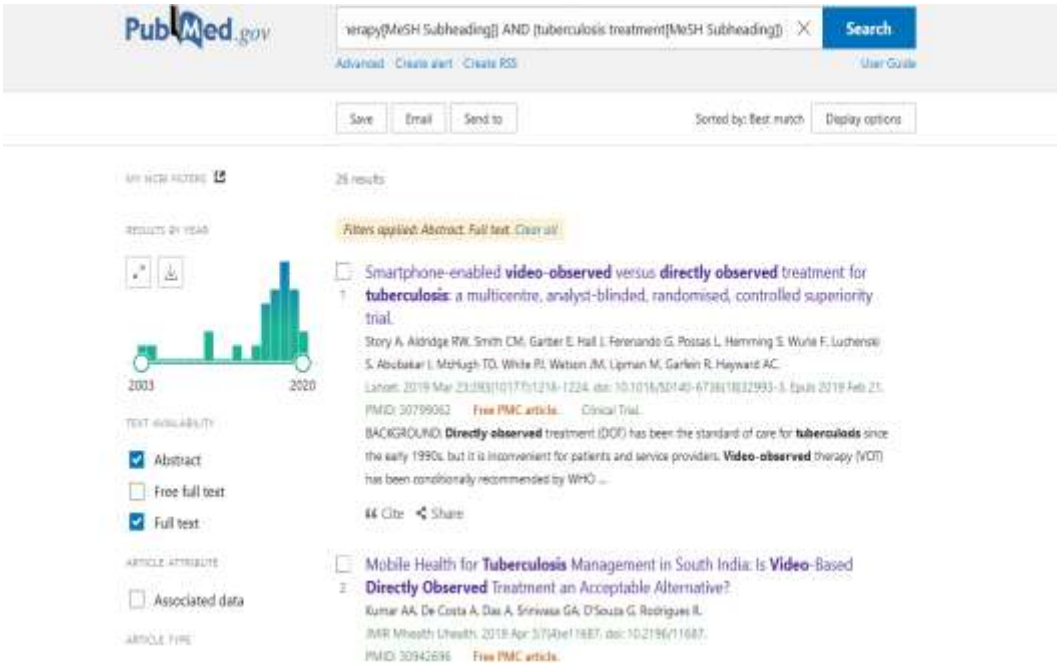
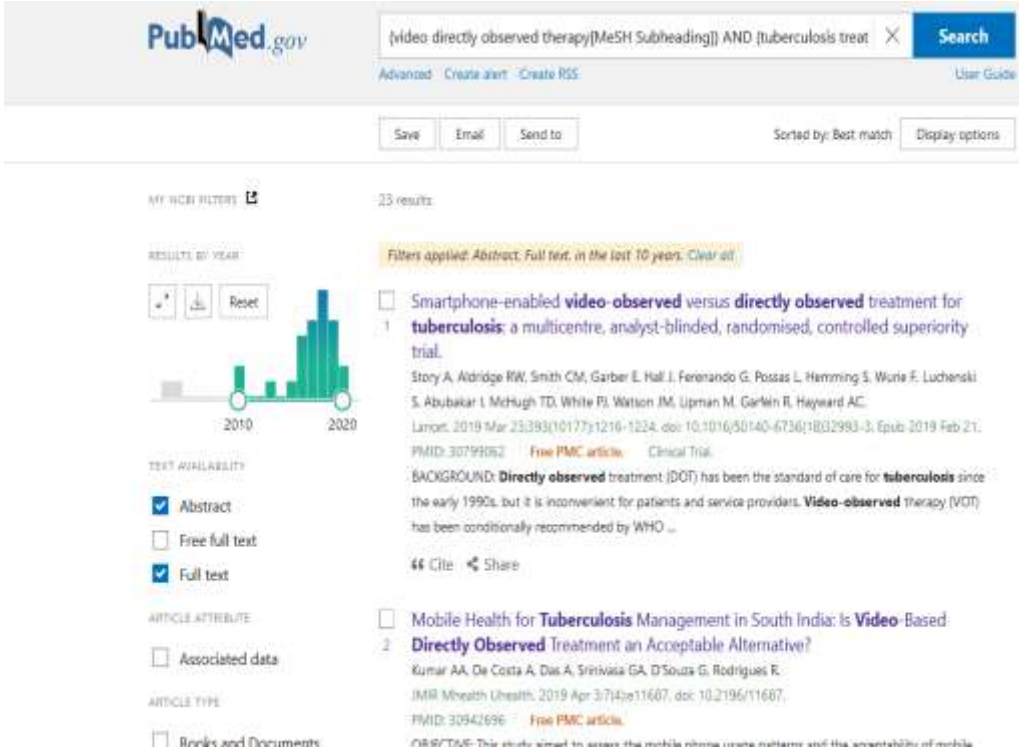
Lampiran 1 langkah – langkah penelusuran Database PUBMED

Langkah 1 : Database search PubMed MesH Sub Heading

Langkah 2 : Result Database search Pubmed MesH Sub Heading filter full text dan abstrak



Langkah 3 : Result Database search Pubmed MesH Sub Heading filter publication date


PubMed.gov
(video directly observed therapy[MeSH Subheading]) AND (tuberculosis treat
Search
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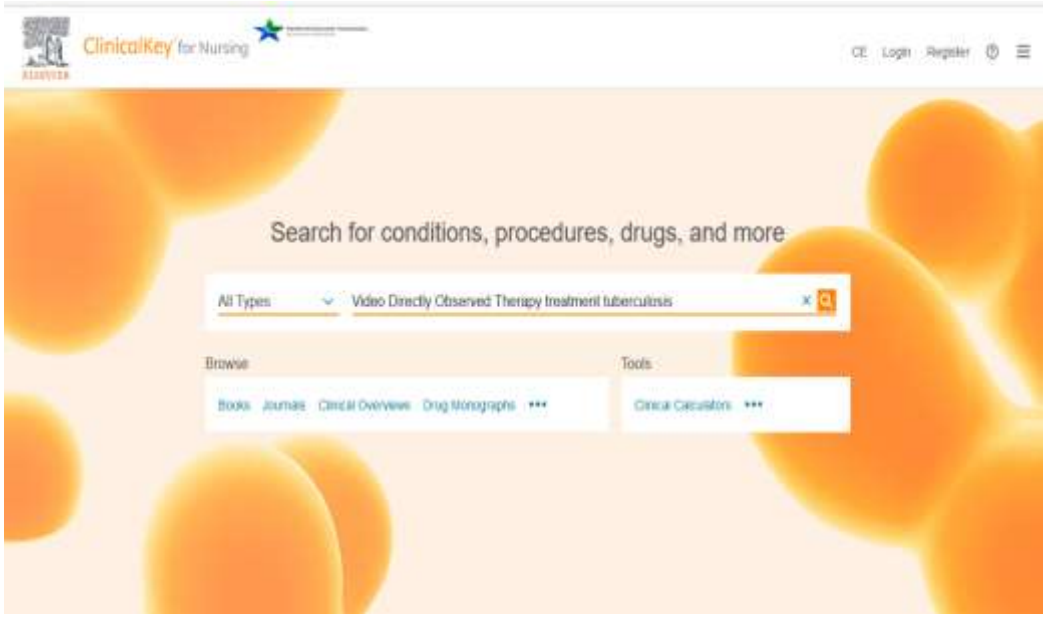
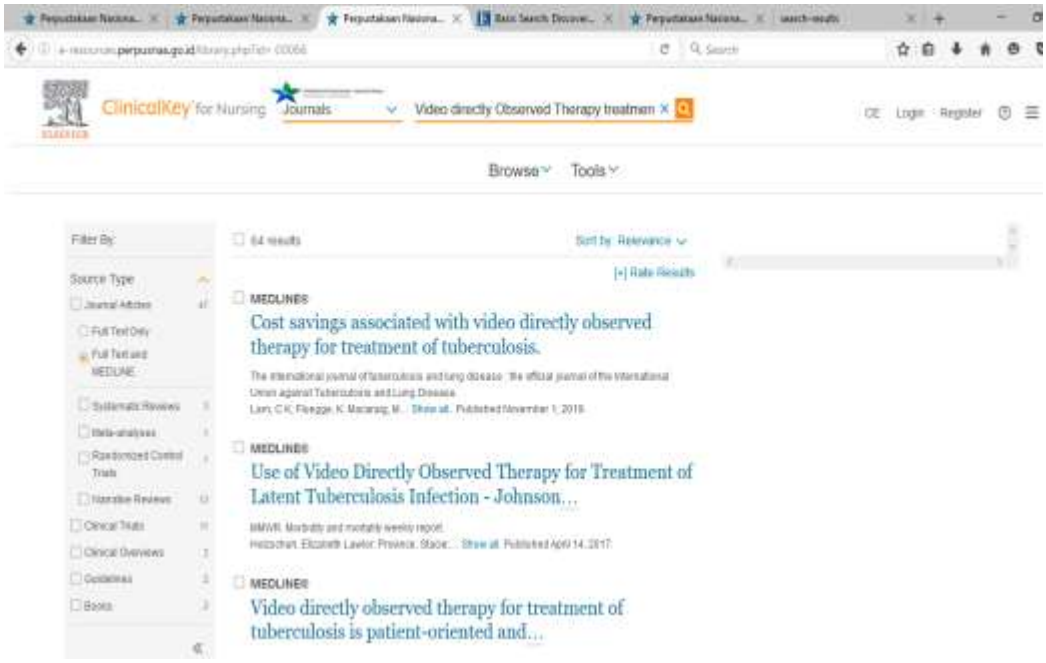
User Guide
Save Email Send to
Sorted by: Best match
Display options
MY NCBI FILTERS
23 results
RESULTS BY YEAR
Reset
2010
2020
Filters applied: Abstract, Full text, in the last 10 years. Clear all
TEXT AVAILABILITY
Abstract
Free full text
Full text
ARTICLE ATTRIBUTE
Associated data
ARTICLE TYPE
Books and Documents
1 Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicentre, analyst-blinded, randomised, controlled superiority trial.
Story A, Aldridge RW, Smith CM, Garber E, Hall J, Ferenando G, Possas L, Hemming S, Wurie F, Luchenski S, Abubakar I, McHugh TD, White PJ, Watson JM, Lipman M, Garfein R, Hayward AC.
Lancet. 2019 Mar 23;393(10177):1216-1224. doi: 10.1016/S0140-6736(18)32993-3. Epub 2019 Feb 21.
PMID: 30799062 Free PMC article. Clinical Trial.
BACKGROUND: Directly observed treatment (DOT) has been the standard of care for tuberculosis since the early 1990s, but it is inconvenient for patients and service providers. Video-observed therapy (VOT) has been conditionally recommended by WHO ...
Cite Share
2 Mobile Health for Tuberculosis Management in South India: Is Video-Based Directly Observed Treatment an Acceptable Alternative?
Kumar AA, De Costa A, Das A, Srinivasa GA, D'Souza G, Rodrigues R.
JMIR Mhealth Uhealth. 2019 Apr 3;7(4):e11687. doi: 10.2196/11687.
PMID: 30942696 Free PMC article.

Lampiran 2 langkah – langkah Database Search Elsevier Clinical Key Nursing

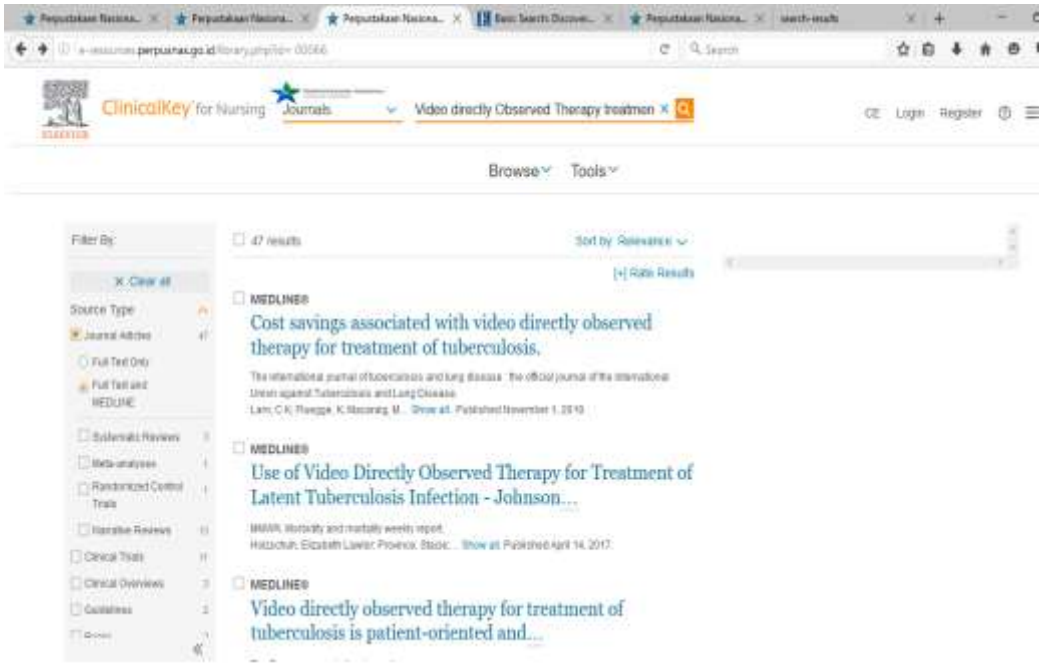
Langkah 1 : Database search Elsevier Clinical Key Nursing



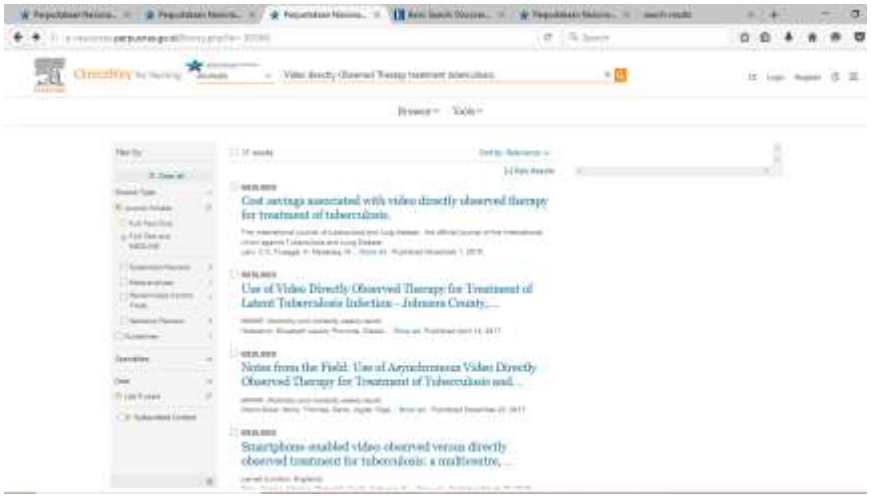
Langkah 2 : Result Database search Elsevier Clinical Key Nursing filter full text dan MEDLINE



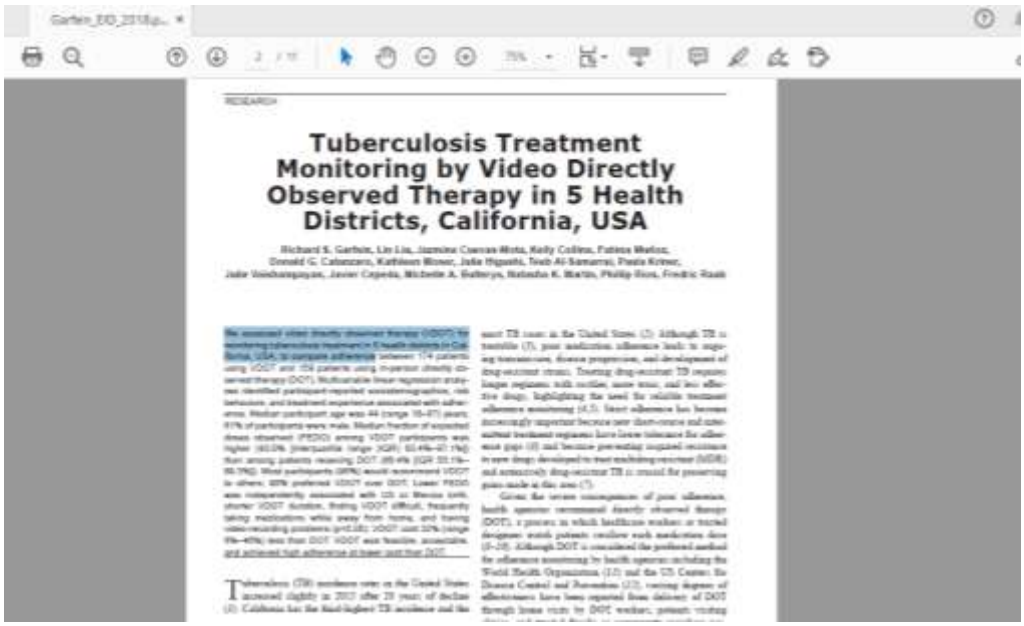
Langkah 3 : Result Database search Elsevier Clinical Key Nursing filter Journal Article



Langkah 4 : Result Database search Elsevier Clinical Key Nursing filter publication date



Lampiran 3 :Langkah- langkah Identifikasi Tujuan penelitian



RESEARCH

Tuberculosis Treatment Monitoring by Video Directly Observed Therapy in 5 Health Districts, California, USA

INT J TUBERC LUNG DIS e-publication ahead of print 30 June 2015
http://dx.doi.org/10.5588/ijtld.14.0923

Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study

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SUMMARY

BACKGROUND: Although directly observed therapy (DOT) is recommended worldwide for monitoring anti-tuberculosis treatment, transportation and personnel requirements limit its use.

OBJECTIVE: To evaluate the feasibility and acceptability of 'video DOT' (VDOT), which allows patients to record and transmit medication ingestion via videos watched remotely by health care providers to document adherence.

METHODS: We conducted a single-arm trial among tuberculosis (TB) patients in San Diego, California, USA, ($n = 43$) and Tijuana, Mexico ($n = 9$) to represent high- and low-resource settings. Pre-/post-treatment interviews assessed participant characteristics and expe-

50% were male, and 88% were non-Caucasian. The mean duration of VDOT use was 5.5 months (range 1–11). Adherence was similar in San Diego (93%) and Tijuana (96%). Compared to time on in-person DOT, 92% preferred VDOT, 81% thought VDOT was more confidential, 89% never/rarely had problems recording videos, and 100% would recommend VDOT to others. Seven (13%) participants were returned to in-person DOT and six (12%) additional participants had their phones lost, broken or stolen.

CONCLUSIONS: VDOT was feasible and acceptable, with high adherence in both high- and low-resource settings. Efficacy and cost-effectiveness studies are needed.

Enhancing management of tuberculosis treatment with video directly observed therapy in New York City

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SUMMARY

SETTING: Directly observed therapy (DOT), the standard of care for monitoring patients on treatment for tuberculosis (TB), requires substantial health department resources, and can be inconvenient and disruptive for patients.

OBJECTIVE: To determine whether video technology for remote observation of patients on anti-tuberculosis treatment (VDOT) is as effective as in-person DOT.

DESIGN: Eligible TB patients in New York City were prospectively enrolled in VDOT from September 2013 to September 2014. We compared treatment outcomes and worker output for VDOT and in-person DOT.

RESULTS: Among 390 patients on DOT for the treatment of TB, 61 (16%) were on VDOT and 329 (84%) on in-person DOT. Adherence to scheduled VDOT sessions was 95% (3292/3455) compared to 91% (32 204/35 442) with in-person DOT ($P < 0.01$). VDOT enabled a DOT worker to observe a maximum of 25 patients per day, similar to DOT workers who observed patients in clinic ($n = 25$), but twice that of DOT workers who observed patients in the community ($n = 12$). Treatment completion with VDOT was similar to that with in-person DOT (96% vs. 97%, $P = 0.63$). The primary problems encountered during VDOT sessions were interruption of video and audio connectivity.

CONCLUSION: Implementation of VDOT resulted in successful anti-tuberculosis treatment outcomes while maximizing health department resources.

KEY WORDS: VDOT; telemedicine; remote monitoring

TREATMENT FOR TUBERCULOSIS (TB) is lengthy, requiring 6–9 months of multiple drugs; however, when treatment is taken as prescribed the cure rate is high.[1] Failure to complete treatment can lead to the development of drug-resistant TB, which is more difficult to treat and can result in continued

2004, concurrent with an increase in the proportion of patients treated under DOT.[11] Furthermore, a recent study showed that NYC patients on DOT had a lower risk of delayed and incomplete treatment.[12] Transmission and development of drug-resistant TB also decreased, and the number of TB cases in NYC

\

Video Directly Observed Therapy to support adherence with treatment for tuberculosis in Vietnam: A prospective cohort study

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Video
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Treatment

ABSTRACT

Background: Assessing patients fully adhere to their treatment is a major challenge for TB control programmes in resource-limited settings. This study was conducted three outpatient tuberculosis clinics in Hanoi, Vietnam. **We aimed to evaluate the feasibility of using asynchronous Video Directly Observed Therapy (VDOT) to support treatment adherence among patients with bacteriologically confirmed pulmonary tuberculosis.**

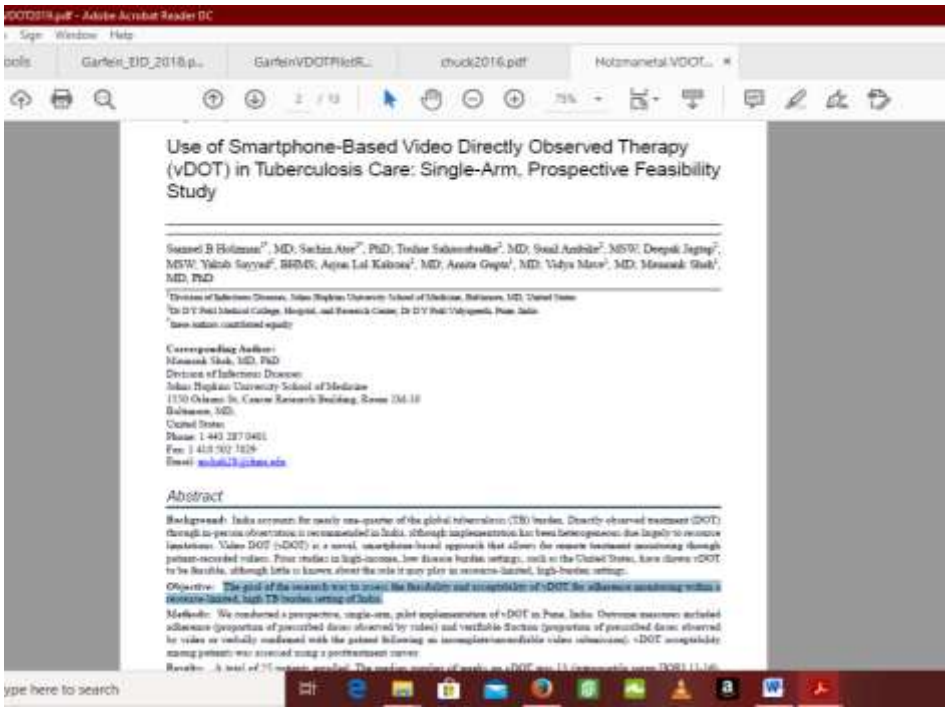
Methods: In this cohort study, consecutive adult patients with bacteriologically confirmed pulmonary TB were invited to enroll in a programme of VDOT. Patients were trained to use a smartphone to record themselves taking treatment for TB. Videos were uploaded to an online server and reviewed daily by study staff for at least two months. Adherence was evaluated based upon monthly pill count.

Results: Between November 2016 and January 2017, 40 of 78 eligible participants (51.3%) agreed to commence VDOT. Among participating patients, 27 (71.1%) of patients took all required doses. A median of 88.4% (interquartile range 71.4%–95.7%) of doses were correctly recorded and uploaded. Participants rated the VDOT interface highly, despite facing some initial technical difficulties.

Conclusion: VDOT was feasible and resulted in high rates of treatment adherence in a resource-limited setting.

Background

Tuberculosis (TB) affects 10.4 million people each year, the vast majority of whom live in resource-limited settings [World Health Organization, 2016]. Optimal regimens for drug susceptible tuberculosis require six months of daily antibiotics [World Health Organization, 2017; Johnston et al., 2017]. However, ensuring patients fully adhere to their treatment is a perennial challenge for [Karma et al., 2004; Adane et al., 2013]. The consequences of incomplete adherence are well-documented, and include an increased risk of treatment failure, acquired drug resistance and continuing propagation of infection [Weiner et al., 2012; Karumbi and Garner, 2015; Sawadkarvine and Pichenchitkun, 2016]. A range of programmatic strategies have been proposed to strengthen adherence [Liefp et al., 2010; Wald et al., 2013; Lange et al., 2015]. However, in many resource-limited settings, intensive adherence



Use of Smartphone-Based Video Directly Observed Therapy (vDOT) in Tuberculosis Care: Single-Arm, Prospective Feasibility Study

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Abstract

Background: India accounts for nearly one-quarter of the global tuberculosis (TB) burden. Directly observed treatment (DOT) through in-person observation is recommended in India, although implementation has been heterogeneous due largely to resource limitations. Video DOT (vDOT) is a novel, smartphone-based approach that allows for remote treatment monitoring through patient-recorded videos. Prior studies in high-income, low disease burden settings, such as the United States, have shown vDOT to be feasible, although little is known about the role it may play in resource-limited, high-burden settings.

Objective: The goal of the research was to assess the feasibility and acceptability of vDOT for adherence monitoring within a resource-limited, high TB burden setting of India.

Methods: We conducted a prospective, single-arm, pilot implementation of vDOT in Pune, India. Outcome measures included adherence (proportion of prescribed doses observed by video) and verifiable fraction (proportion of prescribed doses observed by video or verbally confirmed with the patient following an incomplete/unverifiable video submission). vDOT acceptability among patients was assessed using a post-treatment survey.

Results: A total of 25 patients enrolled. The median number of weeks on vDOT was 13 (interquartile range [IQR] 11-16)

CrossMark

Video directly observed therapy for treatment of tuberculosis is patient-oriented and cost-effective

To the Editor:

Curing tuberculosis (TB) entails adhering to a multidrug regimen for 24 months [1]. Failure to take the medications as prescribed can lead to treatment failure, drug resistance and further spread of TB, resulting in morbidity and death for the patient and a threat to public health. Treatment failure is the most important cause of drug-resistant TB, which is much more long, expensive and toxic to treat, and the outcomes of which are still unsatisfactory [2–4]. The public health consequences of nonadherence to TB treatment led to directly observed therapy (DOT) becoming the universal standard of care [5–6]. While DOT is a best practice model for TB treatment, it is labour intensive and can itself be a barrier to effective therapy because of its inconvenience for patients. The expense may be prohibitive for cash-strapped public healthcare systems [9].

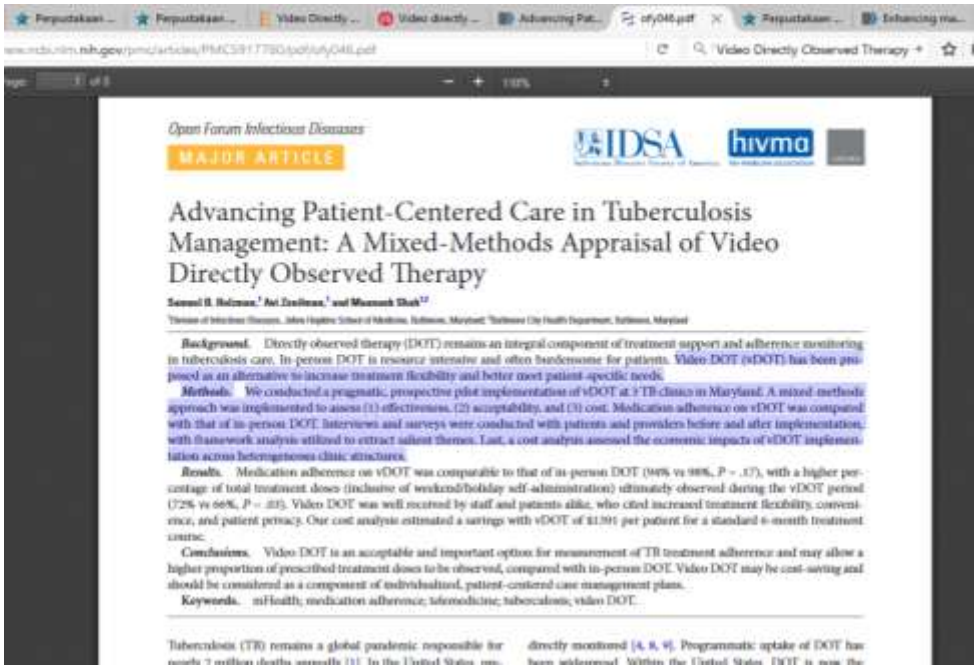
"Telehealth", or the delivery of healthcare services at a distance with information and communications technology, has the potential to overcome deficiencies of direct healthcare delivery. Applying home-phone video for real-time DOT of TB has been reported to be practical in two pilot studies [10, 11]. The objective of this study was to assess the acceptability and cost-effectiveness of real-time video-DOT (V-DOT) on mobile devices as an alternative to in-person DOT for administration of TB medication.

With the approval of Illinois Department of Public Health, DuPage County piloted a V-DOT programme using Skype (Microsoft, Redmond, WA, USA) in January 2013 as an adjunct to the existing in-person DOT programme. In this study, we retrospectively reviewed data from subjects who underwent V-DOT at our DuPage County Health Department Tuberculosis Clinic (Wheaton, IL, USA). The clinic treated 68 adults for active TB from January 2013 to December 2014. Age, sex and treatment duration were collected by chart review of medical records using standardised abstraction forms and pre-established definitions. Inclusion criteria for being on V-DOT were age >18 years, availability of electronic devices, and availability of a member of staff who could speak the patient's language and provide appropriate confidentiality. Patients diagnosed with multidrug resistant TB or who were considered at risk of poor adherence (the homeless, HIV patients or those who were not being truthful) were not offered V-DOT.

We did not provide any equipment to the patients. They used their own smartphones or personal

ERJ open research

Video directly observed therapy for supporting and monitoring adherence to tuberculosis treatment in Uganda: a pilot cohort study



Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA hivma

Advancing Patient-Centered Care in Tuberculosis Management: A Mixed-Methods Appraisal of Video Directly Observed Therapy

Background. Directly observed therapy (DOT) remains an integral component of treatment support and adherence monitoring in tuberculosis care. In-person DOT is resource intensive and often burdensome for patients. Video DOT (vDOT) has been proposed as an alternative to increase treatment flexibility and better meet patient-specific needs.

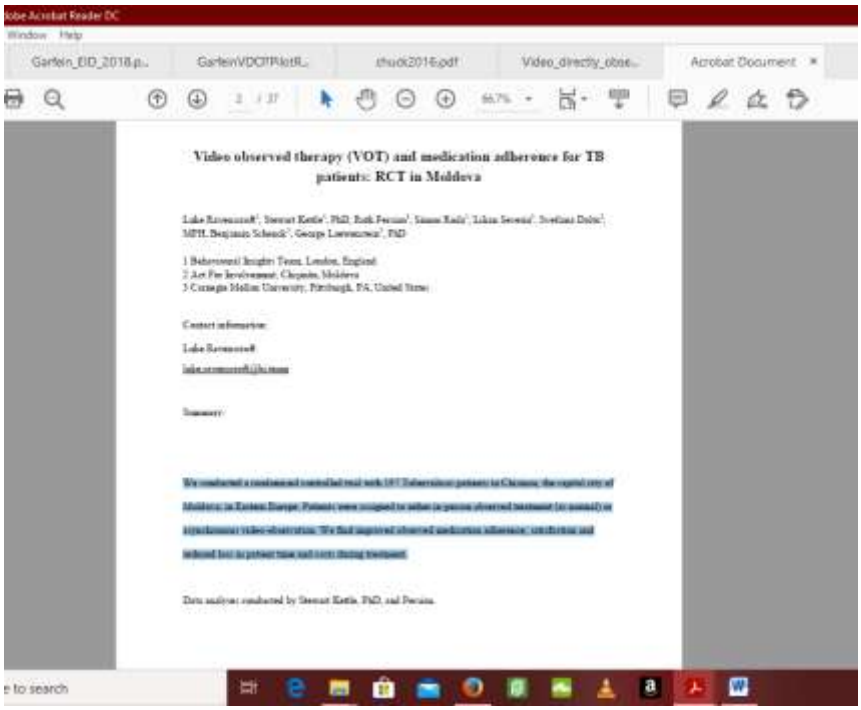
Methods. We conducted a pragmatic, prospective pilot implementation of vDOT at 3 TB clinics in Maryland. A mixed-methods approach was implemented to assess (1) effectiveness, (2) acceptability, and (3) cost. Medication adherence on vDOT was compared with that of in-person DOT. Interviews and surveys were conducted with patients and providers before and after implementation, with framework analysis utilized to extract salient themes. Last, a cost analysis assessed the economic impacts of vDOT implementation across heterogeneous clinic structures.

Results. Medication adherence on vDOT was comparable to that of in-person DOT (96% vs 98%, $P = .17$), with a higher percentage of total treatment doses (inclusive of weekend/holiday self-administration) ultimately observed during the vDOT period (72% vs 66%, $P = .03$). Video DOT was well received by staff and patients alike, who cited increased treatment flexibility, convenience, and patient privacy. Our cost analysis estimated a savings with vDOT of $1391 per patient for a standard 6-month treatment course.

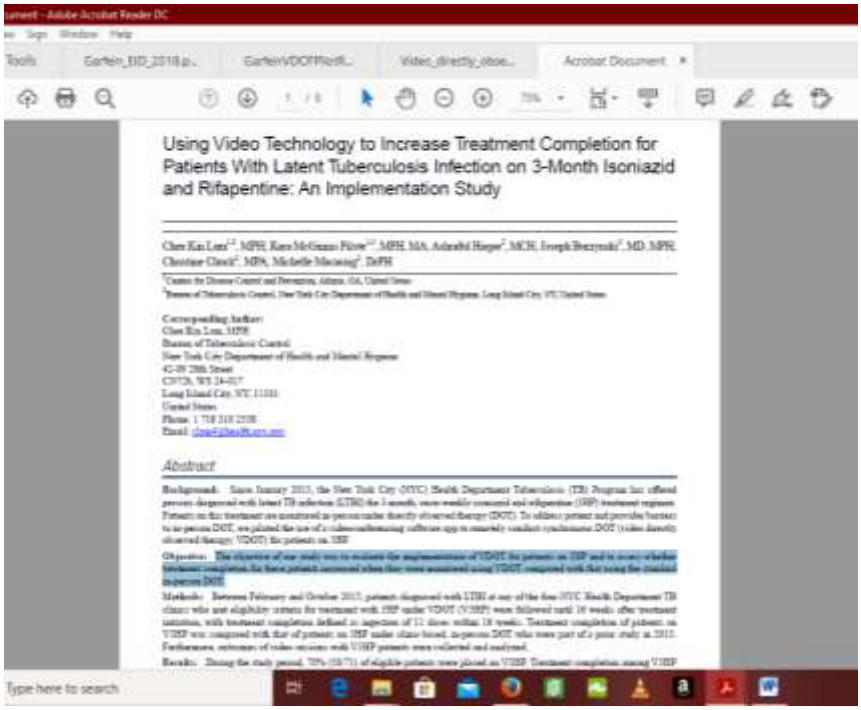
Conclusions. Video DOT is an acceptable and important option for measurement of TB treatment adherence and may allow a higher proportion of prescribed treatment doses to be observed, compared with in-person DOT. Video DOT may be cost-saving and should be considered as a component of individualized, patient-centered care management plans.

Keywords. mHealth; medication adherence; telemedicine; tuberculosis; video DOT.

Tuberculosis (TB) remains a global pandemic responsible for



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



Using Video Technology to Increase Treatment Completion for Patients With Latent Tuberculosis Infection on 3-Month Isoniazid and Rifapentine: An Implementation Study

Lampiran 4

BERITA ACARA REVISI PROPOSAL *LITERATURE REVIEW*

Ketua Penguji : Dr. Aziz Alimul Hidayat.,S.Kep.,Ns.,M.Kes

Nama : Eviolia Mardinda

NIM : 20161660061

Judul : Penggunaan VDOT *(Video Directly Observed Therapy)* dalam kepatuhan pengobatan Tuberculosis

No.	PROPOSAL LITERATURE REVIEW	HAL	PERBAIKAN
1	Judul	Cover	Spesifikan pengambilan judul ke dalam kepatuhan pengobatan TB
2	Latar Belakang (Masalah)	1	Penyesuaian spesifik penulisan tujuan dengan masalah yang diangkat

Surabaya, 04 September 2020

Ketua Penguji

Dr. Aziz Alimul Hidayat.,S.Kep.,Ns.,M.Kes

BERITA ACARA REVISI SEMINAR HASIL *LITERATURE REVIEW*

Ketua Penguji : Dr. Aziz Alimul Hidayat.,S.Kep.,Ns.,M.Kes

Nama : Eviolia Mardinda

NIM : 20161660061

Judul : Penggunaan VDOT *(Video Directly Observed Therapy)* dalam kepatuhan pengobatan Tuberculosis

No.	PROPOSAL LITERATURE REVIEW	HAL	PERBAIKAN
1	BAB5 (Saran)	35	Tambahkan kelemahan kedalam saran yang didapatkan yaitu bahwa penelitian VDOT ini tidak dapat di generalisasikan kepada pasien TB.

Surabaya, 04 September 2020

Ketua Penguji

Dr. Aziz Alimul Hidayat.,S.Kep.,Ns.,M.Kes

BERITA ACARA REVISI PROPOSAL *LITERATURE REVIEW*

Penguji I :Anis Rosyiatul Husna.,S.Kep.,Ns.,M.Kes

Nama : Eviolia Mardinda

NIM : 20161660061

Judul : Penggunaan VDOT *(Video Directly Observed Therapy)* dalam kepatuhan pengobatan Tuberculosis

No.	PROPOSAL LITERATURE REVIEW	HAL	PERBAIKAN
1	Judul	Cover	Spesifikan pengambilan judul ke dalam kepatuhan pengobatan TB
2	Latar Belakang (Masalah)	1	Penyesuaian spesifik penulisan tujuan dengan masalah yang diangkat
3	BAB 3 (Database)	13	Perubahan Database yang lebih spesifik di dalam PNRI
4	Daftar Pustaka	37	Penulisan daftar pustaka menggunakan Mendeley dan referensi yang digunakan dituliskan di daftar pustaka.

Surabaya, 04 September 2020

Penguji I

(Anis Rosyiatul Husna.,S.Kep.,Ns.,M.Kes)

BERITA ACARA REVISI SEMINAR HASIL *LITERATURE REVIEW*

Penguji I : Anis Rosyiatul Husna.,S.Kep.,Ns.,M.Kes

Nama : Eviolia Mardinda

NIM : 20161660061

Judul : Penggunaan VDOT *(Video Directly Observed Therapy)* dalam kepatuhan pengobatan Tuberculosis

No.	LITERATURE REVIEW	HAL	PERBAIKAN
1	BAB 4 (Pembahasan)	31	1. Perluasan pembahasan 2. Penambahan penjelasan durasi VDOT 3. Jelaskan setiap instrumen yang digunakan 4. Dalam pembahsan jika paragraf digunakan merupakan teori sertakan sumber rujukan
2	Daftar Pustaka	37	Perbaikan penulisan menggunakan Mendeley dan cek referensi agar masuk kedalam daftar pustaka

Surabaya, 04 September 2020

Penguji I

(Anis Rosyiatul Husna.,S.Kep.,Ns.,M.Kes)

BERITA ACARA REVISI PROPOSAL

Pembimbing II : Yuanita Wulandari., S.kep., Ns.,MS

Nama : Eviolia Mardinda

NIM : 20161660061

Judul : Penggunaan VDOT *(Video Directly Observed Therapy)* dalam kepatuhan pengobatan Tuberculosis

No.	PROPOSAL SKRIPSI	HAL	PERBAIKAN
1	Latar Belakang (Masalah)	1	Penyesuaian spesifik penulisan tujuan dengan masalah yang diangkat
2	BAB 3 (Database)	13	Perubahan Database yang lebih spesifik
3	Daftar Pustaka	37	Penulisan daftar pustaka menggunakan Mendeley dan referensi yang digunakan dituliskan di daftar pustaka.

Surabaya, 04 September 2020

Pembimbing II

Yuanita Wulandari., S.kep., Ns.,MS

BERITA ACARA REVISI SEMINAR HASIL

Pembimbing II : Yuanita Wulandari., S.kep., Ns.,MS

Nama : Eviolia Mardinda

NIM : 20161660061

Judul : Penggunaan VDOT *(Video Directly Observed Therapy)* dalam kepatuhan pengobatan Tuberculosis

No.	PROPOSAL SKRIPSI	HAL	PERBAIKAN
1	BAB 4 (Pembahasan)	31	1. Perluasan pembahasan 2. Penambahan rentan usia mulai dari minimal hingga maksimal 3. Penambahan penjelasan durasi VDOT 4. Justifikasi pelaksanaan VDOT, penerapan pada usia , outcome yang dihasilkan sama.
2	Daftar Pustaka	37	Perbaikan penulisan menggunakan Mendeley dan cek referensi agar masuk kedalam daftar pustaka

Surabaya, 04 September 2020

Pembimbing II

Yuanita Wulandari., S.kep., Ns.,MS

HALAMAN PERNYATAAN PUBLIKASI TUGAS AKHIR UNTUK KEPENTINGAN AKADEMIK

Sebagai Civitas Akademik Universitas Muhammadiyah Surabaya, saya yang bertanda tangan di bawah ini :

Nama : Eviolia Mardinda

NIM : 20161660061

Fakultas : Ilmu Kesehatan

Program Studi : S1 Keperawatan

Demi pengembangan ilmu pengetahuan, menyetujui untuk memberikan kepada Program Studi S1 Keperawatan Universitas Muhammadiyah Surabaya. Hak bebas Royalty Non- Ekslusif (Non-Exlusive Royalty Free Right) atas karya saya yang berjudul " PENGGUNAAN VDOT *(Video Directly Observed Therapy)* DALAM KEPATUHAN PENGOBATAN TUBERCULOSIS".

Beserta perangkat yang ada (jika diperlukan), Dengan hak bebas Royalty Non-Ekslusif ini, Program Studi S1 Keperawatan Universitas Muhammadiyah Surabaya berhak menyimpan, mengalihkan media/ formatkan mengelola dalam bentuk pangkalan database , merawat, dan mempublikasikan hasil akhir saya selama tetap mencantumkan nama saya sebagai penulis/ pencipta dan atau dengan pembimbing saya sebagai pemilik pencipta,

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Dibuat di : Surabaya

Pada tanggal : 10 September 2020

Yang Menyatakan

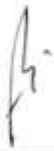
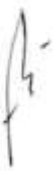
Eviolia Mardinda

Lembar Konsultasi Tugas Akhir

Nama : Eviolia Mardinda

NIM : 20161660061

Nama Pembimbing : Anis Rosyiatul Husna.,S.Kep.,Ns.,M.Kes

NO	Tanggal	Topik	Hasil Revisi	Tanda tangan
1.	2019-09-17	Penentuan Permasalahan pada populasi yang diambil	Mencari permasalahan yang lebih tepat dan spesifik	
2.	2019-09-25	Penentuan Judul	Menguatkan lagi permasalahan yang diangkat	
3.	2019-11-18	Konsultasi bab 1	Penambahan skala terbaru di surabaya khususnya TB Care Aisyiyah Surabaya	
4.	2019-11-27	Konsultasi bab 2	Melengkapi teori yang mendasari dari Self stigma dari penelitian terdahulu	
5.	2019-12-02	Konsultasi bab 123	Mencarian kuisionner yang berhubungan dengan *self stigma* dan *self efficacy* pada TB	
6.	2020-02-03	Konsultasi bab 123	Menambahkan lampirkan instrumen yang dipakai pada setiap variable	

7.	2020-02-24	Mergantian salah satu variabel di judul	*Self efficacy* diganti dengan Kepatuhan minum obat	
8.	2020-02-24	Tambahkan Instrumen Kepatuhan minum obat	Menambahkan instrumen kepatuhan minum obat	
9.	2020-02-29	Pergantian topik Skripsi ke Literature Review	Pengambilan judul diusahakan sesuai dengan ketersediaan jurnal minimal 10	
10.	2020-04-25	Konsultasi judul Literature review	Usahakan cek tujuan dengan permaslahan yang dangkat sesuai dengan 10 jurnal	
11.	2020-06-08	Konsultasi judul Literature review	Pergantian variabel literature review	
12.	2020-06-17	Konsultasi BAB 123	Penggunaan database yang dipilih disesuaikan dengan kebutuhan dengan melihat ketersediaan variabel yang mau diambil	
13.	2020-06-18	Revisi Bab 3	Penggunaan Database Pubmed mengguanakan Mesh	
14.	2020-07-03	Acc Ujian Proposal	Mempersiapkan ujian proposal	
15.	2020-07-10	Revisi Seminar Proposal	1. Untuk judul kata "terhadap "diganti dengan kata "dalam "sehingga lebih	

			spesifikan kepada dalam kepatuhan pengobatan 2. Tujuan disesuaikan ke dalam kepatuhan pengobatan tuberkulosis	
16.	2020-07-28	Konsultasi hasil revisi	Melanjutkan ke bab 4	
17.	2020-08-17	Konsultasi hasil revisi bab 1234 literature review	1. Penulisan dilarang menggunakan simbol, 2. Istilah penderita diganti dengan pasien semua, 3. Tuliskan hasil inklusi dan ekslusi di tiap database yang digunakan. 4. Pada bab 4 beri prolog sebelum tabel pembhasan 5. Tambahakan metoelogi lengkap tiap jurnal	
18.	2020-08-24	Acc Ujian Hasil	Melengkapi dari cover hingga lainya agar bisa maju ujian	
19.	2020-10-01	Revisi hasil Sidang hasil Literature review	1. Tambahkan tingkat kepatuhan yg baik kenapa di pembahasan, 2. Jika menggunakan teori tambahkan sumber rujukan,	

Lembar Konsultasi Tugas Akhir

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NO	Tanggal	Topik	Hasil Revisi	Tanda tangan
1.	2019-09-27	Penentuan Permasalahan pada populasi yang diambil	Ambil Permasalahan yang jarang dibahas pada pasien TB	
2.	2019-09-30	Penentuan Judul	Hubungan self stigma terhadap self efficacy pada pasien TB	
3.	2019-11-26	Konsultasi bab 1	Rumusan masalahnya perkuat lagi	
4.	2019-12-03	Konsultasi bab 2	Tambahkan teori self efficacy yang berkaitan dengan TB	
5.	2019-12-19	Konsultasi bab 123	Mengganti kuisioner *self efficacy* yang lebih spesifik pada pasien TB	
6.	2020-02-07	Konsultasi bab 123	Melampirkan instrumen masing-masing variabel yang di gunakan	
7.	2020-02-16	Perubahan Skripsi ke Literature Review : Konsultasi Clinical Question	Mencocokan Clinical Question dengan Jurnal Yang dicari	

8.	2020-06-17	Penentuan Keyword di berbagai database	Menyesuaikan pencarian jurnal dengan keyword yang di gunakan	
9.	2020-06-05	Konsultasi judul Literature review	Usahakan cek tujuan dengan permaslahan yang dangkat sesuai dengan 10 jurnal	
10.	2020-06-13	Konsultasi BAB 3	Penggunaan Database Pubmed mengguanakan Mesh	
11.	2020-07-05	Acc Ujian Proposal	Mempersiapkan ujian proposal	
12.	2020-07-10	Revisi Seminar Proposal	Tujuan disesuaikan ke dalam kepatuhan pengobatan tuberkulosis	
13.	2020-08-09	Konsultasi hasil revisi	Melanjutkan ke bab 4	
14.	2020-08-23	Acc Ujian Hasil	Melengkapi dari cover hingga lainya agar bisa maju ujian	
15.	2020-08-29	Revisi hasil Sidang hasil Literature review	1. Perluasan pembahasan 2. Penambahan rentan usia mulai dari minimal hingga maksimal 3. Penambahan penjelasan durasi VDOT 4. Justifikasi pelaksanaan VDOT, penerapan pada usia , outcome yang dihasilkan sama	

HALAMAN PERNYATAAN PUBLIKASI TUGAS AKHIR UNTUK KEPENTINGAN AKADEMIK

Sebagai Civitas Akademik Universitas Muhammadiyah Surabaya, saya yang bertanda tangan di bawah ini :

Nama : Eviolia Mardinda

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Program Studi : S1 Keperawatan

Demi pengembangan ilmu pengetahuan, menyetujui untuk memberikan kepada Program Studi S1 Keperawatan Universitas Muhammadiyah Surabaya. Hak bebas Royalty Non- Ekslusif (Non-Exlusive Royalty Free Right) atas karya saya yang berjudul " PENGGUNAAN VDOT *(Video Directly Observed Therapy)* DALAM KEPATUHAN PENGOBATAN TUBERCULOSIS".

Beserta perangkat yang ada (jika diperlukan), Dengan hak bebas Royalty Non-Ekslusif ini, Program Studi S1 Keperawatan Universitas Muhammadiyah Surabaya berhak menyimpan, mengalihkan media/ formatkan mengelola dalam bentuk pangkalan database , merawat, dan mempublikasikan hasil akhir saya selama tetap mencantumkan nama saya sebagai penulis/ pencipta dan atau dengan pembimbing saya sebagai pemilik pencipta,

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Dibuat di : Surabaya

Pada tanggal : 10 September 2020

Yang Menyatakan

Eviolia Mardinda

Abstrak

PENGGUNAAN VDOT (*Video Directly Observed Therapy*) DALAM KEPATUHAN PENGOBATAN TUBERCULOSIS

Literature Review

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Latar belakang : TB merupakan penyakit infeksi menular disebabkan oleh *Mycrobacterium Tuberculosis* . Penyakit TB memerlukan pengobatan rutin sekitar 3- 12 bulan . Lamanya proses pengobatan yang dialami penderita tuberculosis memungkinkan penderita TB mengalami kejenuhan dalam meminum OAT yang mengakibatkan berhentinya minum obat dan ketidakpatuhan dalam mengkonsumsi obat . VDOT salah satu strategi dalam pengamatan minum obat berbasis video perekaman diri dalam meminum rejimen pengobatan. **Tujuan :** Bagaimana penggunaan VDOT dalam kepatuhan pada pasien Tuberculosis dengan menggunakan *Literature Review*. **Metode :** *Literature Review* jurnal VDOT terhadap kepatuhan pasien Tuberculosis. Pencarian artikel melalui database : PUBMED dan *Elsevier Clinical Key Nursing.* Review ini di mulai pada tahun 2010-2020, berbahasa inggris, *full text* kemudian di lakukan sintesis dengan tabel. **Hasil:** Penggunaan VDOT dalam pengobatan TB dapat meningkatkan kepatuhan pengobatan pasien TB dengan rentan antara 74-96%. **Kesimpulan :** Penggunaann VDOT memberikan alternatif yang menguntungkan pada pasien TB seperti penghematan biaya , pemangkasan jarak dan waktu, dan privasi yang lebih terjaga sehingga keunggulan dari VDOT tersebut membuat persepsi baik pada pasien TB yang menggunakan strategi ini. Pemberian motivasi, pemantauan kondisi kesehatan serta komunikasi baik yang diberikan staff pelayanan kesehatan. Hal-hal tersebut mampu mempengaruhi kepatuhan pasien TB dalam pengobatan.

Kata kunci : *Video Directly Observed Therapy; VDOT; Tuberculosis; adherence; treatment*

Abstract

THE USE OF VDOT (Video Directly Observed Therapy) IN COMPLIANCE WITH TUBERCULOSIS

Literature Review

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Background: TB is an infectious disease caused by Mycrobacterium Tuberculosis. TB disease requires routine treatment for about 3- 12 months. The duration of the treatment process experienced by tuberculosis patients allows TB sufferers to experience saturation in taking OAT which results in cessation of taking medication and non-compliance in taking medication. VDOT is one of the strategies in the observation of taking medication based on self-recording videos in taking the treatment regimen. **Objective:** How to use VDOT in adherence to tuberculosis patients using the Literature Review. **Methods:** Literature Review of the journal VDOT on tuberculosis patient adherence. Search for articles through the database: PUBMED and Elsevier Clinical Key Nursing. This review was started in 2010-2020, in English, full text then synthesized with tables. **Results:** The use of VDOT in TB treatment can improve treatment adherence of susceptible TB patients between 74-96%. **Conclusion:** The use of VDOT provides a beneficial alternative to TB patients such as cost savings, time and distance reduction, and more privacy, so that the advantages of VDOT make a good perception of TB patients using this strategy. Providing motivation, monitoring health conditions and good communication provided by health service staff. These things can affect the compliance of TB patients in treatment.

Keywords: Video Directly Observed Therapy, VDOT, Tuberculosis, adherence, treatment

Latar Belakang

Tuberculosis merupakan penyakit infeksi yang menular karena disebabkan oleh *Mycrobacterium Tuberculosis* yang merupakan bakteri tahan asam (BTA). Penyakit ini membahayakan kesehatan penderitanya jika tidak di obati dengan benar. tuberculosis memerlukan pengobatan dengan rutin sekitar 3- 6 bulan bahkan bisa sampai hampir 12 bulan tergantung tingkat resistensi kuman terhadap obat. Lamanya proses pengobatan yang dialami penderita tuberculosis memungkinkan penderita tuberculosis mengalami kejenuhan dalam meminum obat anti tuberculosis yang bisa mengakibatkan berhentinya minum obat dan tidak teratur dalam meminum obat. Dampak dari ketidakpatuhan dapat menyebabkan penderita jatuh dalam resistensi obat yang dapat menimbulkan kegagalan obat. Sehingga penderita TB dapat mengalami kematian (Infodatin, 2018).

Menurut (WHO, 2019) melaporkan jika penyakit *Tuberculosis* pada tahun 2016 terdapat 10,4 juta kasus atau sebanding dengan 120 kasus per 100.000 penduduk. tahun 2016 pada Asia Tenggara mencapai 45 % dan indonesia merupakan salah satu negara dengan TBC yang tinggi. Lalu disusul dengan Afrika 25% , pasifik barat 17%, Mediterania Timur 7%, Eropa 3% dan Amerika 3%. (Kemenkes,2018).

Di Indonesia penyakit Tuberculosis pada tahun 2017 ditemukan sebanyak 420.994 kasus. tahun 2017 peningkatannya cukup tinggi yaitu 42,4 %.

Proses pengobatan tuberculosis berlangsung selama 6 hingga 12 bulan dengan beberapa macam obat yang diminum setiap hari. Lama pengobatan tuberculosis tergantung pada kekuatan kuman *Mycrobacterium* terhadap OAT dan keteraturan dalam pengobatan. Kendala yang sering di temukan pada penderita tb yaitu ketidakpatuhan dalam meminum OAT Proses pengobatan yang dilakukan mempunyai tujuan yaitu kesembuhan penderita TB. Keberhasilan dalam pengobatan TB dengan mentaati pengobatan Berbagai macam startegi yang dapat dilakukan dalam pengobatan TB agar tercapainya keberhasilan dalam pengobatan seperti pendampingan dalam meminum obat oleh pelayanan kesehatan. Video Observed Therapy (VOT) atau Video Directly Ovserved Therapy (VDOT). VDOT adalah suatu strategi pengamatan/pendampingan yang digunakan pada proses pengobatan penderita tuberculosis menggunakan video perekaman diri bahwa penderita TB mematuhi rejimen terapi seperti perekaman diri saat meninum obat. Sehingga diharapkan dengan menggunakan strategi ini dapat berkurangnya penderita TB yang melewatkan dalam proses pengobatab TB.

Berdasarkan permasalahn diatas peneliti ingin mengetahui bagaimana penggunaan VDOT dalam kepatuhan pengobatan Tuberculosis dengan melakukan Literatur Review.

Strategi Pencarian Data

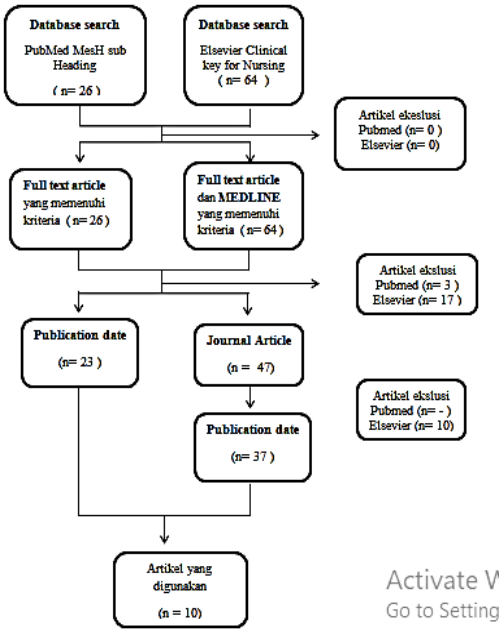
Database yang digunakan dalam strategi pencarian *literatur review* ini

menggunakan PubMed dan Elsevier Clinical key for Nursing dari tahun 2010 sampai tahun 2020 menggunakan keyword *"Video Directly Observed Therapy " OR VDOT, Tuberculosis, treatment OR Adherence"*

Kriteria Inklusi

1. Di terbitkan pada tahun 2010 sampai 2020 (10 tahun terakhir)
2. Ketersediaan artikel jurnal *full text*
3. Populasi yang di teliti yaitu pasien tuberculosis.
4. Dipublikasikan dalam bahasa inggris dan indonesia

Sintesis Tematik



Hasil

Mengenai kerangka kerja dalam pencarian artikel seperti ketika melakukkan penelusuran artikel di database Pubmed didapatkan 26 artikel dan di Elsevier clinical key Nursing didapatkan 64 artikel, kemudian setelah dibaca hanya diambil yang sesuai kriteria sejumlah 23 artikel dari Pubmed dan 37 dari Elsevier clinical Key Nursing. Dan yang diambil sesuai tujuan sejumlah 10 artikel.

Tabel 1. Hasil *Review Article*

NO.	Judul Jurnal	Bulan	Hasil Kepatuhan
1.	Tuberculosis Treatment Monitoring by Video Directly Observed Therapy in 5 Health Districts, California, USA	6	93%
2.	Feasibility of Tuberculosis Treatment	5,5	93%

	Monitoring by Video Directly Observed Therapy: A Binational Pilot Study		
3.	Enhancing management of tuberculosis treatment with video	2	88,4 %
	directly observed therapy in New York City		
4.	Video Directly Observed Therapy to support adherence with treatment for tuberculosis in Vietnam: a prospective cohort study	6	74%
5.	Use of Smartphone-Based Video Directly Observed Therapy (vDOT) in Tuberculosis Care: Single-Arm, Prospective Feasibility Study	6	74%
6.	Video directly observed therapy for treatment of tuberculosis is patient-oriented and cost-effective	4	97%
7.	Video directly observed therapy for supporting and monitoring adherence to tuberculosis treatment in Uganda: a pilot cohort study	6	85%
8.	Advancing Patient-Centered Care in Tuberculosis Management: A Mixed-Methods Appraisal of Video Directly Observed Therapy	24	94%
9.	Video observed therapy (vot and medication adherence for TB patients : RCT in maldova	4	95%
10.	Using Video Technology to Increase Treatment Completion forPatients With Latent Tuberculosis Infection on 3-Month Isoniazidand Rifapentine: An Implementation Study	3	88%

Pembahasan

Stratregi VDOT ini diterapkan pada usia > 18 tahun dengan kisaran umur 27 – 44 tahun. Dengan Outcome yang sama yaitu kepatuhan pengobatan pasien TB dengan rentan antara 74-96%. Dengan waktu yang digunakan dalam kesepuluh jurnal penelitian antara 2 bulan-24 bulan.

1. Usia
   Hasil usia yang ditemukan semuanya adalah dewasa dengan rentan usia minimal rata-rata 27 tahun sampai 44 tahun. Sampel dewasa yang digunakan pada penelitian ini harus mengetahui penggunaan teknologi berbasis internet dengan smarthphone/ tablet/ komputer.

2. Instrumen
   Dari kesepuluh jurnal didapatkan pengukuran dalam kepatuhan pengobatan menggunakan VDOT dengan instrumen yang berbeda-beda, namun dengan outcome yang sama yaitu Kepatuhan pengobatan

3. Kelebihan VDOT

   a) Menjaga Privasi

      Penggunaan VDOT ini dapat kerahasiaan pada pasien TB karena mampu menjaga privasi pasien saat melakukan pemantauan minum obat di tempat yang lebih tertutup sesuai keinginan pasien. Rata-rata didapatkan dari kesepuluh jurnal pasien merasa VDOT bersifat lebih rahasia daripada DOT karena VDOT bersifat lebih privasi. Sehingga pasien nyaman dalam melakukan pengobatan.

   b) Penghematan Biaya, Jarak, dan Waktu

      Penggunaan VDOT ini dapat dilakukan di berbagai tempat saat pasien melakukan sesi jadwal peminuman obat hanya dengan berbasis melakuakan perekaman video dari smarthphone atau komputer yang terkoneksi dengan internet. Sehingga tidak membutuhkan pengunjungan oleh staff pelayanan kesehatan setiap kali minum obat atau yang biasa di sebut dengan DOT(Directly Observed Therapy). Hal ini mampu memangkas biaya, jarak dan waktu yang digunakan dalam pemantauan minum obat baik dari staff pelayanan kesehatan dan pasien tuberculosis sendiri.

   c) Pemberian Motivasi
      Dalam proses VDOT pemberian konsultasi medis diberikan untuk pasien, dalam konsultasi tersebut Petugas pelayanan kesehatan memberikan motivasi terkait kondisi yang dirasakan dan mendampingi setiap pengobatan yang dilakukan setiap hari dengan mengevaluasi kondisi terkait efek samping yang dirasakan. Stimulus yang diberikan staff pelayanan kesehatan dapat mempengaruhi kepatuhan dari pasien TB.

Dari penelitian yang didapatkan pada kesepuluh jurnal, proses yang terjadi dalam VDOT sehingga dapat meningkatkan kepatuhan dengan

pemberian stimulus seperti komunikasi yang baik, pemberian pesan pengingat jadwal sebelum dilakukanya sesi VDOT, pemberian konsultasi medis, pemberian dukungan dan motivasi agar selalu semangat dalam menjalani pengobatan oleh staff pelayanan kesehatan pada peserta selama mengikuti VDOT.

Stimulus-sttimulus yang diberikan mampu mempengaruhi sikap/ perilaku peserta VDOT yaitu kepatuhan dalam pengobatan . Hal ini sejalan dengan teori S-O-R dari Skinner bahwa stimulus yang diberikan dari komunikator yaitu staff pelayanan dapat diterima dandi resapi serta di proses oleh organisme yaitu peserta VDOT dengan membentuk respon perilaku kepatuhan dalam pengobatan.

Keunggulan yang diberikan VDOT seperti penghematan waktu, penghematan jarak, penghematan biaya, terjaganya privasi setiap pasien . Keunggulan tersebut mempengaruhi persepsi sehingga peserta merasa nyaman menggunakan . Persepsi dapat membentuk perilaku seseorang. Hasil dari persepsi yang baik akan mempengaruhi tindakan/ perilaku seperti kepatuhan dalam pengobatan . Hal ini sejalan dengan teori Lawrence Green jika persepsi seseorang akan mempengaruhi perilaku kesehatan yaitu pada kepatuhan.

Kesimpulan

Berdasarkan uraian diatas maka ditarik kesimpulan bahwa VDOT (*Video Directly Observed Therapy*) merupakan strategi yang digunakan untuk pemantauan program pengobatan pasien TB . Penggunaann VDOT memberikan alternatif yang menguntungkan pada pasien TB seperti penghematan biaya , pemangkasan jarak dan waktu, dan privasi yang lebih terjaga sehingga keunggulan dari VDOT tersebut membuat persepsi baik pada pasien TB yang menggunakan strategi ini. Pemberian motivasi, pemantauan kondisi kesehatan serta komunikasi baik yang diberikan staff pelayanan kesehatan. Hal-hal tersebut mampu mempengaruhi kepatuhan pasien TB dalam pengobatan

Saran

Kelemahan dari 10 jurnal yang didapatkan yaitu hanya menggunakan 2 database (Pubmed dan Elsevier clinical key Nursing) yang mana artikel-artikel yang didapat hanya mengikat di batasan wilayang masing-masing penelitian tidak secara global, serta pemilihan sampel hanya dilakukan penelitian pada sampel tuberculosis tertentu dipilih yang hanya bisa menggunakan teknologi dan diinklusikan para peneliti sehingga , hasil penelitian ini tidak dapat digeneralisasikan .

Bagi penelitian selanjutnya diperlukan pengembangan database yang lebih luas, penggunaan desain penelitian yang lebih bervariasi sehingga hasil yang didapatkan lebih luas. Serta perlu dilakukan pengembangan penelitian khusus di Indonesia menggunakan strategi upaya VDOT sebagai salah satu upaya meningkatkan kepatuhan pengobatan tuberculosis.

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Lampiran 5 Artikel yang digunakan

Lampiran artikel 1

RESEARCH

Tuberculosis Treatment Monitoring by Video Directly Observed Therapy in 5 Health Districts, California, USA

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We assessed video directly observed therapy (VDOT) for monitoring tuberculosis treatment in 5 health districts in California, USA, to compare adherence between 174 patients using VDOT and 159 patients using in-person directly observed therapy (DOT). Multivariable linear regression analyses identified participant-reported sociodemographics, risk behaviors, and treatment experience associated with adherence. Median participant age was 44 (range 18–87) years; 61% of participants were male. Median fraction of expected doses observed (FEDO) among VDOT participants was higher (93.0% [interquartile range (IQR) 83.4%–97.1%]) than among patients receiving DOT (66.4% [IQR 55.1%–89.3%]). Most participants (96%) would recommend VDOT to others; 90% preferred VDOT over DOT. Lower FEDO was independently associated with US or Mexico birth, shorter VDOT duration, finding VDOT difficult, frequently taking medications while away from home, and having video-recording problems ($p<0.05$). VDOT cost 32% (range 6%–46%) less than DOT. VDOT was feasible, acceptable, and achieved high adherence at lower cost than DOT.

Tuberculosis (TB) incidence rates in the United States increased slightly in 2015 after 20 years of decline (*1*). California has the third-highest TB incidence and the most TB cases in the United States (*2*). Although TB is treatable (*3*), poor medication adherence leads to ongoing transmission, disease progression, and development of drug-resistant strains. Treating drug-resistant TB requires longer regimens with costlier, more toxic, and less effective drugs, highlighting the need for reliable treatment adherence monitoring (*4*,*5*). Strict adherence has become increasingly important because new short-course and intermittent treatment regimens have lower tolerance for adherence gaps (*6*) and because preventing acquired resistance to new drugs developed to treat multidrug-resistant (MDR) and extensively drug-resistant TB is crucial for preserving gains made in this area (*7*).

Given the severe consequences of poor adherence, health agencies recommend directly observed therapy (DOT), a process in which healthcare workers or trusted designees watch patients swallow each medication dose (*8*–*10*). Although DOT is considered the preferred method for adherence monitoring by health agencies including the World Health Organization (*11*) and the US Centers for Disease Control and Prevention (*12*), varying degrees of effectiveness have been reported from delivery of DOT through home visits by DOT workers, patients visiting clinics, and trusted family or community members performing observations (*13*). Furthermore, the DOT process itself can hinder treatment because of its high cost, personnel requirements, potential for stigma, impact on patient income and mobility, and travel required by patients or healthcare workers (*14*).

These barriers to DOT prompted some US TB programs to use videoconferencing technology through videophones, computers, or smartphones to remotely observe patients swallowing pills (*15*,*16*). This live (synchronous) approach became known as video directly observed therapy (VDOT). Studies of synchronous VDOT indicate that patients adhere to their regimens and mostly prefer VDOT over in-person DOT and that VDOT saves TB programs

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money by reducing travel and personnel costs (*17–19*). However, barriers such as limiting observation to business hours, network interruptions, and requirements of the Health Insurance Portability and Accountability Act (HIPAA) prompted development of smartphone applications to enable recorded (asynchronous) VDOT. A pilot study in Kenya provided the first published evidence of asynchronous VDOT's acceptance (*20*). Subsequently, the first study to systematically evaluate asynchronous VDOT among TB patients in San Diego, California, and Tijuana, Mexico, showed that patients and providers found VDOT to be feasible and acceptable, with >95% of expected doses observed, but lacked a comparison group (*21*). We assessed treatment adherence for patients using VDOT versus traditional DOT and evaluated adherence, feasibility, acceptability, and cost differences between urban and rural TB programs.

Methods

Design

We conducted a prospective, multisite, single-arm trial in which all participants had TB treatment monitored using asynchronous VDOT. As a comparator, medical record reviews provided adherence data from a sample of patients who were monitored using in-person DOT at the same clinics. All VDOT participants used DOT for the first 2 weeks or until medication tolerance was established (whichever was longer) before initiating VDOT. Participants continued using VDOT until treatment completion or their provider switched them back to DOT.

A University of California–San Diego Institutional Review Board approved this study, as did each participating health department. Study participation did not affect treatment prescribed by participants' physicians.

Population and Recruitment

The study population consisted of patients receiving DOT for active or suspected pulmonary TB in 3 urban (San Diego, San Francisco, Santa Clara) and 2 rural (San Joaquin, Imperial) California health jurisdictions. Patients ≥18 years of age with no plans to move from the jurisdiction before completing treatment and ≥30 days of treatment remaining were eligible. Patients with MDR TB were eligible; however, only 1.4% of California's TB patients had MDR TB (*22*).

TB program staff recruited patients sequentially during routine DOT visits. Research staff explained VDOT and study procedures to interested patients and obtained written informed consent. Asynchronous VDOT was available only to study participants; patients who declined participation continued treatment through DOT. In San Diego and Santa Clara counties, synchronous VDOT was also offered to patients who were unsuitable for DOT. Two patients declined to participate before enrollment, and 5 who initially consented withdrew before starting VDOT.

Historical controls (n = 159) were group-matched by age, race or ethnicity, and sex from a random sample of patients at the 5 study sites to obtain estimates of adherence to in-person DOT. To avoid selection bias from using patients who were not offered VDOT, controls were selected from patients who completed TB treatment during the year before asynchronous VDOT introduction at each site.

VDOT Description

The VDOT application (Figure 1) enabled participants to record themselves swallowing each treatment dose and send videos for review by a DOT worker. Each recorded dose was automatically date- and time-stamped, encrypted, and uploaded to a secure server over a cellular or wireless network. Once the data were received by the server, the smartphone application deleted videos from the device to prevent unintentional disclosure of participant information and conserve device memory. Videos were stored on the smartphone in a manner that prevented viewing, editing, resending, or deleting them to protect participant privacy and ensure video fidelity. The asynchronous design allowed participants to take their medications regardless of network connectivity (e.g., while traveling) because videos uploaded automatically whenever cellular or WiFi connections were established. An application status screen allowed participants to see when videos were uploaded or pending. The system sent daily medication reminders by text message or email. Participants were loaned smartphones with cellular data plans to ensure that the application performed identically for all participants and avoided service outages.

TB program staff trained participants to use VDOT during routine clinic or home visits. As with DOT, whenever possible, participants were seen by staff who spoke their preferred language; otherwise, telephone-based translation services were used. Once participants demonstrated VDOT competency, they were given smartphones and instructed to record their next dose alone at the prescribed time. If the participant or DOT worker had concerns about the procedures, the DOT worker kept the phone and repeated the training during subsequent in-person DOT visits; thus, the number of training days could vary by participant. Participants also received a VDOT reference pamphlet. To minimize health risks, participants were instructed to call or visit their healthcare provider before taking medications when side effects occurred, rather than reporting side effects through videos. DOT workers regularly logged onto a password-protected website to view videos and document their observations. If expected videos were missing or videos did not clearly show participants ingesting medications, participants

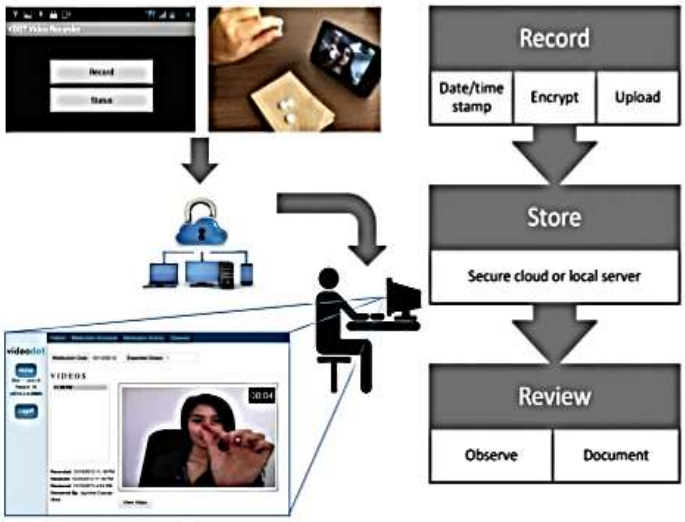

Figure 1. Schematic of asynchronous VDOT in a study assessing VDOT for monitoring tuberculosis treatment, 5 California health districts, 2015–2016. Patients use VDOT smartphone application to record a video of themselves ingesting their medications. After recording stops, the application encrypts the video and transfers it through a cellular or Wi-Fi connection to a server for storage and playback. On a routine basis, treatment monitors log into a secure website to view each video and document their observations. Missing videos or videos not showing complete dose ingestion trigger follow-up procedures to investigate missed doses and provide patient support as needed. VDOT, video directly observed therapy.

were contacted to identify problems and provide support as needed. Decisions about returning participants to DOT were made on a case-by-case basis rather than by using strict adherence-based criteria because some missed doses were unavoidable and requiring DOT for participants who could not meet in-person might adversely affect adherence. Routine medication refill and health monitoring visits occurred per standards of care.

Data Collection

We conducted brief (15–20 minute) baseline (before initiating VDOT) and follow-up (after ending VDOT) telephone interviews to assess sociodemographic variables, experience using mobile technology, TB history and risk factors, privacy concerns, and perceptions of TB treatment monitoring. Research staff, rather than care providers, conducted interviews to minimize response bias. Participants received $10 USD for each interview; no remuneration was paid for sending videos.

To measure treatment adherence among control patients, TB program staff reviewed their DOT records abstracting treatment start and end dates; DOT start and end dates; treatment outcome; and the number of doses expected, observed, and unobserved (i.e., self-administered, not taken, or treatment suspended). DOT was predominantly community-based and required staff travel; however, San Francisco also offered clinic-based DOT to patients who could conveniently access the clinic. Nonclinical personnel conducted most DOT visits; nurses also provided some DOT based on clinical needs and staffing considerations. Control patients were not interviewed.

VDOT versus DOT

Because VDOT was introduced after participants had initiated treatment using DOT, we calculated the fraction of expected doses observed (FEDO) while the patient was on VDOT as a measure of adherence. FEDO equals the number of observed doses divided by the sum of observed doses, missed doses, and self-administered doses. For each day that medication doses were expected, DOT workers documented whether they observed all, some, or no pills being ingested. For this analysis, doses were only considered observed if all pills were taken. If no video was received or ingestion of fewer than all pills was observed, the dose was considered missed, as were self-administered doses. Because weekend doses are not ordinarily observed in DOT, they were excluded from this calculation. FEDO was calculated for VDOT and control patients. Adherence (doses observed divided by total doses prescribed) was also computed for control patients because they used DOT throughout their treatment.

Cost Analysis

Employing a healthcare provider perspective, we used an ingredients-based, bottom-up approach (*23*,*24*) to estimate the average per-patient cost of a standard, Centers for Disease Control and Prevention–recommended (*3*), 6-month treatment regimen for drug-susceptible TB using DOT or VDOT. Because the likelihood of medication side effects differs between the intensive (56 daily doses) and continuation (126 daily doses) phases of treatment, costs were stratified by treatment phase and then summed to calculate the overall average patient treatment cost. Nurses from 4

sites completed a standardized questionnaire assessing personnel time, personnel salaries, and resources required to administer DOT and VDOT. Staff turnover precluded data collection from the fifth site. Completed questionnaires were discussed jointly by teleconference to ensure that all sites interpreted the questions and responded uniformly. Cost data were collected during March–June 2017 and presented in 2017 USD.

DOT personnel costs included time for patient contact, administrative tasks, and travel. VDOT personnel costs included time for community-based visits before initiating VDOT, patient VDOT training, administrative tasks, video observation, and follow-up when expected videos were not received. Some in-person observations also occurred among patients using VDOT because all patients received DOT for ≥2 weeks before starting VDOT and patients in San Francisco were observed in-person during weekly medication refill visits to the clinic. We converted annual salaries, including fringe benefits, into an hourly rate, assuming a 40-hour workweek. All personnel reported full-time employment. The total time for each DOT-related task (administrative, patient contact, and travel) needed to treat each patient was multiplied by the hourly rate and then summed for all personnel.

To calculate an overall per-patient travel cost, we multiplied the average number of miles per patient visit and total number of in-person visits by the current federal mileage reimbursement rate ($0.54 per mile). This approach conservatively estimated travel costs because it assumed that DOT workers used personal vehicles rather than costlier county-owned vehicles. Because DOT workers often visited multiple patients in a single outing rather than returning to the health department between each patient visit, we calculated the average number of miles per visit by dividing the average number of miles driven per day for DOT-related activities by the average number of in-person visits on any given day.

Corporate prices paid by the investigators for smartphones ($100) and service plans ($54/month) during the study were applied to all sites. An estimated VDOT application cost of $35/month/patient was applied on the basis of products commercially available at the time this article was written. Costs of antibiotics, laboratory tests, chest radiographs, and clinical examinations were excluded because they were assumed to be equivalent for VDOT and DOT.

Statistical Analysis

We used Kruskal-Wallis and Fisher exact tests to determine differences in sociodemographic characteristics, TB history, TB risk factors, and VDOT perception variables across study sites. We assessed associations between FEDO and independent variables by using Kruskal-Wallis tests (categorical variables), Wilcoxon rank sum tests (binary variables), and Spearman correlation coefficients (continuous variables). We used simple linear regression to identify factors associated with FEDO and considered significant variables ($p<0.15$) for inclusion in multivariable linear regression analysis. We used backward stepwise elimination to remove nonsignificant variables until only variables with $p<0.05$ remained in the final model and assessed normal assumption of residuals by using normal probability plot, and influential observations were assessed by residuals and Cook's distance. We performed Wilcoxon rank sum tests to compare FEDO between VDOT and DOT and used R statistical software (*25*) to conduct analyses.

Results

Participant Characteristics and VDOT Perceptions

Overall, 274 participants (248 urban and 26 rural) enrolled during October 2014–October 2015 contributed adherence and baseline interview data (Table 1). Median participant age was 44 (range 18–87) years; 61% were male, 57% were Asian, 30% were Hispanic or Latino, and 7% were white. Most (67%) were born in other countries (predominantly countries in Asia), followed by the United States (17%) and Mexico (16%). Education and income were low overall, but most participants had health insurance. Most participants (90%) owned cell phones; 72% owned smartphones. Substance use, other than smoking (42%), was uncommon, and no participants were homeless. Only race or ethnicity, education level, and country of birth differed across sites ($p<0.05$).

We obtained VDOT observation data from the 274 enrolled participants, 214 (78%) of whom completed follow-up interviews (Table 2). Twenty-seven percent of participants reported not sharing their VDOT experience with family members, and 66% did not share with others. Although 34% disclosed having concerns about being seen recording VDOT videos, only 8% failed to record >1 dose because of privacy concerns. At follow-up, only 2% of participants thought VDOT was less confidential than DOT, and 96% reported that VDOT was "very or somewhat easy to perform"; only 3% would choose DOT over VDOT if they had to repeat treatment, and 96% would recommend VDOT to other patients. Training VDOT procedures to participants took a median of 1 day across sites; 74% of participants required 1 day, whereas 4% needed ≥4 days (data not shown). Only 12 (4.4%) participants were returned to DOT before completing treatment because of poor adherence (n = 5), a lost or broken phone (n = 4), or technical or connectivity problems (n = 3).

FEDO by Treatment Monitoring Method

Study participants used VDOT a median of 5.4 months (interquartile range [IQR] 3.5–7.1 months), generating 42,211

Table 1. Baseline characteristics of patients participating in a study assessing VDOT for monitoring tuberculosis treatment, by site, 5 California health districts, 2015–2016*

Characteristic	Total	Site					p value†
		San Diego	San Francisco	Santa Clara	Imperial	San Joaquin	
No. patients	272	99	99	49	10	15	
Age, y							
Mean (SD)	43.8 (16.5)	42.0 (16.9)	46.5 (15.5)	42.2 (16.2)	46.6 (22.0)	41.7 (16.1)	0.19
Range	18–87	18–87	24–86	21–83	21–69	21–76	
Education							
≤Primary school	26 (10)	10 (10)	12 (12)	3 (6)	1 (10)	0	0.02
High school	105 (39)	39 (40)	39 (40)	13 (27)	5 (50)	9 (60)	
Some college or technical school	67 (25)	25 (26)	17 (18)	15 (31)	4 (40)	6 (40)	
≥Bachelor's degree	71 (26)	24 (24)	29 (30)	18 (37)	0	0	
Sex							
M	167 (61)	59 (60)	61 (62)	34 (69)	5 (50)	8 (53)	0.65
F	105 (39)	40 (40)	38 (38)	15 (31)	5 (50)	7 (47)	
Race or ethnicity							
Asian	154 (57)	41 (41)	68 (69)	37 (76)	10 (10)	7 (47)	<0.001
Caucasian or white	19 (7)	7 (7)	7 (7)	1 (2)	0	4 (27)	
Hispanic or Latino	82 (30)	42 (42)	21 (21)	6 (12)	9 (90)	4 (27)	
Other‡	17 (6)	9 (9)	3 (3)	5 (10)	0	0	
Country of birth							
United States	47 (17)	22 (22)	9 (9)	4 (8)	4 (40)	8 (53)	<0.001
Mexico	44 (16)	26 (26)	7 (7)	5 (10)	5 (50)	1 (7)	
Other§	181 (67)	51 (52)	83 (84)	40 (82)	1 (10)	6 (40)	
Annual household income, USD							
<10,000	110 (44)	43 (46)	43 (47)	13 (29)	6 (55)	8 (57)	0.09
10,000–30,000	74 (30)	24 (28)	29 (32)	15 (33)	3 (27)	3 (21)	
30,000–50,000	26 (10)	13 (15)	9 (10)	2 (4)	0 (0)	2 (14)	
>50,000	39 (16)	10 (11)	11 (12)	15 (33)	2 (18)	1 (7)	
Had health insurance, yes vs. no	229 (85)	76 (78)	85 (86)	43 (90)	10 (91)	15 (100)	0.12
Owned cell phone, yes vs. no	247 (90)	90 (91)	92 (93)	44 (90)	9 (82)	12 (80)	0.33
Owned smartphone, yes vs. no	196 (72)	71 (72)	67 (68)	41 (84)	7 (64)	10 (67)	0.26
Homeless, yes vs. no¶	0	0	0	0	0	0	NA
Ever smoked cigarettes, yes vs. no	116 (42)	43 (43)	41 (41)	17 (35)	7 (64)	8 (53)	0.41
Marijuana use, yes vs. no¶	18 (7)	5 (5)	7 (7)	2 (4)	2 (18)	2 (13)	0.26
Noninjection drug use, yes vs. no¶	4 (1)	1 (1)	2 (2)	1 (2)	0	0	1
Ever injection drug use, yes vs. no	3 (1)	1 (1)	0	1 (2)	1 (9)	0	0.07

*Values are no. (%) participants unless otherwise indicated. VDOT, video directly observed therapy; NA, not applicable.
†p values based on Fisher exact test or Kruskal-Wallis test. Variable totals might not sum to column totals because of missing data.
‡Other race group includes African American (n = 3), American Indian (n = 2), Pacific Islander (n = 1), and mixed and other races (n = 11).
§Other countries were predominantly in Asia.
¶Referent period is the previous 6 months.

videos (Table 2). Median FEDO was 93.0% (IQR 83.4%–97.1%), compared with 66.4% (IQR 55.1%–89.3%) for control patients using only DOT (Figure 2). By contrast, median adherence was 100% (IQR 97.0%–100%) for control patients because of an unwavering commitment by TB program staff to ensure patients completed their treatment.

Correlates of FEDO

Median FEDO differed across individual sites (range 84.5%–96.1%; p<0.001); however, the extreme values occurred in the 2 rural sites (Table 2). Thus, FEDO did not differ between the combined urban and rural sites (92.8% vs. 94.2%; p = 0.51) in bivariate analysis (Table 3, https://wwwnc.cdc.gov/EID/article/24/10/18-0459-T3.htm). FEDO differed by race or ethnicity and country of birth, increased with longer VDOT use and higher annual income, and decreased with marijuana use in the prior 6 months. Participants who found VDOT more difficult, more often took medications while away from home, more often had problems using the VDOT application, and more often had problems uploading videos because of poor network connectivity had lower FEDOs.

In multivariable analysis (Table 4), higher FEDO was independently associated with longer duration of VDOT use. Lower FEDO was associated with birth in Mexico or the United States compared with other countries; feeling VDOT was somewhat or very difficult compared with very easy; taking medication away from home most or every time compared with never; and having problems using VDOT more than half the time compared with "never."

VDOT versus DOT Costs

The estimated cost for monitoring a 6-month treatment regimen using VDOT (Table 5) varied by site (range $3,031–$3,911) and was 6%–46% cheaper than community-based

DOT (range $3,212–$5,788) across sites. Reduced personnel costs drove savings, which offset smartphone-related costs.

Discussion

VDOT was feasible and acceptable for monitoring TB medication ingestion in urban and rural California health districts. A higher proportion of expected doses was observed as scheduled among VDOT participants than among in-person DOT participants, resulting in shorter treatment duration.

Median FEDO for VDOT was lower than previously reported (95%) (*21*), possibly because the earlier study oversampled low-risk patients during the first trial of the VDOT application. Alternatively, the disparity could be attributable to our conservative approach to calculating

Table 2. Reported experiences of patients participating in a study assessing VDOT for monitoring tuberculosis treatment, by site, 5 California health districts, 2015–2016*

Characteristic	Total	Site					p value†
		San Diego	San Francisco	Santa Clara	Imperial	San Joaquin	
No. patients	274‡	100	99	49	11	15	
VDOT use							
Months on VDOT, median (IQR)	5.4 (3.5–7.1)	5.2 (3.2–6.3)	5.4 (3.5–7.3)	5.5 (4.1–8.1)	4.0 (2.1–5.6)	6.1 (4.4–7.7)	0.08
FEDO, median (SD), IQR	93.0 (13.5), 83–97	88.7 (15.1), 77–94	95.5 (11.8), 87–98	95.2 (10.3), 89–98	84.5 (20.0), 78–94	96.1 (7.9), 93–98	<0.001
No. patients in follow-up interviews	214	74	84	39	9	7	
Tuberculosis and treatment perceptions							
Did you share your VDOT experience with family members?							
Yes	156 (73)	55 (74)	55 (66)	30 (77)	9 (100)	6 (86)	0.18
No	58 (27)	19 (26)	29 (34)	9 (23)	0	1 (14)	
Did you share your VDOT experience with friends, neighbors, classmates, or coworkers?							
Yes	73 (34)	24 (32)	28 (33)	13 (33)	3 (33)	5 (71)	0.38
No	141 (66)	50 (68)	57 (67)	26 (67)	6 (67)	2 (29)	
Were you concerned someone would see you using the VDOT cell phone?							
Yes	73 (34)	19 (26)	34 (40)	15 (38)	4 (44)	1 (14)	0.23
No	141 (66)	55 (74)	51 (60)	24 (62)	5 (56)	6 (86)	
Did you ever fail to record a video because you were worried someone was watching you?							
Yes	18 (8)	7 (9)	9 (11)	2 (5)	0	0	0.87
No	196 (92)	67 (91)	76 (89)	37 (95)	9 (100)	7 (100)	
Confidentiality of VDOT vs. DOT?							
More	146 (70)	49 (67)	55 (66)	30 (77)	7 (78)	5 (83)	0.68
Less	5 (2)	2 (3)	1 (1)	2 (5)	0	0	
Same	59 (28)	22 (30)	27 (33)	7 (18)	2 (22)	1 (17)	
VDOT experience							
Overall, how easy/difficult did you find the VDOT process?							
Very easy	174 (81)	58 (78)	68 (79)	36 (92)	6 (67)	6 (86)	0.19
Somewhat easy	32 (15)	14 (19)	13 (15)	3 (8)	1 (11)	1 (14)	
Somewhat or very difficult	9 (4)	2 (3)	5 (6)	0	2 (22)	0	
If you had to redo tuberculosis treatment, would you choose VDOT or DOT?							
VDOT	192 (90)	67 (92)	75 (87)	35 (90)	9 (100)	6 (86)	
DOT	6 (3)	1 (1)	4 (5)	1 (3)	0	0	0.9
No preference	16 (7)	5 (7)	7 (8)	3 (8)	0	1 (14)	
Would you recommend VDOT to other tuberculosis patients?							
Yes	202 (96)	70 (95)	81 (96)	35 (97)	9 (100)	7 (100)	0.95
No	8 (4)	4 (5)	3 (4)	1 (3)	0	0	
How often did you take tuberculosis medication away from home?							
Never or rarely	120 (56)	39 (53)	54 (64)	19 (49)	5 (56)	3 (43)	0.36
Less than half or half the time	48 (22)	18 (24)	12 (14)	13 (33)	2 (22)	3 (43)	
Most of the time or every time	46 (21)	17 (23)	19 (22)	7 (18)	2 (22)	1 (14)	
How often did you have problems using the VDOT application?							
Never	82 (38)	24 (32)	41 (48)	16 (41)	1 (11)	0	0.06
Rarely	99 (46)	35 (47)	33 (39)	20 (51)	5 (56)	6 (86)	
Less than half the time	23 (11)	9 (12)	9 (11)	2 (5)	2 (22)	1 (14)	
Half the time or more	10 (5)	6 (8)	2 (2)	1 (3)	1 (11)	0	
How often did poor reception cause you problems uploading videos?							
Never	65 (31)	13 (18)	34 (40)	12 (31)	3 (33)	3 (43)	
Rarely	103 (49)	41 (56)	35 (42)	20 (51)	3 (33)	4 (57)	0.15
Less than half the time	24 (11)	11 (15)	7 (8)	3 (8)	3 (33)	0	
Half the time or more	20 (9)	8 (11)	8 (10)	4 (10)	0	0	

*Values are no. (%) participants unless otherwise indicated. DOT, directly observed therapy; FEDO, fraction of expected doses observed = number of complete doses observed via VDOT divided by the number of doses expected; IQR, interquartile range; VDOT, video directly observed therapy.
†p values based on Fisher exact test or Kruskal-Wallis test. Variable totals might not sum to column totals because of missing data.
‡Includes 2 participants who used VDOT but had missing baseline interview data.

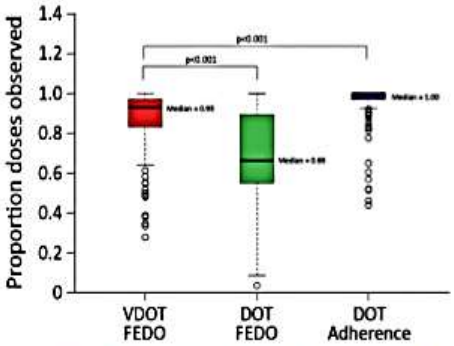

Figure 2. FEDO among patients monitored ingesting medication for tuberculosis by VDOT compared with FEDO and adherence for patients monitored using in-person DOT in a study assessing VDOT for monitoring tuberculosis treatment, 5 California health districts, 2015–2016. FEDO assessed by number of complete doses observed through VDOT divided by the number of doses expected. Adherence assessed by number of doses observed through DOT divided by the number of prescribed doses. Because missed or self-administered doses had to be rescheduled, the number of times a dose was expected could exceed the number of doses prescribed. DOT, directly observed therapy; FEDO, fraction of expected doses observed; VDOT, video directly observed therapy.

FEDO by only counting doses when all pills were taken and treating all doses as missed when a software error caused 5% of videos received to be unviewable. If unviewable videos and partial doses were counted as observed, FEDO in our study (median 96.4%, IQR 89%–99%) would have matched the prior study.

Defining eligibility criteria for VDOT a priori appears unnecessary. Despite efforts to define VDOT eligibility criteria using these data, only 1 variable known before treatment (country of birth) was associated with FEDO. DOT studies similarly found few predictors of adherence (*26*). Initial concerns about older patients or those unfamiliar with smartphones having difficulty using VDOT were unfounded because these factors did not predict FEDO. Travel was also not problematic; study staff often reported that patients who traveled or had nontraditional work hours could adhere better after switching to VDOT. Monitoring anti-TB therapy involves ongoing communication, negotiation, and cooperation between patients and healthcare providers (*27*,*28*), and patient-centered care increased when patients had VDOT as an option. Other than ensuring that patients could tolerate their medications, operate the VDOT application, and access smartphones and service, no evidence was found to support requiring other eligibility criteria.

We observed an association between VDOT problems and lower FEDO, which was driven by only 10 participants who reported having problems half the time or more. Similarly, the association between FEDO and difficulty using VDOT resulted from 9 participants reporting that VDOT was somewhat or very difficult. However, most of these participants encountered the software error described previously, which lowered their FEDO and could explain why they felt VDOT was difficult. Lower FEDO among participants taking medications away from home most or every time could be attributable to difficulty finding a private location to make videos while away from home, which might have also made DOT difficult.

Unlike DOT or synchronous VDOT, asynchronous VDOT enabled patients to take medications outside normal business hours (e.g., at mealtimes or bedtime), which could minimize side effects and improve adherence (*16*). VDOT also allowed participants to fast during religious holidays, because medication doses could be observed at night after fasting ended. Avoiding intermittent dosing by allowing observations after hours and on weekends and holidays through VDOT could also improve treatment efficacy (*29*).

Table 4. Multivariable linear regression analysis of factors associated with FEDO among patients treated for tuberculosis, 5 California health districts, 2015–2016*

Characteristic	Beta coefficient	SE	p value
Months on VDOT (per month)	0.008	0.003	0.01
Country of birth (referent: other)			
Mexico	−0.095	0.022	<0.001
United States	−0.048	0.022	0.03
Perceived ease or difficulty of VDOT (referent: very easy)			
Somewhat easy	−0.003	0.024	0.90
Somewhat or very difficult	−0.130	0.042	0.002
Took medications while away from home (referent: never or rarely)			
Less than half or half the time	−0.004	0.020	0.83
Most of the time or always	−0.049	0.021	0.02
Had problems using the VDOT application (referent: never)			
Rarely	−0.001	0.018	0.97
Less than half the time	−0.040	0.029	0.16
More than half the time	−0.220	0.041	<0.001

*FEDO, fraction of expected doses observed = number of complete doses observed through VDOT divided by the number of doses expected; VDOT, video directly observed therapy.

Table 5. Average in-person DOT and VDOT costs per treatment course, by site, based on standard drug-susceptible tuberculosis treatment regimen consisting of 56 intensive-phase and 126 continuation-phase doses, 4 California health districts, 2015–2016*

Characteristic	San Diego	San Francisco	San Joaquin	Imperial
In-person DOT costs				
Personnel				
Administrative tasks	1,038	3,043	1,913	842
In-person patient contact	1,207	622	2,223	656
Travel	1,939	1,065	702	1,293
Total personnel (% of total)	4,185 (91)	4,729 (97)	4,838 (84)	2,791 (87)
Mileage (% of total)	364 (9)	158 (3)	950 (16)	421 (13)
Grand total	4,549	4,888	5,788	3,212
VDOT costs				
Personnel				
Administrative tasks	796	1,922	1,771	1,183
In-person patient contact	671	291	393	346
Watching videos	80	131	152	473
Other, e.g., training and follow-up	869	933	156	348
Total personnel (% of total)	2,526 (79)	3,277 (88)	2,472 (83)	2,350 (78)
Mileage (% of total)	20 (1)	0	31 (1)	46 (2)
Smartphone costs, device and service (% of total)	424 (13)	424 (7)	424 (8)	424 (14)
VDOT application service fee, $35/mo/patient (% of total)	210 (7)	210 (5)	210 (7)	210 (7)
Grand total	3,179	3,911	3,137	3,031
% Change for VDOT versus in-person DOT				
Personnel costs, %	–40	–31	–49	–16
Overall costs, %	–30	–20	–46	–6

*All values are USD unless otherwise indicated. Comparable data could not be obtained from the Santa Clara site because of staff turnover. DOT, directly observed therapy; VDOT, video directly observed therapy.

All sites, except 1, included participants with MDR TB (VDOT duration range 30–537 days) whose adherence was comparable to the cohort overall. Because MDR tuberculosis patients at times require dosing more than once daily, VDOT reduced stress on the TB programs and facilitated quicker return to daily activities for patients on these much longer regimens. Additionally, asynchronous VDOT does not require consistent network connectivity, making it useful for patients in remote areas.

Although asynchronous VDOT offers greater flexibility and reduces self-administered doses, DOT and synchronous VDOT might allow more frequent patient–provider interaction and facilitate patient support. However, asynchronous VDOT could improve case management efficiency by shifting the focus of in-person visits from treatment monitoring, perceived by patients as punitive (*30*,*31*), to patient care, support, and other key TB program activities such as contact tracing. The appropriate mix of remote monitoring and direct interaction to support patients throughout treatment remains to be determined with further research. Cost-effectiveness studies are also needed to inform policies around treatment monitoring.

TB risk factors were self-reported and could be underestimated if participants chose not to disclose stigmatized behaviors. Because no patients were homeless, we could not examine this risk factor. Three sites (Santa Clara, Imperial and San Joaquin) had never used asynchronous VDOT previously, potentially promoting conservative patient selection; however, their results were similar to sites with VDOT experience. In addition, San Francisco differed from the other sites by requiring weekly, rather than monthly, refill visits, which could have increased adherence; however, adherence was comparable across sites. Because providers could switch participants from VDOT back to DOT, observed FEDOs could have been skewed upward if nonadherent participants were removed from VDOT early. However, only 12 (4.3%) participants returned to DOT before completing treatment, of whom only 5 did so because of poor adherence. Removing these participants had little effect on FEDO overall. This study was conducted in a high-income country and might not reflect VDOT performance in low- and middle-income countries.

To our knowledge, our study is the largest prospective study of asynchronous VDOT to date. Patients with TB treatment monitored by VDOT had more expected medication doses observed than patients monitored using DOT. VDOT performed similarly in urban and rural health departments, with high observation rates and positive patient perceptions across sites. Although some participants returned to DOT, most were effectively monitored to completion by using VDOT. VDOT reduced TB-control program costs compared with DOT. Other than country of birth, patient characteristics did not predict adherence, suggesting that TB-control programs could offer VDOT broadly and provide additional support, or switch to DOT if adherence declines rather than restricting VDOT use to patients with prespecified characteristics. Asynchronous VDOT was found to be a cost-effective method of monitoring TB treatment in the United States; however, similar studies are needed in countries with high burdens of TB

and limited resources, where smartphone penetration and cultural acceptance of transmitting personal images over the Internet could differ.

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Author contributions: R.S.G. conceptualized and designed the study, supervised its implementation, drafted the manuscript, and led the writing process. L.L. analyzed the data, interpreted results, and wrote sections of the paper. J.C.-M., K.C., F.M., and M. B. assisted in research staff training, study implementation, data collection, data quality assurance, and manuscript preparation. D.G.C. assisted with management, processing, and analysis of data and contributed to the manuscript. J.C. and N.K.M. conducted the economic analysis and wrote sections of the manuscript. K.M., J.H., T.A-S., P.K., and J.V. supervised study implementation at their respective health departments, ensured fidelity to study protocols, contributed to interpretation of results, and assisted in manuscript preparation and final review. F.R. and P.R. developed, programmed, and maintained the VDOT software application. All authors critically reviewed and approved the manuscript.

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Feasibility of Tuberculosis Treatment Monitoring by Video Directly Observed Therapy: A Binational Pilot Study

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Abstract

Objective—Directly observed therapy is recommended worldwide for monitoring tuberculosis (TB) treatment; yet transportation and personnel requirements limit its use. We evaluated the feasibility and acceptability of "Video DOT" (VDOT), which allowed patients to record and transmit medication ingestion videos that were watched remotely by healthcare providers to document adherence.

Methods—We conducted a single-arm trial among TB patients in San Diego, CA (n=43) and Tijuana, B.C., Mexico (n=9) to represent high- and low-resources settings. Pre/post treatment interviews assessed participant characteristics and experiences. Adherence was defined as the proportion of observed doses to expected doses.

Results—Mean age was 34 years (range: 18–86), 54% were male, and 77% were non-Caucasian. Mean duration of VDOT use was 5.5 months (range: 1–11). Adherence was similar in San Diego (93%) and Tijuana (96%). Compared to time on in-person DOT, 92% preferred VDOT; 81% thought VDOT was more confidential; 89% never/rarely had problems recording videos; and 100% would recommend VDOT to others. Overall, 7 (13%) participants were returned to in-person DOT and 6 (12%) separate participants had their phone lost, broken or stolen.

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Conclusions—VDOT was feasible and acceptable with high adherence in high- and low-resource settings. Efficacy and cost-effectiveness studies are needed.

Keywords

US-Mexico border; drug resistance; medication adherence; directly observed therapy; cellular phone; mHealth

INTRODUCTION

Tuberculosis (TB) is an airborne infectious disease that remains a global health threat affecting over two billion people—one third of the world's population—and is the third leading cause of infectious disease deaths worldwide.[1,2] Globally, there are 8.8 million new TB cases per year resulting in 1.4 million deaths.[1,2] In 2013, the United States (US) had 9,582 new TB cases reported (3.0 cases per 100,000 population).[3] While TB incidence in the US has declined, case rates in San Diego County were twice the national average with 206 active TB cases reported in 2013 (6.5 cases/100,000 pop.).[4] Baja California, which shares the busiest land border-crossing in the worlds with California,[5] has Mexico's highest TB incidence (55.2 cases per 100,000 pop.); triple the national average.[4] In San Diego County, 69% of cases in 2011 were foreign-born; 44% from Mexico.[6]

While TB is curable with antibiotics, poor compliance to treatment regimens lasting 6 months or more leads to increased mortality, ongoing disease transmission, and acquired drug resistance. The consequences to patients and the community of poor adherence are so great that the World Health Organization and the US Centers for Disease Control and Prevention recommend directly observed therapy (DOT) for administering TB treatment,[7–9] because it is more effective than other interventions for achieving treatment completion.[10] DOT is a patient-centered approach in which patients are observed ingesting each medication dose to ensure adherence and achieve completion. In the US, DOT workers typically travel to the patient, but in resource-constrained areas, including Mexico, DOT is largely clinic-based. Either way, DOT is labor-intensive, requires transportation, can restrict patients' daily activities, and may be impractical for patients living far from health centers. The effectiveness of DOT compared with self-administered therapy has been questioned,[11,12] possibly due to implementation barriers, suggest the need for improvement in DOT delivery. In low/middle income countries, resource constraints significantly limit DOT's use.[13] To reduce treatment monitoring costs and allow greater patient autonomy, mobile technology is increasingly used to improve patient care and treatment outcomes.[14–16] Most mobile solutions involve for patient reminders and few actually document medication ingestion.[15] We developed a flexible, low-burden method of providing remote DOT via smartphones called Video DOT (VDOT), which involves patients video-recording themselves taking their medications and securely transferring the videos to DOT workers for review. We then pilot tested VDOT for feasibility, acceptability, and potential efficacy in high (San Diego, California, USA) and low (Tijuana, Baja California, Mexico) resource settings.

METHODS

In 2010–2012, we conducted a single-arm trial among TB patients initially receiving treatment via in-person DOT. Informed by focus groups involving TB patients, care providers, and health officials in San Diego and Tijuana,[17] we developed the VDOT System and then pilot-tested it in public health departments among newly diagnosed patients with drug-susceptible pulmonary TB.

Eligibility and recruitment

TB Control Program staff in both cities recruited individuals currently receiving treatment for confirmed or suspected pulmonary TB. Eligibility criteria included: 1) ability to speak English or Spanish; 2) age 18 years; 3) 1 month of treatment remaining; and 4) willing and able to provide informed consent. Minors, patients with confirmed or suspected drug-resistant TB, and patients with physical conditions that hindered smartphone use (i.e., severe arthritis, diminished vision) were excluded. Patients could be enrolled in the study any time after their providers determined that they were tolerating their medications (minimum of 2 weeks), prior to which patients received traditional in-person DOT. Patients who met the eligibility criteria were sequentially enrolled. Of the patients approached, two in San Diego and two in Tijuana refused to participate—three noting confidentiality concerns and one did not think he could keep the phone safe.

VDOT Procedures

Participants used smartphones provided by the study to record videos of themselves taking each dose of TB medication. Uploaded videos were watched by DOT workers via a secure website to document whether the complete dose was ingested (Figure 1). The VDOT system includes a smartphone application for securely recording, transferring and storing videos; and a web-based client management system used by DOT workers to view and document each event. Daily text message reminders were sent to participants' phones—one before doses were due and one after expected videos were not received. The smartphone application automatically sent encrypted, time/date-stamped videos to a secure server via cellular or Wi-Fi network. If service was unavailable, videos remained on the phone until connectivity was restored. For confidentiality, videos could not be viewed on the phone and were automatically deleted after videos were sent. The VDOT software application was developed at by the investigators exclusively for this study.

All participants received in-person DOT for 2 weeks before switching to VDOT. DOT workers trained participants on VDOT procedures during routine DOT visits until the participant demonstrated competency (median=2 times; IQR=2–5 times). Participants continued on the same schedule as non-participants for routine clinic visits (i.e., monthly) for medication refills and health status monitoring. Participants were told they could use study smartphones for TB care purposes (e.g., call their doctor, find TB information, schedule appointments).

Data Collection

The primary outcome measure was adherence rate, calculated as the number of medication doses observed in videos divided by the number of doses expected during the treatment period. If missed or self-administered doses were added to the end of treatment, the number of doses expected was correspondingly increased. DOT workers in each city checked the VDOT website daily and documented whether: 1) a video was received, and 2) all tablets were swallowed. If ingestion was not visible or no video was received, participants were contacted to determine problems and retrained if necessary. Some videos were lost due to technical problems with the newly developed application. Since we could not confirm whether those doses were actually ingested, we treated lost videos as missing doses in calculating adherence rates.

Participant characteristics and perceptions of VDOT were obtained through brief (15–20 minute) structured interviews conducted by phone or in-person before (baseline) and after (follow-up) participants used VDOT. Baseline interviews included socio-demographics, comfort using smartphones, and concerns about privacy (i.e., TB-related stigma). Binational participants were those who spent 1 night during the study period across the border from their enrollment city. Alcohol and illicit drug use were also assessed. Follow-up interviews captured participant VDOT experiences, including days needed to learn VDOT process, problems recording videos, confidentiality and satisfaction with VDOT. Change in comfort using smartphones for phone calls, text messaging, taking photos/videos, and accessing the internet were assessed by asking participants to report their level of comfort with each on a 10-point scale (1=very uncomfortable to 10=very comfortable) on each interview.

To minimize response bias, interviews were conducted by research assistants uninvolved in patient care. Participants received $25 USD in San Diego and 200.00 pesos ($15.25 USD) in Tijuana for completing each interview, but not for using VDOT. The University of California, San Diego Institutional Review Board and Tijuana General Hospital Bioethics Committee approved this study.

Data Analysis

We described the study sample using frequencies (categorical variables), means and ranges (continuous variables). Bivariate analyses were conducted using baseline and follow-up data to identify factors associated with adherence using t-tests or rank sum tests for continuous variables; categorical variables were examined using chi-square or Fisher's exact test. Paired t-tests were used to assess changes in comfort with smartphones. Multivariable analyses were precluded due to the small sample size. Analyses were conducted using SAS 9.3. Patient comments provided during the follow-up interview are presented to contextualize quantitative findings.

RESULTS

We enrolled 43 participants in San Diego and nine in Tijuana. Overall, mean age was 37 years (range: 18–86); 50% were male, 88% were non-Caucasian and 51% were Hispanic (Table 1). There were 6 binational participants in San Diego and none in Tijuana.

Participants used VDOT for a mean of 5.5 months (range: 1–11) following 2–22 weeks on in-person DOT in San Diego and 2–4 weeks on in-person DOT in Tijuana. Forty-five (87%) participants used VDOT until they completed treatment. Seven participants (13%) were returned to in-person DOT because: one had problems operating the smartphone, one who received assistance from a family member had to stop when that person moved out, two were non-compliant, one preferred in-person DOT, and two received baseline drug susceptibility test results revealing drug-resistant TB after enrollment rendering them ineligible. All participants returned to in-person DOT successfully completed treatment. Overall, 3 (6%) phones were stolen and 3 (6%) were lost or broken.

Mean adherence was 93% (51%–100%) in San Diego and 96% (88%–100%) in Tijuana (Figure 2). Overall, 5,626 videos were received, showing complete doses swallowed (96.0%), partial doses swallowed (0.4%), no pills swallowed (1.5%), and unable to tell if doses were swallowed (2.1%). No socio-demographic or behavioral factors were found to be associated with adherence (data not shown). Throughout treatment, daily text messages were sent to each participant as reminders to take their medication. DOT worker follow-up responses to missed doses included contacting participants to encourage adherence, provide re-training on VDOT procedures, and/or to troubleshoot technical problems with recording videos. Advanced age was not a barrier to using VDOT. Older participants in particular enjoyed learning to use a smartphone and reported feeling that VDOT allowed them to remain in control of their care rather than feeling like their provider did not trust them to take their medications.

Fifty (94%) participants completed follow-up interviews. Overall, 92% reported never/rarely having problems recording videos, 92% preferred VDOT over in-person DOT, 84% thought VDOT was more confidential and 100% said they would recommend VDOT to others (Table 2). Nearly two-thirds of participants thought text message reminders were useful. Open-ended questions revealed that participants in both cities thought VDOT was more confidential than in-person DOT. For example, a Tijuana participant said, "[with the VDOT system], I always had the confidence of confidentiality." A San Diego participant said, "The phone is a great step for the person to find their own private space..." Additionally, participants valued the mobility that VDOT allowed and the convenience of taking medications on their own schedule. A San Diego participant stated that, "[VDOT] is a convenient, easy, good system..." Another San Diego participant said, "The phone was very convenient [for me]. I could take my pills on my own time instead of waiting for someone to watch me." TB Control Program staff reported that patients had more autonomy and were grateful to have been able to use VDOT. They also reported that time and travel saved using VDOT allowed them to concentrate on less compliant patients.

While comfort using smartphone functions were generally high at baseline (Figure 3), further increases were reported after using VDOT. These increases were statistically significant for making phone calls (+0.77, p=0.008), taking pictures (+1.43, p=0.006), and recording videos (+1.68, p=0.009).

DISCUSSION

VDOT was highly feasible and acceptable among TB patients and providers in both high- and low-resource settings. Most participants preferred VDOT over in-person DOT. Documented observation of nearly all expected doses (mean 93% in San Diego and 96% in Tijuana) was achieved using VDOT. VDOT provided a convenient alternative to in-person DOT without sacrificing treatment adherence because participants could ingest their medications at the time and location of their choosing without needing to coordinate with a DOT worker. Furthermore, DOT workers could observe the videos during normal business hours. Adherence was conceivably increased using VDOT because it had fewer barriers to medication-taking than in-person DOT. While findings from this pilot study might not be generalized to all TB patients, we enrolled 43 (21%) of San Diego's 206 annually-reported cases and obtained similar results in Tijuana where 9 (1%) of that city's approximately 1,000 cases were enrolled. Further studies with fewer eligibility criteria in more healthcare settings are needed to determine which patients are best suited for VDOT.

Inability to monitor medication taking while patients are out of the health department's jurisdiction can prolong treatment. VDOT allows observation of all doses, even among mobile patients. For example, six San Diego participants spent part of the week in Mexico making it impractical for San Diego DOT workers to observe these doses in-person. VDOT enabled DOT workers to remotely observe the doses taken while participants were in Mexico. Hence, participants reached the number of observed doses needed to complete treatment sooner than they would have with in-person DOT.

Asynchronous ("store-and-forward") VDOT used in this study may have advantages over synchronous ("video conferencing") forms of remote DOT. For example, in 2004, the San Diego County TB Control Branch pilot tested video-conferencing over landline phones to reduce costs and improve efficiency of DOT. On weekdays, a DOT worker called patients using a video-phone and watched them ingest their pills. Among 33 patients over the nine-month trial, the county saved 27,840 miles in travel and 795 staff hours.[18] More recently, health departments have attempted to replicate this process using mobile devices to overcome the problem of tying patients to their homes and the growing trend toward switching from landline to mobile phones. However, patients could still only be observed during business hours and when there was a consistent phone connection. Using asynchronous VDOT, patients can take their medications whenever and wherever they choose, and DOT workers can manage more patients in less time during business hours.

Attention should also be given to those who did not complete treatment on VDOT. Of the seven participants who returned to in-person DOT, two began treatment presumptively for drug-sensitive TB, but were later found to have drug-resistant TB once drug susceptibility testing was complete. Two participants, both college students, repeatedly failed to record videos; their adherence improved after returning to in-person DOT. Only one participant requested to return to in-person DOT. After 2 weeks on VDOT, she explained that as a parent of three young children, having a DOT worker visit her home was easier than self-managing her treatment. Another patient with mild cognitive deficits initially performed VDOT with the assistance of a family member, but when that person moved out, the

participant was not comfortable recording videos himself. One 83 year-old participant had difficulty using the phone's touchscreen for VDOT because he did not "feel" a button being pushed. Despite retraining attempts, the participant was unable to consistently use the application correctly and was returned to in-person DOT. Conversely, an 86 year-old participant used VDOT successfully for 7.6 months with 99% adherence, suggesting that age alone should not disqualify individuals from using VDOT. These findings suggest that VDOT should complement, rather than replace, in-person DOT. Further research is needed to identify patient characteristics for determining which method best suits each patient, and what criteria should be used to withdrawal a patient from VDOT.

Some study limitations must be considered. First, the VDOT application was developed specifically to assess whether this concept was feasible and acceptable; therefore, some early participants had lower documented adherence because videos that were lost due to software error were treated as missed doses in calculating adherence rates. Consequently, our adherence estimates were conservative. Second, since we were uncertain about how VDOT would work in practice, patients with drug-resistant TB or a history of poor adherence on in-person DOT were ineligible. Thus, patient selection could have been biased toward adherent patients limiting generalizability of adherence rates to all TB patients; however, such bias is unlikely to have affected satisfaction with VDOT. Notably, after gaining experience implementing VDOT for this study, TB Control Program staff reported feeling comfortable expanding eligibility to include patients with drug resistant TB and some patients who had low adherence using in-person DOT. Third, this study lacked a control group and we were unable to compare adherence between VDOT and in-person DOT. Since participants were allowed personal use of the study smartphones, providing smartphones could have had an intervention effect; however, providing enablers is not uncommonly practiced by health departments for TB.

CONCLUSIONS

We found VDOT feasible to implement and highly acceptable to patients and providers in both high- and low-resource settings. VDOT effectively captured medication-taking behavior allowing DOT workers to observe ingestion of nearly all expected doses. VDOT provides a promising, low-burden alternative to in-person DOT for monitoring TB treatment adherence. The reduced burden on patients and providers using VDOT could also make DOT feasible in resource-limited settings where in-person DOT is impractical, as well as allow TB program staff more time to support to less-adherent patients. VDOT may also be used to monitor other health conditions where strict medication adherence is essential. Larger, controlled trials are needed to evaluate the efficacy and cost-effectiveness of VDOT for improving and maintaining adherence throughout treatment. Studies in high-burden, low-resource settings are also needed to evaluate VDOT's generalizability. As mobile technology plays an increasingly important role in healthcare, VDOT has great potential to expand the coverage of TB treatment monitoring to more patients worldwide by reducing the burden on both patients and providers, resulting in higher treatment completion rates, fewer new cases of TB, and prevention of acquired drug resistant TB.

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Enhancing management of tuberculosis treatment with video directly observed therapy in New York City

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SUMMARY

SETTING: Directly observed therapy (DOT), the standard of care for monitoring patients on treatment for tuberculosis (TB), requires substantial health department resources, and can be inconvenient and disruptive for patients.

OBJECTIVE: To determine whether video technology for remote observation of patients on anti-tuberculosis treatment (VDOT) is as effective as in-person DOT.

DESIGN: Eligible TB patients in New York City were prospectively enrolled in VDOT from September 2013 to September 2014. We compared treatment outcomes and worker output for VDOT and in-person DOT.

RESULTS: Among 390 patients on DOT for the treatment of TB, 61 (16%) were on VDOT and 329 (84%) on in-person DOT. Adherence to scheduled VDOT sessions was 95% (3292/3455) compared to 91% (32 204/35 442) with in-person DOT ($P < 0.01$). VDOT enabled a DOT worker to observe a maximum of 25 patients per day, similar to DOT workers who observed patients in clinic ($n = 25$), but twice that of DOT workers who observed patients in the community ($n = 12$). Treatment completion with VDOT was similar to that with in-person DOT (96% vs. 97%, $P = 0.63$). The primary problems encountered during VDOT sessions were interruption of video and audio connectivity.

CONCLUSION: Implementation of VDOT resulted in successful anti-tuberculosis treatment outcomes while maximizing health department resources.

KEY WORDS: VDOT; telemedicine; remote monitoring

TREATMENT FOR TUBERCULOSIS (TB) is lengthy, requiring 6–9 months of multiple drugs; however, when treatment is taken as prescribed the cure rate is high.[1] Failure to complete treatment can lead to the development of drug-resistant TB, which is more difficult to treat and can result in continued community transmission and increased morbidity and mortality.[2,3] To ensure adherence to anti-tuberculosis treatment, the Centers for Disease Control and Prevention and other health agencies recommend directly observed therapy (DOT) as the standard of care for TB patients.[4,5] DOT involves a trained health care worker observing patients ingest each dose of their medication. Studies show that DOT increases treatment completion, reduces disease recurrence, and prevents the development of drug resistance.[6–8] During the TB resurgence in the 1990s in the United States, DOT was credited with reducing primary drug resistance from 13% to 7% and acquired drug resistance from 14% to 2% in some areas.[9]

In New York City (NYC), DOT was recognized as being instrumental in curbing the 1990s TB epidemic.[10] The proportion of patients who completed treatment increased from 44% in 1984 to 86% in 2004, concurrent with an increase in the proportion of patients treated under DOT.[11] Furthermore, a recent study showed that NYC patients on DOT had a lower risk of delayed and incomplete treatment.[12] Transmission and development of drug-resistant TB also decreased, and the number of TB cases in NYC dropped from 3756 in 1992 to 585 in 2014.[13] The NYC Department of Health and Mental Hygiene (DOHMH) offers DOT to all patients taking treatment for TB who are not hospitalized or in a prison, treatment facility, or nursing home. DOT is offered at all TB clinics and in the community at locations convenient for the patient, such as home or worksite. NYC DOHMH conducts about 40 000 DOT observations annually.[13] State-approved NYC hospitals offer DOT to patients in their clinics, and report DOT information to the DOHMH.

DOT requires substantial personnel time, costs for transportation, and vehicle maintenance. In addition, DOT can be inconvenient and disruptive for patients,[14] and ethical and privacy concerns about the use of DOT have been raised.[9,15] To address some of these concerns, the use of live-streaming video conferencing technology was introduced to allow

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patients to be observed remotely in the privacy of their own homes or other preferred locations, eliminating the need for DOT workers to enter personal space or for patients to travel to the clinic. A study in Canada reported that patients on anti-tuberculosis treatment were highly satisfied with the flexibility, privacy, and efficiency of monitoring using video DOT (VDOT).[16] VDOT has also been found to be a cost-effective alternative to in-person DOT.[17–19] One study reported an average cost savings of US$2448 per patient over the course of treatment.[17] Another study showed that recorded VDOT, allowing patients to send video recordings of themselves ingesting these medications, was preferred by patients to in-person DOT.[20]

In 2013, NYC DOHMH implemented the use of live VDOT for eligible patients on anti-tuberculosis treatment. The objectives of the project were to determine if treatment completion with VDOT was comparable to that of in-person DOT, to ascertain whether the use of VDOT for NYC TB patients was feasible and acceptable, and to describe the resource and staffing needs for monitoring treatment with VDOT.

STUDY POPULATION AND METHODS

Patients were enrolled prospectively from September 2013 to September 2014, and were followed for 9 months or until discharge, e.g., completed treatment, lost to care, or refused to continue treatment. Patients on VDOT had to be eligible for DOT, aged $\geqslant 18$ years, and speak English or Spanish, as these were the languages spoken by the assigned VDOT worker. Patients were required to have private space to conduct VDOT, to be proficient at using a smartphone with video conferencing capability after receiving training, and to be able to identify and self-administer the prescribed medications. Patients were not eligible if they had a history of adverse reaction(s) to the prescribed medications, were at increased risk for hepatic complications, or had a history of non-adherence. Prior to beginning VDOT, patients were observed for 2 weeks in the clinic, as is standard for all patients enrolling in DOT.

Patients meeting the inclusion criteria were offered VDOT and signed an agreement form. Once enrolled, patients were loaned a DOHMH smartphone pre-programmed with video conferencing software. Patients were trained by DOHMH staff to use the smartphones and follow the VDOT process. At enrollment, the VDOT worker asked the patients three open-ended questions about their reasons for accepting VDOT.

VDOT process

Two staff members were trained and assigned to conduct all VDOT sessions: one VDOT worker with previous experience conducting in-person DOT and one back-up staff member. The VDOT worker and patient pre-arranged a schedule for the VDOT calls. The VDOT worker received calls using a webcam-equipped computer. Patients were asked about side effects, and if none were reported, the patient showed and named each pill in front of the camera before swallowing it. To demonstrate that the pills had been swallowed, the patients opened their mouths in front of the camera and engaged in conversation with the VDOT worker for several minutes. If any side effects were reported, a DOHMH physician was connected by video or audio to provide medical advice. Each VDOT session was documented in the DOHMH electronic medical record (EMR) system. Technical or operational issues were directed to supervisors for resolution and tracked in a separate database. Missed VDOT appointments were followed up by phone calls and, if these were unsuccessful, home visits. The VDOT worker recorded the start and end time of each session, including the time it took to document the session, in the EMR and the VDOT database.

Analysis

The characteristics and treatment outcomes of patients enrolled in the VDOT project from September 2013 to September 2014 were compared to those of patients aged $\geqslant 18$ years receiving standard in-person DOT during the same period. Patients on in-person DOT were defined as those who had at least one dose of medication observed at a health department or hospital clinic or in the community and underwent no VDOT observation. For both VDOT and in-person DOT, analysis for treatment completion was limited to patients eligible to complete treatment. Patients were excluded if they were determined not to have TB, died during treatment, moved outside of the United States prior to completing treatment, or were still on treatment at the end of the study.

The proportion of successful VDOT sessions was calculated and compared to the proportion of successful in-person DOT sessions conducted by DOHMH DOT workers during the study period. A session was considered successful if a patient was observed ingesting the full dose of prescribed medication on the scheduled day and time. The median time in minutes of VDOT sessions was calculated. Technical issues encountered during VDOT sessions and patients' reasons for accepting VDOT were reviewed and grouped. The number of VDOT observations that a DOT worker was able to conduct each day was compared to those conducted with in-person DOT.

Data were obtained from the NYC TB registry, the TB clinic EMR, and the VDOT database. Pearson's χ^2 or Fisher's exact test was used to test for statistical significance for categorical variables and the Wilcox-

Table 1 Characteristics of patients treated for tuberculosis under in-person DOT and VDOT, New York City, September 2013–September 2014

	In-person DOT *n* (%)	VDOT *n* (%)	*P* value
Total	329	61	
Male sex	199 (60)	38 (62)	0.79
Age, years, median (range)	48 (18–101)	36 (18–85)	<0.01
US-born*	35 (11)	5 (8)	0.56
Human immunodeficiency virus			
Positive	15 (5)	6 (10)	0.22
Negative	270 (82)	51 (84)	
Unknown	44 (13)	4 (7)	
Pulmonary disease	275 (84)	47 (77)	0.22
Cavitary chest radiograph†	43 (16)	10 (21)	0.18
Ever respiratory smear-positive†	145 (53)	30 (64)	0.16
Culture-positive	249 (76)	51 (84)	0.18
Drug resistance‡	20 (8)	22 (43)	<0.01
Treated at DOHMH TB clinic§	187 (57)	55 (90)	<0.01

* Includes patients born in the United States, Puerto Rico, and other US territories.
† Among patients with pulmonary TB disease.
‡ Among patients with a positive culture for *Mycobacterium tuberculosis*.
§ Last treatment provider was the New York City DOHMH TB clinic.
DOT = directly observed therapy; VDOT = video DOT; DOHMH = Department of Health and Mental Hygiene; TB = tuberculosis.

on rank-sum test for continuous data. A 5% significance level was used for both tests.

Ethics

The DOHMH's legal team and information technology (IT) office ensured that the implementation of VDOT met the Health Insurance Portability and Accountability Act (HIPAA) patient privacy requirements, and that the video conferencing software met IT security standards. The study did not require patient informed consent, as the data were collected as part of routine TB case management practice. The NYC DOHMH Institutional Review Board determined the study to be a public health program evaluation that was not research, and ethical approval was not required. Twenty-five smartphones with data plans and three licenses for use of the video conferencing software were donated for the study.

RESULTS

From September 2013 to September 2014, 390 patients were enrolled on DOT, 61 (16%) on VDOT and 329 (84%) on in-person DOT. Compared to patients receiving in-person DOT, VDOT patients were younger, more likely to have resistance to at least one anti-tuberculosis medication, and more likely to be treated at one of the DOHMH TB clinics (Table 1). Among those eligible to complete treatment, 47 (96%) of 49 patients on VDOT completed treatment compared to 260/267 (97%) patients on in-person DOT ($P = 0.63$) (Table 2). Fifty-nine patients (53 on in-person DOT and 6 on VDOT) were still on treatment after 9 months of follow-up due to intolerance of or resistance to rifampin, extensive

Table 2 Treatment outcomes of patients treated for tuberculosis under DOT and VDOT, New York City, September 2013–September 2014

	In-person DOT *n* (%)	VDOT *n* (%)	*P* value
Total patients eligible to complete treatment	267	49	
Completed	260 (97)	47 (96)	0.80
Lost	2 (1)	1 (2)	
Refused	4 (1)	1 (2)	
Adverse reaction	1 (1)	0	
Total patients not eligible to complete treatment*	62	12	
Moved out of the United States	6 (10)	1 (8)	<0.01
Died	3 (5)	1 (8)	
Currently on treatment	53 (85)	6 (50)	
Not a TB case	0	4 (33)	

* Reasons patients were not eligible to complete treatment at the time of the study include leaving the United States prior to treatment completion, died prior to completing treatment, treatment extended due to intolerance or resistance to rifampin, extensive TB disease or treatment interruption, and treatment stopped after TB diagnosis was ruled out.
DOT = directly observed therapy; VDOT = video DOT; TB = tuberculosis.

TB disease, or interruption of treatment due to side effects. Of 61 patients who responded to the open-ended questions, 59 (97%) reported choosing VDOT due to its convenience ($n = 58$), followed by privacy ($n = 4$) and flexibility ($n = 1$).

Of the 3455 sessions scheduled for patients on VDOT, 3292 (95%) were successfully conducted, compared to 32 204/35 442 (91%) among patients on in-person DOT ($P < 0.01$). The median period on VDOT was 161 days (interquartile range [IQR] 39–239). The median time for a VDOT session was 5 min (IQR 5–6). Four sessions extended beyond 20 min due to medical consultations for side effects. After consultation, three patients were able to continue treatment on VDOT. TB was ruled out for the remaining patient, and treatment was discontinued. VDOT enabled a DOT worker to observe a maximum of 25 patients/day compared with 25 patients/day for DOT workers who conducted observations in the clinic, and 12 patients/day for DOT workers who conducted observations in the community.

Of 346 VDOT-related issues identified for 54 patients, 276 were technical problems; 49 were patient-related challenges such as patients forgetting their appointment, having schedule conflicts, or patient being out of camera view; and 21 were due to smartphone misuse (Table 3). Staff worked with the DOHMH Information Technology department, the video conferencing software support group, and patients to resolve many of the technical problems specific to video and audio connections (Table 4).

DISCUSSION

For over 20 years, DOT has been an integral part of the NYC DOHMH's TB control efforts, and has improved patient outcomes by increasing treatment

and solve the problems.[16,18,19] As technology improves and the population becomes more comfortable with video technology, there will be fewer technical challenges. Further understanding of these obstacles and the VDOT worker-patient relationship is needed.

Use of video technology for monitoring patients on treatment for TB has been shown to be cost-effective and require less staff time.[18,19] While our study did not include a cost calculation, it found that VDOT maximized staff resources, allowing staff to observe twice the number of patients seen under community-based DOT. This could enable the DOHMH to sustain DOT services while reassigning staff to other essential TB control efforts. The ability to have real-time video consultations with physicians also reduces the need for clinic visits, and VDOT furthermore reduces the costs of car maintenance and transportation. However, the need to purchase smartphones (for patients who do not have access to a private or video-compatible smartphone), data plans, and HIPAA-compliant video conferencing software are expenses that need to be taken into account. The DOHMH has recently begun allowing patients to use video conferencing software on their personal devices for VDOT, and prioritizes lending smartphones to those without access to a video-enabled device. This reduces costs for the DOHMH and is likely preferred by patients, as it eliminates the need to learn to use a new device. Published cost-analysis studies on VDOT have been limited to fewer than 100 patients.[18,19] As VDOT is expanded, large-scale cost-effectiveness analysis is needed to determine the economic impact of VDOT.

The concept of remote monitoring of patients was new to staff. Staff training and support ensured that VDOT workers were comfortable with the process, the need for patient confidentiality and privacy, and the video conferencing software and equipment, effecting successful integration of VDOT into the existing DOT program. However, because the VDOT project was program-based and was not designed as a research study, certain data were not collected or available for analysis. First, as enrollment of patients to VDOT was limited by the availability of phones, the overall proportion of patients eligible for and accepting and refusing VDOT could not be assessed. Second, the number of days during which patients remained on in-person DOT was not available for comparison with VDOT. However, analysis of overall adherence was reported and compared to in-person DOT. Finally, the VDOT eligibility criteria could have favored patients who were more likely to complete treatment. However, this study shows that VDOT is an effective option for those eligible patients who elect to use it.

In conclusion, the study found that treatment completion with VDOT was high. VDOT maximized staff utilization, and offered a more flexible and convenient alternative to in-person DOT for many patients. Further study is needed to analyze the economic benefits of VDOT.

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Video Directly Observed Therapy to support adherence with treatment for tuberculosis in Vietnam: A prospective cohort study

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ABSTRACT

Background: Ensuring patients fully adhere to their treatment is a major challenge for TB control programmes in resource-limited settings. This study was conducted three outpatient tuberculosis clinics in Hanoi, Vietnam. We aimed to evaluate the feasibility of using asynchronous Video Directly Observed Therapy (VDOT) to support treatment adherence among patients with bacteriologically confirmed pulmonary tuberculosis.
Methods: In this cohort study, consecutive adult patients with bacteriologically confirmed pulmonary TB were invited to enroll in a programme of VDOT. Patients were trained to use a smartphone to record themselves taking treatment for TB. Videos were uploaded to an online server and reviewed daily by study staff for at least two months. Adherence was evaluated based upon monthly pill count.
Results: Between November 2016 and January 2017, 40 of 78 eligible participants (51.3%) agreed to commence VDOT. Among participating patients, 27 (71.1%) of patients took all required doses. A median of 88.4% (interquartile range 75.8%–93.7%) of doses were correctly recorded and uploaded. Participants rated the VDOT interface highly, despite facing some initial technical difficulties.
Conclusion: VDOT was feasible and resulted in high rates of treatment adherence in a resource-limited setting.

Background

Tuberculosis (TB) affects 10.4 million people each year, the vast majority of whom live in resource-limited settings (World Health Organization, 2016). Optimal regimens for drug susceptible tuberculosis require six months of daily antibiotics (World Health Organization, 2017; Johnston et al., 2017). However, ensuring patients fully adhere to their treatment is a perennial challenge for TB control programmes, particularly during the final months of treatment when patients' symptoms have largely resolved (Kaona et al., 2004; Adane et al., 2013). The consequences of incomplete adherence are well-documented, and include an increased risk of treatment failure, acquired drug resistance and continuing propagation of infection (Weaver et al., 2015; Karumbi and Garner, 2015; Suwankeeree and Picheansathian, 2014). A range of programmatic strategies have been proposed to strengthen adherence (Story et al., 2016; Wald et al., 2015; Lutge et al., 2015). However, in many resource-limited settings, intensive adherence support strategies such as Direct Observation of Therapy (DOT) are often infeasible due to limitations in the health workforce, and barriers to patients accessing care. New scaleable methods to improve adherence, and hence treatment outcomes, will be essential if the global ambition of TB elimination is to be realised (Uplekar et al., 2015).

Advances in digital communications technology hold considerable promise to transform adherence support. Recognising this potential, the WHO Digital Health for the End TB Strategy calls for evidence-based approaches to underpin the scale-up of new

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technologies (World Health Organization, 2015). However, there is limited evidence to demonstrate the feasibility of digital strategies to support adherence in resource-limited settings (Story et al., 2016; Liu et al., 2015).

Video Directly Observed Therapy (VDOT) is a method of adherence monitoring that involves patients transmitting digital images of their ingestion of treatment to a central location for review. Two broad approaches have been applied. 'Synchronous' VDOT involves the review of transmitted images in real time by health care workers. In contrast, 'asynchronous' VDOT allows videos to be recorded, uploaded and reviewed at a later time – providing greater flexibility to patients and clinical staff. VDOT has been shown to be feasible and acceptable to patients in some high-income settings (Story et al., 2016; Mirsaeidi et al., 2015; Garfein et al., 2015). However, these studies may not be applicable to resource-limited settings, where the burden of TB is the highest. We aimed to evaluate the feasibility and acceptability of asynchronous VDOT for patients with bacteriologically confirmed pulmonary TB in Vietnam, a high prevalence country for TB.

Methods

Study setting

Vietnam is a low middle-income country in Southeast Asia with a TB incidence of 137 (110-166) per 100,000 population in 2015, which remains persistently high despite more than 90% of patients reporting treatment completion over the past two decades (World Health Organization, 2016). Tuberculosis control is delivered by a centrally administered National TB Program (NTP). Treatment is routinely overseen by nominated household members, 'Family DOT supporters' or community volunteers. Treatment is not directly observed by health workers, in accordance with national guidelines. Medications are dispensed free-of-charge, most commonly once each week by health workers at district clinics, or commune health post. Clinical review occurs at district clinics second monthly throughout treatment.

The country has among the highest rates of mobile phone ownership in the world (International Telecommunication Union, 2017), with 131 mobile phone subscriptions per 100 people (International Telecommunication Union, 2017). One third of the adult population owns a smartphone, with use increasing annually (Poushter, 2016).

Study design

We conducted a prospective cohort study in three outpatient facilities conducted within tuberculosis outpatient facilities in Hanoi, Vietnam.

Patients with bacteriologically confirmed pulmonary tuberculosis were recruited from the outpatient departments at three clinics of the National Tuberculosis Program (NTP) in Hanoi, Vietnam. Patients were eligible to enroll in the study if they were at least 15 years of age, receiving a regimen containing only oral medications at an outpatient facility, and had at least two months of standardised TB treatment remaining. Patients were excluded if they had a current or prior diagnosis of multidrug-resistant (MDR)-TB or a severe mental illness. Consecutive patients presenting to the clinic were invited to participate.

The primary outcome was the proportion of patients completing all doses of self-administered treatment during the study period, according to pill count by health workers. The secondary outcomes included the proportion of videos uploaded as scheduled, and the proportion of patients discontinuing using VDOT.

Study procedures

Staff working at participating outpatient facilities invited consecutive patients attending the clinic to receive scheduled treatment for TB to enroll in the study. Consenting participants were asked for information about their demographics, socioeconomic factors, medical history and mobile phone use. Additional information about their diagnosis and treatment regimen was collected from the patient's medical file.

VDOT was performed using the SureAdhere platform (SureAdhere, San Diego, CA), an asynchronous smartphone application ('App') that allowed videos to be recorded, uploaded and viewed at a later time by study staff (Garfein et al., 2015). The platform could be used either with an Android or iOS smartphone. Videos could be transmitted over a 3G or 4G mobile network, or through a WiFi connection. Continuous connectivity was not necessarily, as the app stored videos and repeatedly attempted to transmit them, until a network was detected and transmission succeeded. Study participants who already owned a smart phone could use their own phone to participate in the study. Low-cost smartphones with 3G connectivity were loaned to patients who did not own a smartphone. Cellular data charges were paid for by the study.

At enrolment, consenting study participants received a 30 minute training session about how to use the smartphone and the VDOT app. This included practice recording and uploading a video and provision of written instructions. Additional face-to-face training was provided by the study staff to any patients reporting technical difficulties during the intervention period.

Adherence monitoring using VDOT was to be carried out for at least 60 days. Each day, at a time nominated by the study participant, a Short Messaging Service (SMS) message was automatically generated to remind the participant to upload a video. If the video had not been received after one hour, a second SMS was sent. If a video upload was missed, despite the SMS, study staff called the patient to provide support, and remind them to take treatment.

Videos were automatically uploaded via the mobile network, including date and time of recording, and viewed by the study staff on a secure website to verify adherence. Patients reported side effects verbally, by describing them during the daily video recording. Adherence was recorded by study staff as adequate if a participant held up all required tablets, placed them in their mouth and swallowed. The video and audio quality were reported.

At the end of each month, study staff interviewed study participants during a scheduled clinic visit. Follow-up was completed when patients returned for a scheduled visit at the end of two months of follow-up. Treatment adherence was assessed based upon pill count of remaining tablets. A questionnaire evaluating difficulties with using the smartphone, or the app, was completed at each visit. Adverse events were managed routinely by the staff of the NTP.

At each visit, participants were asked to provide feedback about the VDOT system. At the end of follow-up, participants were asked to evaluate their experience, and rate the ease of use the technology on a Likert Scale from 1 to 10 (where 1 = "Very hard to use" and 10 = "Very easy to use").

Sample size

Assuming that 90% of patients would take all expected doses over a 2 month period of follow-up, and aiming to estimate the proportion of treatment completion with a precision of 10%, we estimated that at least 35 patients would be required. We aimed to recruit at least 10 people from each of the three study sites.

Ethical issues

Participants provided written informed consent. Participants were given a small financial reimbursement to cover their travel expenses to attend each visit. Ethical approval was provided by the Human Research Ethics Committee at the University of Sydney and the Ethics Committee of the Vietnam National Lung Hospital. AES 128-bit digital image encryption was used during data transfer to a secure server. Access to smartphones and the website used to review the videos were password protected.

Results

Participant characteristics

Between November 2016 and January 2017, among the 78 eligible patients invited to participate, 40 patients (51%) agreed to participate in the study (Figure 1). This included 23 of 56 eligible patients (50%) from the National Lung Hospital and 17 of 22 eligible patients (77%) from the two district clinics. Among the 38 non-participants, 13 patients (34.2%) were unwilling to use a smartphone, five patients (13.2%) refused to participate in research study, two (5.3%) did not participate due to concerns about confidentiality, two (5.3%) gave other reasons, and 16 (42.1%) did not provide a reason for their refusal. A median of 0 (interquartile range 0-7) days of therapy had been supervised by the nominated treatment supporter in the week preceding enrolment.

The characteristics of study participants are shown in Table 1. Thirty-nine participating patients (97.5%) used a mobile phone regularly prior to the study, and 32 (80.0%) patients had used a smartphone in the previous month. The VDOT App was installed on the personal smartphones of 21 (52.5%) patients, while 18 (45.0%) patients borrowed a study phone and one patient (2.5%) used the phone of a family member.

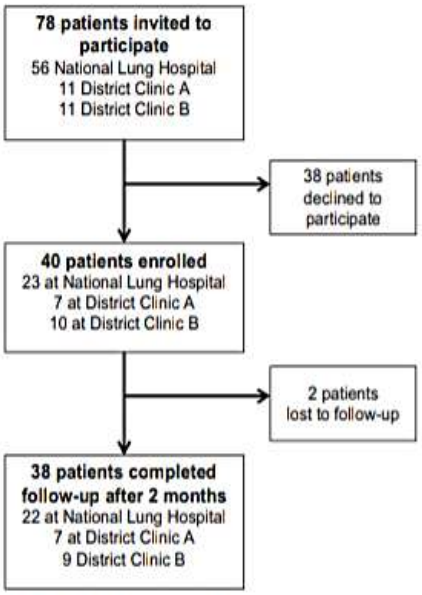

Figure 1. Flow diagram showing participation and follow-up during adherence support with Video Directly Observed Therapy (VDOT).

Table 1
Baseline characteristics of study participants.

Variable	Number (n)	Percentage (%)
Total patients enrolled	40	–
Male	30	(75.0%)
Age (median, IQR)	33.5 years[a]	(22.5-42.5 years)[b]
Highest education level		
University or equivalent	14	(35.0%)
Upper secondary	18	(45.0%)
Lower secondary	4	(10.0%)
Primary	4	(10.0%)
Current technology use		
Mobile reception in house	39	(97.5%)
Wifi in house	29	(72.5%)
Current usage of mobile phones		
For internet access	28	(70.0%)
Playing games	15	(37.5%)
Taking photos	25	(62.5%)
Taking videos	25	(62.5%)
Social networking	28	(70.0%)
Short messaging service (SMS)	30	(75.0%)
Other activities	19	(47.5%)
Type of phone used in last month		
Smart phone	32	(80.0%)
Non-smart phone	11	(27.5%)
Tablet computer	3	(7.5%)
Fixed line phone at home	2	(5.0%)
Fixed line at work	1	(2.5%)
Number of phones used in last month (median, IQR)	1	(1.0-1.0)
Phone credit used in past month ($USD) (median, IQR)	$6.60	($4.40-$15.40)
Phone used for the study		
Patient's own smartphone	21	(52.5%)
Study phone	18	(45.0%)
Family member's phone	1	(2.5%)
Phone used for the study		
Tuberculosis treatment regimen		
First-line	34	(85.0%)
Retreatment	6	(15.0%)
Microbiological status at time of diagnosis with tuberculosis		
Smear positive	37	(92.5%)
Smear negative, culture positive	2	(5.0%)
Smear negative, PCR positive	1	(2.5%)
Abnormal chest radiograph	40	(100.0%)
HIV status		
Positive	0	(0.0%)
Negative	12	(30.0%)
Not performed	28	(70.0%)
Home treatment supervisor was known by patient	34	(85.0%)

[a] Median.
[b] Interquartile range.

All patients reported that it was important to take their TB medications, and were concerned about the potential for harm if they did not take treatment.

Adherence with VDOT by pill count

The median duration of follow-up was 62 days (IQR 60-68 days). The median proportion of doses taken by patients was 100% (IQR 98.4%-100%). Twenty-seven (71.1%) patients took every required dose, according to pill-count. Four patients missed four or more doses (Table 2). Two participants did not complete follow-up.

Adherence with uploading of videos

A median of 88.4% (IQR 75.8% – 93.7%) of daily videos were correctly uploaded. Thirty-four (85%) patients missed less than four video uploads during the follow-up period.

Table 2
Treatment adherence and technical difficulties during the intervention period.

Variable	Number (n)	Percentage (%)
Total participants	40	
Daily doses missed over 2 months		
0	33	(82.5%)
1	4	(10.0%)
2	1	(2.5%)
3	0	(0.0%)
4	2	(5.0%)
Days when video uploads missed over 2 months		
0 days	19	(47.5%)
1-4 days	15	(37.5%)
5-8 days	3	(7.5%)
9-12 days	1	(2.5%)
13 days and above	2	(2.5%)
Lost mobile phone	1	(2.5%)
Experienced technical difficulties using VDOT		
Never	24	(80%)
Rarely	3	(10.0%)
Sometimes	1	(3.3%)
Frequently	2	(6.7%)
No response	10	(25.0%)

Technical issues relating to smartphone and app use

One loaned study phone was not returned (2.5%) and one loaned phone had minor damage which did not prevent VDOT use. Sixteen patients (40%) reported having some technical difficulties using the VDOT platform during the implementation period. Reasons given by patients for missing uploads included other commitments, flat batteries, travel, technical difficulties, a perception that internet access was required to upload videos, or slow upload speeds.

Observation of dosing by research staff also identified three patients were taking TB treatment at a dose, or composition, that was inconsistent with the National Guidelines. In these cases, research staff liaised with the treating doctors, who amended the prescribed regimen.

Participant rating of VDOT

Participants rated the system highly, with 35 (87.5%) finding the system easy to use, and 35 (87.5%) patients stating they would recommend the method to other patients. Table 3 shows patient attitudes toward the VDOT system after two months of use. The median score for overall ease of use was 9 (IQR 9-10), where 1 = "Very hard to use" and 10 = "Very easy to use".

Discussion

We have shown that VDOT is a feasible technology to support adherence with TB treatment in Vietnam, a high prevalence setting for the disease. Enrolled patients were able to record a high proportion of daily videos, and indicated they would recommend the technology to other patients. However, in this setting where self-administered therapy is the standard of care, only 51% of eligible patients at National and District clinics agreed to participate in the study, despite the free availability of a smartphone and the availability of technical support.

This study suggests that smartphone-based technologies could be useful to support patients with TB, even in resource-limited settings. The scale-up of mobile-phone technologies has become increasingly feasible, given the rapid decline in market prices of smartphones, the growing prevalence of smartphone ownership in resource-limited settings (Poushter, 2016), and coverage of the majority of the world's population by mobile networks (World Bank, 2017). This trend is likely to continue. However, technological solutions to adherence may not be suitable for all patients. Given that TB predominantly affects those patients with a low socioeconomic status (Lonnroth et al., 2009), familiarity with this technology may be more limited than in the general population. Older populations may also face challenges adapting to new technological tools to support adherence (Westerman and Davies, 2000). However, we found most patients were able to learn to use the technology, after intensive initial training. A small number of eligible patients expressed concerns that the digital video recording would be overly intrusive. This is consistent with other reports suggesting that privacy concerns could limit the uptake of digital technologies by some people (DiStefano and Schmidt, 2016). Further research is required to evaluate approaches that minimize stigma and avoid intrusiveness of monitoring technologies.

Importantly, the measured treatment adherence in our study exceeded the proportion of patients able to successfully upload videos. This suggests that the intervention may still improve their adherence, and increase their engagement with health care workers, even if technical problems sometimes prevent videos from being submitted.

Table 3
Patient attitudes towards the Video Directly Observed Therapy system.

Question	Agree or strongly agree (n)	Percentage (%)
I found the system easy to use[a,b]	35	(87.5%)
I had problems recording a video[a]	4	(10.0%)
I had problems uploading videos[a]	16	(40.0%)
I had problems using the system due to poor mobile phone reception	1	(2.5%)
Would you recommend the system to other patients		
Yes	35	(87.5%)
No	0	(0.0%)
Don't know	3	(7.5%)
Did not respond	2	(5.0%)
Technical condition of phone at end of follow-up		
Fully functional	37	(92.5%)
Minor technical problem	1	(2.5%)
Did not respond	2	(5.0%)
Overall rating for use[c]		
Ease of use (median, IQR)[a]	9.0	(9.0-10.0)

[a] Out of 38 responses. 2 participants lost to follow-up.
[b] 1 respondent indicated "Don't know/not applicable".
[c] At end of 2 month period. Rated out of 10, where 10 is very easy.

This study has a number of limitations. Firstly, the patient population was selected based upon those who were willing to use the technology. Therefore, participants may have been more likely to take treatment than the general patient population. Therefore, the intervention itself may not have improved adherence. Secondly, we were also unable to compare treatment adherence with VDOT to that without use of the technology. While accurate estimates of adherence in Vietnam are not available, research from other Asian settings found that up to 30% of patients were non adherent (Liu et al., 2015). This is supported by other studies. Nevertheless, further appropriately controlled studies are required to evaluate the effect of VDOT upon adherence, compared to self-administration of treatment. A third limitation was our use of pill count as an indirect measure of adherence, namely monthly pill count, rather than daily electronic pill counting. Nevertheless, we observed a close correlation between the proportions of video uploads and pill count. This indicates that true adherence rates were, in fact, high.

Building upon this study, further research is required to compare the effectiveness of VDOT, in combination with other adherence support strategies, in improving treatment outcomes. Adequately powered studies must evaluate the effect of adherence on patient-important outcomes, including treatment completion and retention in care. In addition to smartphone-based approaches, simpler SMS-based interventions may also be integrated within the TB control programmes. Further studies are required to establish the characteristics of patients who are likely to benefit from VDOT or alternative digital technologies, and those who may respond better to traditional in-person monitoring.

Importantly, use of data generated through digital adherence support technologies can be used by TB control programmes to direct greater resources to the sub-populations identified as having a higher risk of non-adherence (Liu et al., 2015). Digital monitoring can also provide real-time feedback to National TB Programmes, allowing them to monitor the effectiveness of adherence support across their network.

In conclusion, VDOT is a feasible and acceptable method of adherence support among patients treated at both central and district (local) levels of the Vietnamese health system. Expansion of the use of digital technologies will be increasingly feasible, as the rapid global deployment of smartphones and mobile phone networks continues (World Bank, 2017). As costs of mobile devices continue to plummet, new technological solutions promise to overcome longstanding barriers to TB control, underpinning renewed global efforts to eliminate TB (Suthar et al., 2016).

Conflict of interest

The data collection, analysis and reporting of this study was conducted by the authors, independently of the technology provider, SureAdhere. The authors did not receive any financial support from SureAdhere, nor did SureAdhere determine the suitability of this manuscript for publication.

Author contributions

NTA, NVN, NBH and GJF contributed to the design, conduct, analysis and manuscript preparation. PMT, NTL and PDC contributed to the conduct of the study, collection of data and manuscript preparation.

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Lampiran Artikel 5

Original Paper

Use of Smartphone-Based Video Directly Observed Therapy (vDOT) in Tuberculosis Care: Single-Arm, Prospective Feasibility Study

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Abstract

Background: India accounts for nearly one-quarter of the global tuberculosis (TB) burden. Directly observed treatment (DOT) through in-person observation is recommended in India, although implementation has been heterogeneous due largely to resource limitations. Video DOT (vDOT) is a novel, smartphone-based approach that allows for remote treatment monitoring through patient-recorded videos. Prior studies in high-income, low disease burden settings, such as the United States, have shown vDOT to be feasible, although little is known about the role it may play in resource-limited, high-burden settings.

Objective: The goal of the research was to assess the feasibility and acceptability of vDOT for adherence monitoring within a resource-limited, high TB burden setting of India.

Methods: We conducted a prospective, single-arm, pilot implementation of vDOT in Pune, India. Outcome measures included adherence (proportion of prescribed doses observed by video) and verifiable fraction (proportion of prescribed doses observed by video or verbally confirmed with the patient following an incomplete/unverifiable video submission). vDOT acceptability among patients was assessed using a posttreatment survey.

Results: A total of 25 patients enrolled. The median number of weeks on vDOT was 13 (interquartile range [IQR] 11-16). Median adherence was 74% (IQR 62%-84%), and median verifiable fraction was 86% (IQR 74%-98%). More than 90% of patients reported recording and uploading videos without difficulty.

Conclusions: We have demonstrated that vDOT may be a feasible and acceptable approach to TB treatment monitoring in India. Our work expands the evidence base around vDOT by being one of the first efforts to evaluate vDOT within a resource-limited, high TB burden setting. To our knowledge, this is the first reported use of vDOT in India.

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KEYWORDS

Video DOT; mHealth; tuberculosis; medication adherence; telemedicine; India; mobile phone; smartphone

Introduction

Globally, tuberculosis (TB) is the leading cause of infectious disease-related mortality, responsible for 1.6 million deaths annually [1]. The incidence of TB is higher in India than anywhere in the world, with roughly 2.8 million cases reported in 2017, nearly 27% of the global TB burden [1]. To achieve positive treatment outcomes, adherence to TB therapy is critical [2,3]. However, socioeconomic and health system barriers in India are common and negatively impact adherence [4-6]. Failure to complete treatment can lead to relapse and the emergence of multidrug-resistant TB (MDR-TB), resulting in further disease transmission.

The World Health Organization (WHO) encourages the tailored use of multidimensional adherence interventions, including social, material, and psychological support, and emphasizes monitoring through directly observed treatment (DOT) [7]. Compared with self-administered therapy, those managed with DOT have demonstrated an improved rate of treatment completion [7,8]. Completion of therapy is vital not only for the patient but also the community, as public health efforts to mitigate disease spread require treatment success.

Unfortunately, DOT is often burdensome for patients and, paradoxically, can have a negative impact on adherence for some [9]. In India, DOT has historically been largely clinic-based (although there are differences in the public and private sector), wherein patients are required to bear the financial and logistical burden of frequent travel to and from the clinic for treatment monitoring. In doing so, patients risk lost wages due to time away from work. Additionally, providers must record and dispense daily treatments, a process that can be onerous and prohibitive in resource-constrained settings. While DOT is formally recommended under the current TB treatment guidelines set forth by India's Revised National Tuberculosis Control Program (RNTCP), in practice, DOT implementation (ie, observing and documenting each prescribed dose) in the community is inconsistent, and associated barriers can lead to treatment default [10-15].

More recently, video directly observed therapy (vDOT) has been introduced as a patient-centered alternative to in-person DOT, with pill ingestion monitored remotely via digital video capture. vDOT has been implemented using synchronous technologies [16-19] such as Skype and FaceTime as well as asynchronous technologies [20,21], where recorded videos are uploaded and digitally stored for future review. This latter method allows for video capture to occur at times convenient for the patient and eliminates the need for vDOT to be scheduled around staff availability. Recent work has shown asynchronous vDOT to be feasible, well received by patients and providers, and associated with high rates of treatment adherence [20-27]. Further, two economic evaluations in the United States have suggested vDOT to be cost effective over in-person DOT [20,27]. These encouraging findings have led both the US Centers for Disease Control and Prevention and WHO to suggest vDOT as a viable alternative to in-person DOT [28-30].

While data on vDOT are becoming increasingly robust, vDOT has yet to be rigorously evaluated within low- and middle-income countries of high disease burden such as India. Despite resource constraints, cellular technology has spread rapidly through India. As of 2017, there were a recorded 1.2 billion cellular connections and 291.6 million smartphone users within the country, suggesting that vDOT may have a role in this setting [31,32]. Additionally, recent changes to RNTCP guidelines have prioritized daily therapy (ie, 7 days per week) over three-times-per-week therapy, a change that further questions the feasibility of in-person DOT within a system already stretched thin and underscores the need for alternative approaches to adherence monitoring and support [14,33,34].

To address this critical knowledge gap, we conducted a prospective pilot of vDOT in Pune, India. Specifically, we addressed the feasibility and acceptability of vDOT within this resource-limited setting of high disease burden.

Methods

Overview

We conducted a prospective, single-arm, pilot implementation of vDOT in Pune, India. The mobile app emocha vDOT (emocha Mobile Health Inc) was used for treatment monitoring and adherence support (Figure 1). The patient-facing portion of the platform (ie, the mobile app) allows patients to record and transmit treatment videos. The interface also prompts patients to report any medication-related side effects (by checking off relevant symptoms from a prepopulated list). Through a calendar function, patients are able to review treatment progress and track adherence. Use of the software requires a camera-enabled tablet or smartphone device with at least intermittent access to Wi-Fi or cellular data. The app supports both Android and iOS operating systems. The provider portion of the platform can be accessed on a desktop, laptop, tablet, or smartphone (using a mobile browser) and is used by medical staff to review treatment videos. Providers are notified of any patient-reported treatment side effects. Given the system's asynchronous nature, submitted videos can be reviewed at any time following digital capture and transmission.

The emocha app is compliant with US Health Insurance Portability and Accountability Act (HIPAA) regulations and allows for asynchronous vDOT (Figure 2). Video capture occurs via the app. In the event that the device loses internet service or does not have access to internet service during video capture or upload, the videos (or any untransmitted component) remain encrypted on the device; all videos are uploaded automatically to secure servers when connection is restored (Wi-Fi or cellular data). Following transmission, videos are automatically wiped from the smartphone memory. Encrypted patient data, therefore, remain within the device only for the period between video capture and Web upload. Providers are able to access uploaded data via a secure Web interface through which they review submitted videos and track treatment progress.

The study was conducted at the Dr DY Patil Medical College Center and took place between January 2017 and June 2018. Study procedures were approved by the local institutional ethics committee and the institutional review board at Johns Hopkins University in Baltimore, Maryland.

Figure 1. The patient-facing portion of the emocha video directly observed therapy mobile app allows patients to record and transmit treatment videos, report any medication-related side effects, and review treatment progress and track adherence. The provider portion of the platform can be used by medical staff to review treatment videos and accessed from multiple devices.

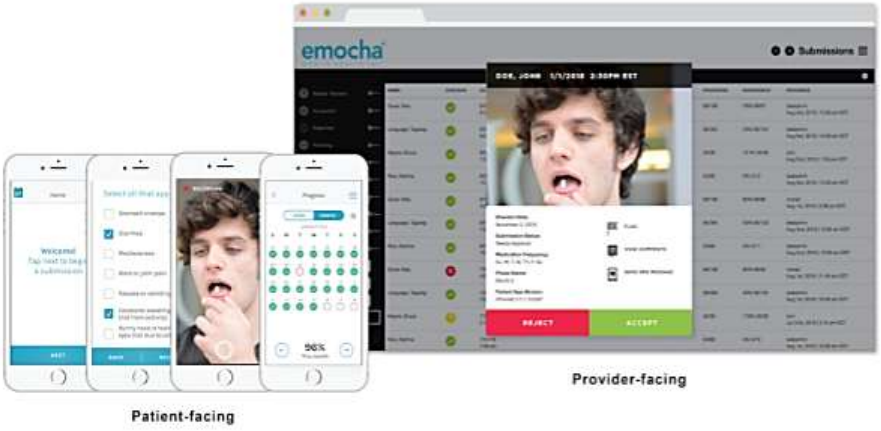
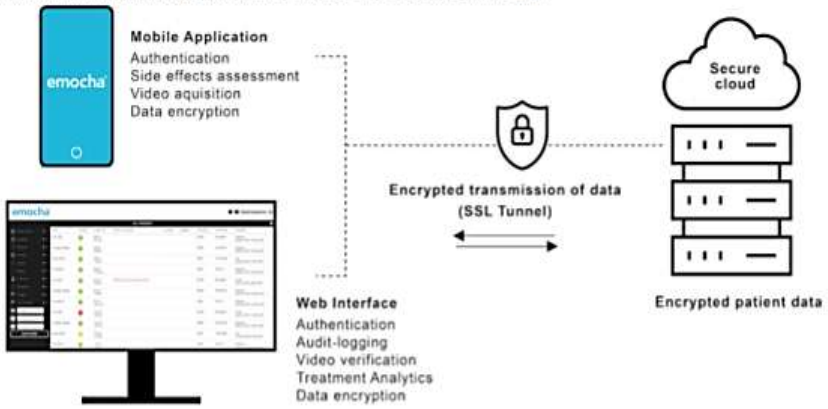


Figure 2. Data flow and security with the emocha video directly observed therapy mobile app.



Participants

Dr DY Patil Medical College Hospital is a private hospital that contains a government (public) TB treatment center (directly observed treatment, short-course, or DOTS center) as a public-private mix initiative. Patients diagnosed with or treated for TB at either Dr DY Patil or local DOTS centers were eligible for the study. Inclusion required age >18 years, signed informed consent, and >2 remaining months of TB therapy. Patients with MDR disease and HIV were excluded. Given this was a pilot study, we enrolled a convenience sample. Some patients were approached at the time of diagnosis, although many were assessed for eligibility midtreatment. Those not participating in the study received treatment and observation as per the local standard of care. Local guidelines recommend DOT for all intensive phase doses and for at least one dose per week during the continuation phase [14], although implementation is heterogenous and largely determined by local resources and patient preference (oral communication, T Sahasrabudhe, MD, November 2018).

Prior to enrollment, patients were required to establish basic smartphone proficiency and demonstrate the ability to successfully navigate the emocha app. A version of emocha translated into Marathi (the primary local language) was available to those with limited English. Patients without access to a smartphone were provided one by the study. Regardless of the device used, each participant was provided Rs 200 (US $3) each month to cover the cost of video submissions and a one-time incentive payment of Rs 100 (US $1.50) to cover travel expenses.

Study Procedures

A total of 35 patients were selected for this study based on a convenience sampling method. All patients provided written informed consent and were permitted to withdraw from the study at any time. Demographic information including

participant medical history and TB diagnosis were collected using a standardized case report form. Data were subsequently entered into a digital database by study staff. During their first study visit, participants were introduced to vDOT by a study staff member who provided each with a unique username and password and conducted a step-by-step tutorial outlining the process for how to create and submit a treatment video. Patients were then observed as they attempted to submit a dummy video independently. Additional training was provided on an as-needed basis.

Prior to formal enrollment, patients underwent a conditional 1-week run-in period, during which they were closely monitored for their continued ability to successfully record and submit videos. Any technical or logistical barriers arising during this period were addressed prior to formal study enrollment, which was only able to occur following successful completion of this trial period. For those enrolled, vDOT continued through treatment completion or until consent was withdrawn. Text message reminders via the emocha app were automatically sent to patients in the absence of expected video submissions. All incomplete or unverifiable videos (eg, medication could not be seen or video did not transmit due to network issue) were followed up with a staff phone call to verbally verify whether the dose was taken.

Feasibility

Feasibility was assessed by two primary outcomes. The first was treatment adherence, or the proportion of all prescribed treatment doses directly observed by video. As noted above, incomplete or unverifiable videos were followed up with a phone call for verbal verification. As such, a second metric, verifiable fraction, was used to describe the proportion of all prescribed doses that were either directly observed (by video) or verbally confirmed (following incomplete/unverifiable videos). All data analysis was completed in Stata 14 (StataCorp LLC).

Acceptability

To assess vDOT acceptability among patients, a posttreatment survey was administered comprising a series of categorical and Likert scale questions addressing issues such as mobile phone and internet access, emocha ease of use, convenience, and privacy. To increase our understanding of potential implementation barriers, patients were also informally asked to comment on their experiences and highlight any challenges or concerns they had related to the use of vDOT. Patient responses were noted by study staff at the time of survey administration. Staff were also asked to comment on patient-level barriers observed during the study.

Results

Study Participants

Of 35 patients who were consented and initiated the run-in phase (Figure 3), 10 did not complete the run-in and left the study. Reasons for run-in failure were related to technological (eg, inability to effectively use platform or poor cellular/Wi-Fi connectivity) and psychosocial (eg, concerns regarding privacy) barriers. Twenty-five patients were ultimately enrolled and formally initiated on vDOT with emocha. There was no study drop out, and all 25 patients completed therapy on vDOT.

Patient characteristics are described in Table 1. The median age was 27 (interquartile range [IQR] 24-42) years, 40% (10/25) were female, and 72% (18/25) reported their local language as Marathi. Most patients were low income with a monthly income less than Rs 16,000 (US $225). The majority of patients (22/25, 88%) had access to a smartphone and the internet. Three patients (3/25, 12%) required the use of a study phone. Almost three-quarters (18/25, 72%) of patients had pulmonary TB, and the remainder (07/25, 28%) had extrapulmonary disease.

Figure 3. Study flow diagram. vDOT: video directly observed therapy.

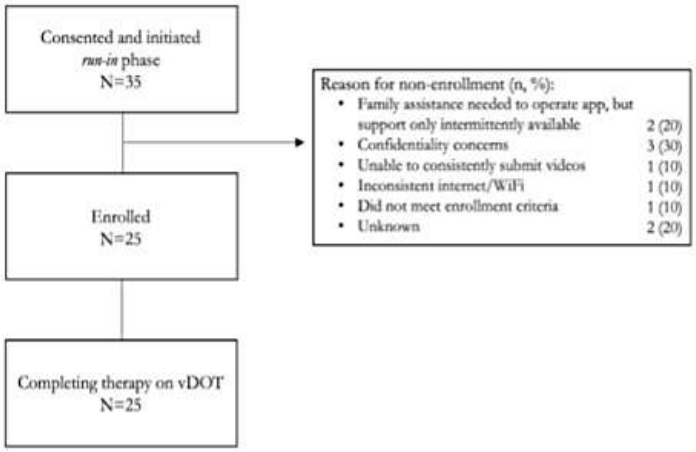


Table 1. Patient and disease characteristics (n=25).

Variable	Value
Age, year (median, IQR[a])	27 (24-42)
Female, n (%)	10 (40)
Indian state of origin, n (%)	
Maharashtra	18 (72)
Haryana	2 (8)
Karnataka	1 (4)
Tamil Nadu	1 (4)
Other	3 (12)
Primary language, n (%)	
Marathi	18 (72)
Hindi	6 (24)
Kannada	1 (4)
Employed, n (%)	10 (40)
Average monthly income (Rs), n (%)	
<2000	6 (24)
2000-4000	0 (0)
4000-8000	6 (24)
8000-16,000	13 (52)
>16,000	0 (0)
Homeless, n (%)	1 (4)
Residence, n (%)	
Urban	21 (84)
Rural	4 (16)
Married, n (%)	13 (52)
Primary mode of transportation, n (%)	
Private vehicle	0 (0)
Bus/train	0 (0)
Auto-rickshaw	8 (32)
Other private transportation	17 (68)
Substance use, n (%)[b]	
Alcohol	1 (4)
Tobacco use	0 (0)
Illicit drug use	0 (0)
Medical comorbidities, n (%)[b]	
Diabetes	3 (12)
Hypertension	1 (4)
Cancer	0 (0)
Technology, n (%)	
Regular access to a smartphone	22 (88)
Daily access to Wi-Fi or cellular data	22 (88)
Used personal device for study	22 (88)

fully seen. The median video length was 44 (IQR 31-52) seconds and associated with a median file size of 1.5 (IQR 1.1-1.7) MB.

Acceptability

A total of 22 posttreatment surveys were completed; 3 patients declined participation. Study outcomes for those declining involvement were similar to those of the general study population; each patient completed >14 weeks on vDOT with an adherence >70%.

A total of 91% (20/22) of surveyed patients described emocha as easy to use (Table 3). All patients (22/22, 100%) reported being able to record videos without difficulty, 95% (21/22) were able to upload without difficulty, and 91% (20/22) found text message reminders helpful. Further, all found they were able to communicate concerns and medication side effects effectively through the emocha platform. The majority felt vDOT would be more convenient (20/22, 91%) and preferred (20/22, 91%) over in-person DOT (Table 4). While 82% (18/22) felt vDOT would preserve patient privacy over in-person DOT, 18% (4/22) disagreed and felt in-person DOT would be more private.

Table 3. Responses from patient agreeability survey (n=22).

Survey statements (rated on a 5-point Likert scale)	Agree[a] n (%)	Disagree[b] n (%)
emocha was easy to use	20 (91)	2 (9)
I was able to record videos without difficulty	22 (100)	0 (0)
I was able to upload videos without difficulty	21 (95)	1 (5)
emocha text message reminders were helpful	20 (91)	2 (9)
I was able to communicate concerns and side effects using emocha effectively	22 (100)	0 (0)

[a]Agree/strongly agree were grouped.

[b]Neutral/disagree/strongly disagree were grouped.

Table 4. Responses from patient preference survey (n=22).

Survey statements (categorical)	Value, n (%)
Videos were most often uploaded using	
Wi-Fi at the clinic	0 (0)
Wi-Fi at home or other location	0 (0)
Cellular data (3G/4G)	22 (100)
Which better preserves patient privacy?[a]	
vDOT[b]	18 (82)
In-person DOT[c]	4 (18)
No preference	0 (0)
Which is more convenient?[a]	
vDOT	20 (91)
In-person DOT	2 (9)
No preference	0 (0)
Preference for therapeutic monitoring[a]	
vDOT	20 (91)
In-person DOT	2 (9)
No preference	0 (0)

[a]In-person directly observed therapy (DOT), either prior to enrollment or while on video directly observed therapy (vDOT), was inconsistently performed and/or documented based on chart reviews. Answers referring to in-person DOT are therefore based on patient perceptions of what in-person DOT would be like.

[b]vDOT: video directly observed therapy.

[c]DOT: directly observed therapy.

Study coordinator notes were reviewed and summarized in Table 5. Broadly, these notes revealed patient-level barriers impacting the successful implementation and use of vDOT. Included were psychosocial factors, such as the privacy concerns and stigma,

and mental health barriers. Despite survey data suggesting that most were able to record and upload videos without issue, poor connectivity and cellphone-related challenges (eg, subscriber identity module [SIM] card malfunction) were noted in a few cases.

Table 5. Patient-level barriers to successful video directly observed therapy use as identified by study staff.

Barrier to vDOT[a] use	Representative patient quotes and/or problem details
Psychosocial	
Stigma	"Recently one of my close relatives expired. As you know, we need to be at home to complete all the rituals up to 15 days after death. All the relatives are there, around all the time, and it became difficult to go out as well. So I could not take videos. Otherwise they would have started asking. Due to that, sometimes I missed my medicines."
Hospital admission	One patient suffered from severe alcohol dependence. The patient was successful on vDOT for a period but later admitted for detoxification. The patient's phone was confiscated at the time of admission, leaving him unable to upload videos during his hospital stay.
Stress	"My 1-year-old son fell from the bed and his hand got fractured. He was unwell, so we were under stress. I took tablets but during that time, I did not record videos."
Technology-related	
Connectivity	"I went to my village for 8 days for some work. As we do not have range and connectivity to the internet, I could not send videos."
vDOT-related challenges	"The registration process is a bit complicated and time-consuming. Can it be simplified?"
	"The [vDOT] app got hanged in my mobile. I did not know how to reinstall it. So I could not send videos."
	"When [recording a] video, if I get a call, the application used to suddenly shut down. So the video [would get lost]."
SIM[b] card	"I did not submit Know Your Customer documents required for SIM verification. Hence my SIM card was deactivated for some time...I was not able to send videos."

[a]vDOT: video directly observed therapy.

[b]SIM: subscriber identity module.

Discussion

Principal Findings

Our pilot study suggests that vDOT may be a feasible option for verification of medication adherence for TB patients in India. Among enrolled participants who completed a short run-in period to assess technological literacy, we found that a median 74% of all prescribed doses were observed. Further, when including doses verbally confirmed (following incomplete video submissions), the proportion of verified doses (verifiable fraction) increased to 86% (based on 1722 submitted and reviewed videos), exceeding the adherence goal of >80% set forth by current treatment guidelines [28]. This degree of adherence is comparable to that described using vDOT in other settings, such as the United States, and advances current evidence supporting vDOT, as prior work has largely focused on implementation within resource-rich settings [16,20,27,35]. To the best of our knowledge, this is the first reported use of vDOT in India.

Our demonstration of vDOT feasibility within the Indian context is both timely and critical given the recent RNTCP guideline changes emphasizing the need for daily over intermittent (3 times per week) therapy [14,33,34]. While a DOTS strategy, based on the principle of direct treatment observation, has been in place in India for over two decades, in practice, DOT implementation has been inconsistent.

In Pune, our experience has been that patients are often provided medication weekly or biweekly, with adherence monitoring largely based on self-report. At best, clinic services, including in-person DOT, are generally available 6 days per week, permitting a maximum of only 85% of prescribed (daily) doses to be observed. In contrast, by decoupling video capture from provider review, asynchronous vDOT potentially allows for all (100%) doses to be observed and obviates the need to coordinate DOT around staff availability.

To successfully and sustainably implement DOT in India, alternatives to in-person DOT are clearly needed. vDOT has the potential to be this alternative and to fill the needed gap. Our study is among the first in a resource-limited setting to demonstrate that daily therapy can be confirmed through the use of innovative mobile technologies. vDOT saves health care worker time and obviates the need for in-person visits to observe treatment [22]. For settings where home visits are employed solely for DOT, vDOT may reduce costs and save time even further [18,20,27,36,37]. vDOT may also have other previously unrecognized benefits related to infection control. Provisions for personal protective equipment (ie, masks for health care workers) or environmental controls (isolation rooms) are limited in India; vDOT offers a mechanism to closely monitor patients while reducing potential transmission opportunities. Additionally, we observed that patients derived benefit from avoiding frequent clinic visits, for which associated travel leads to lost time and, often, wages. Most importantly, vDOT provides

solid evidence of treatment adherence. Our study also highlights a need for patient training (eg, run-in period with onboarding to the technology), counseling, and follow up in cases of missed doses to assure successful treatment completion.

Of note, India has already endorsed another electronic form of treatment monitoring, 99DOTS: when a patient removes a pill from a blister pack, a number is revealed that completes a toll-free phone number printed on the pack, which the patient then calls to report having taken daily medication [12,33]. While 99DOTS may be a feasible means for basic adherence monitoring [38], vDOT has the distinct advantage of providing video confirmation of pill ingestion. It is also important to consider that the use of vDOT allows for adherence support in addition to adherence tracking. The platform used in this study captures side effects and TB symptoms, and videos can also be used to notify providers of treatment concerns, such as rashes, which can be preliminarily evaluated from afar through submitted videos. Moreover, the current platform allows automated messaging reminders, which patients reported to be a benefit. Newer versions of the software offer secure chat functionality (with health care providers) and case management tools that may further support treatment adherence. India recently rolled out a direct benefits transfer scheme that encourages treatment adherence through the use of financial incentives (Rs 500 per month while on therapy) [39,40]. 99DOTS is currently being used as a mechanism to monitor treatment adherence, but it is limited. For the reasons noted above, a more reliable tamper-proof means of adherence monitoring would be beneficial.

Limitations and Strengths

While our work supports further evaluation of vDOT within India, we acknowledge several study limitations. First, our sample size was small and, while we have shown vDOT to be feasible in one location, its acceptability and feasibility in other parts of India remain unknown. Second, we were unable to compare adherence on vDOT to that under the existing standard of care, which at our site was primarily self-administration (thus precluding documentation of prestudy adherence). Our findings, however, suggest that vDOT implementation could substantially improve adherence documentation compared with current practice. Through broader implementation, vDOT has the potential to enable enhanced accountability among TB clinics with regard to treatment adherence. Improvements in documentation would also increase the availability of high-quality data on TB treatment completion for public health reporting practices. Whether vDOT is associated with improved patient outcomes compared with standard of care is still unknown and was not assessed within the scope of this pilot study.

We also acknowledge a significant attrition over the course of our run-in period. One-third of those who consented did not ultimately participate in the study. Drop out during this period was largely driven by technological barriers related to infrastructure (eg, inconsistent cellular coverage) or inability/unease with smartphone operation. Further, despite the fact that we used a HIPAA-compliant app (emocha) with stringent security controls, several participants withdrew consent over privacy concerns. Some patients noted a fear that their treatment videos might end up publicly viewable on the internet. While cellphone technology has spread rapidly across India, cellular coverage remains incomplete and not all have become immediately facile with the technology. With time, these barriers may diminish. A strength of our study was the use of a run-in period, which was advantageous in that it allowed for rapid identification of those with sufficient mobile phone literacy to be candidates for vDOT. In our study, all those who completed the run-in period and enrolled in the study successfully finished therapy on vDOT.

Conclusions

Despite its promise, there remain questions regarding vDOT that must be addressed. Larger controlled and comparative trials will be needed to better evaluate the effectiveness of vDOT against the current standard of care or alternative technologies in resource-limited, high disease burden settings. Future studies addressing cost and cost effectiveness are also needed. Last, in other settings such as the United States, vDOT has successfully been coupled with individualized case management to allow real-time intervention after missed doses; the role of this approach in India is unknown [20]. Overall, our work has shown that despite socioeconomic and structural barriers, vDOT may be a feasible approach for treatment monitoring in India.

Acknowledgments

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Authors' Contributions

MS created the study concept and design. SA, SBH, SA, DJ, TS, SM, MB, and AK were responsible for the acquisition of data and SA and SBH for statistical analyses. SBH, MS, SA, and TS performed data interpretation. SA and SBH drafted the initial manuscript, and all authors participated in manuscript revision.

Conflicts of Interest

MS is one of the inventors of the miDOT technology. Under a license agreement between emocha Mobile Health Inc and Johns Hopkins University, MS and the university are entitled to royalties on technology described in this article. This arrangement has

been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. To mitigate any potential conflicts of interest, all clinical decision making regarding use of miDOT or enrollment in the study was made by nonconflicted department of health clinicians and staff; MS recused himself from all data analysis but assisted with results interpretation.

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Abbreviations

DOT: directly observed treatment
DOTS: directly observed treatment, short-course
HIPAA: Health Insurance Portability and Accountability Act
IQR: interquartile range
MDR-TB: multidrug-resistant tuberculosis
RNTCP: Revised National Tuberculosis Control Program
SIM: subscriber identity module
TB: tuberculosis
vDOT: video directly observed therapy

WHO: World Health Organization

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Video directly observed therapy for treatment of tuberculosis is patient-oriented and cost-effective

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To the Editor

Curing tuberculosis (TB) entails adhering to a multidrug regimen for 6 months [1]. Failure to take the medications as prescribed can lead to treatment failure, drug resistance and further spread of TB, resulting in morbidity and death for the patient and a threat to public health. Treatment failure is the most important cause of drug-resistant TB, which is much more long, expensive and toxic to treat, and the outcomes of which are still unsatisfactory [2–4]. The public health consequences of nonadherence to TB treatment led to directly observed therapy (DOT) becoming the universal standard of care [5–8]. While DOT is a best practice model for TB treatment, it is labour intensive and can itself be a barrier to effective therapy because of its inconvenience for patients. The expense may be prohibitive for cash-strapped public healthcare systems [9].

"Telehealth" or the delivery of healthcare services at a distance with information and communications technology, has the potential to overcome deficiencies of direct healthcare delivery. Applying home-phone video for real-time DOT of TB has been reported to be practical in two pilot studies [10, 11]. The objective of this study was to assess the acceptability and cost-effectiveness of real-time video-DOT (V-DOT) on mobile devices as an alternative to in-person DOT for administration of TB medication.

With the approval of Illinois Department of Public Health, DuPage County piloted a V-DOT programme using Skype (Microsoft, Redmond, WA, USA) in January 2013 as an adjunct to the existing in-person DOT programme. In this study, we retrospectively reviewed data from subjects who underwent V-DOT at our DuPage County Health Department Tuberculosis Clinic (Wheaton, IL, USA). The clinic treated 68 adults for active TB from January 2013 to December 2014. Age, sex and treatment duration were collected by chart review of medical records using standardised abstraction forms and pre-established definitions. Inclusion criteria for being on V-DOT were age >18 years, availability of electronic devices, and availability of a member of staff who could speak the patient's language and provide appropriate confidentiality. Patients diagnosed with multidrug-resistant TB or who were

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considered at risk of poor adherence (the homeless, HIV patients or those who were not being truthful) were not offered V-DOT.

We did not provide any equipment to the patients. They used their own smartphones or personal computers. Skype is free software and our nursing staff spent about an hour for training each patient.

Each V-DOT session consisted of six steps with an average duration ~5 min. Figure 1a illustrates the V-DOT process. We evaluated the experience by a multiple-choice questionnaire. The questionnaire was mailed to the patients and responses were voluntary (fig. 1b). Adherence of patients to V-DOT was measured by compliance to treatment and responses to the questionnaire.

Expense calculations included the mileage cost of the distance between the TB clinic and the patients' addresses, and the staff's time. The patients'time and lost wages of standard DOT could not be calculated because of the heterogeneity of the patients.

68 patients with active TB were treated in our clinic from January 2013 through December 2014. 20 patients met the V-DOT inclusion criteria and 11 consented to be in the V-DOT programme. Out of 11 subjects, six were females and five were males, and age ranged from 19 to 64 years old. Three subjects were born in the Philippines, three in India, and one in each Korea, Mexico and Myanmar. Two subjects were US-born. Nine subjects spoke English, one Hindi and one Spanish. Six of the patients were college students or graduates and the rest were under diploma. Nine subjects used smartphones and two used personal computers at home for V-DOT. 11 successfully completed treatment with cure outcomes; 1083 V-DOT observations were performed with a 97% compliance rate.

The total cost savings for mileage was US$7583.00. The average savings of miles driven for each patient was 9499 miles (15 287 km). Approximately 579 h, valued at US$144750 in human resource costs and travel expenses of staff travel time, was saved. The incalculable costs to the patients are additional savings.

Out of 11 patients, eight patients participated in the voluntary questionnaire. Patient experience included that seven (88%) out 11 patients were well satisfied with V-DOT, and all respondents (100%) considered V-DOT an improvement over to the traditional DOT and strongly recommended it to other TB patients (fig. 1b).

The current study showed that V-DOT is a patient-oriented and cost-effective method that could be useful in a variety of TB treatment settings for a select group of patients. The drawbacks of conventional DOT not only include cost and staff time, but the fixed-time commitments detract from a patient- centred approach [12]. For example, a patient experiencing nausea may do better if the drugs are given at night or with food, but the more regimented DOT is not as flexible as V-DOT. An advantage of DOT is patient interaction and the ability to reinforce commitment to therapy, but these can also be employed with V-DOT.

Several other studies have sought to explore the role of technology in facilitating patient interaction, reinforcing behaviour and improving adherence. a study conducted in South Australia used home video observation as a patient-centred, resource-efficient way of delivering direct observation for TB, which was found to be cost-effective when compared with a drive-around service [13]. KRUEGER *et al.* [10] demonstrated that videophone observation of medication ingestion was a cost-effective and reliable method, while significantly saving travel costs and staff salaries of almost US$140000. Our small study showed an equally impressive saving in travel and human resource costs. The high rate of V-DOT adherence compared favourably to our historic adherence rates.

However, a main positive outcome is that V-DOT is more patient friendly. It can be more flexible in time and allow greater freedom for the patient, saving them time and travel expense, which cannot be translated into monetary savings. The V-DOT increase in patient-oriented TB treatment may improves compliance and lower stigma for TB patients.

The limitation of V-DOT is that this approach may not apply to all patients in all settings: the Internet technology may not be available; patients may not be technologically savvy enough to use an Internet-based video system; patients may not have a permanent home; and it may be challenging in vulnerable populations. Another concern of V-DOT is privacy; transmitting protected health information through the Internet has the potential to be compromised, even with encryption software. Other limitations are the relative small sample size, lack of controls and the failure to control for biases. As with all interventions, it is the responsibility of healthcare professionals to weigh the risks of V-DOT with the benefits, which may vary across healthcare settings.

This study shows that a video-based approach using mobile devices provides meaningful direct observation for TB patients, which is associated with high compliance and fewer healthcare resources. V-DOT fully fits the vision of TB Elimination, which recently developed recommendations on how to reach it [14, 15]. Larger trials should be conducted to establish the role of V-DOT in other TB care settings. V-DOT could be important in other diseases requiring long treatment regimens, such as HIV/AIDS and viral hepatitis.

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a)

b)

Question	Patients %
How long have you been using V-DOT through Skype?	
2–4 months	44
4–6 months	12
6–8 months	24
How long were you on DOT at home/work before starting V-DOT through Skype?	
1–2 months	76
2–4 months	12
>6 months	12
How convenient are the V-DOT appointments?	
Excellent	88
Good	12
If you were on DOT before, how convenient were the DOT visits?	
Excellent	76
Good	12
Fair	12
How hard was it to set up and access Skype on your computer?	
Very easy	88
Easy	12
How easy was it to establish a convenient time for V-DOT?	
Very easy	88
Easy	12
Do you feel that V-DOT saves you time?	
Yes	100
Do you feel that V-DOT protects your confidentiality?	
Yes	100
How easy has it been to utilise the V-DOT system and staff?	
Excellent	88
Good	12
How would you rate your overall satisfaction with V-DOT?	
Excellent	88
Good	12
Do you feel that V-DOT is an improvement over traditional DOT?	
Yes	100
Would you recommend V-DOT to another patient?	
Yes	100

Figure 1.
a) video directly observed therapy (V-DOT) process and b) results of the survey on the patients using it DOT: directly observed therapy.

Lampiran Artikel 7

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ORIGINAL ARTICLE
TUBERCULOSIS

Video directly observed therapy for supporting and monitoring adherence to tuberculosis treatment in Uganda: a pilot cohort study

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ABSTRACT

Introduction: Nonadherence to treatment remains an obstacle to tuberculosis (TB) control worldwide. The aim of this study was to evaluate the feasibility of using video directly observed therapy (VDOT) for supporting TB treatment adherence in Uganda.

Methods: From May to December 2018, we conducted a pilot cohort study at a TB clinic in Kampala City. We enrolled patients aged 18–65 years with ⩾3 months remaining of their TB treatment. Participants were trained to use a smartphone app to record videos of medication intake and submit them to a secured system. Trained health workers logged into the system to watch the submitted videos. The primary outcome was adherence measured as the fraction of expected doses observed (FEDO). In a secondary analysis, we examined differences in FEDO by sex, age, phone ownership, duration of follow-up, reasons for missed videos and patients' satisfaction at study exit.

Results: Of 52 patients enrolled, 50 were analysed. 28 (56%) were male, the mean age was 31 years (range 19–50 years) and 35 (70%) owned smartphones. Of the 5150 videos expected, 4231 (82.2%) were received. The median FEDO was 85% (interquartile range 66%–94%) and this significantly differed by follow-up duration. Phone malfunction, uncharged battery and VDOT app malfunctions were the commonest reasons for missed videos. 92% of patients reported being very satisfied with using VDOT.

Conclusion: VDOT was feasible and acceptable for monitoring and supporting TB treatment. It resulted in high levels of adherence, suggesting that digital technology holds promise in improving patient monitoring in Uganda.

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Video directly observed therapy is feasible and acceptable for supporting and monitoring TB treatment adherence in a low-resource setting like Uganda. Digital health interventions hold promise as alternative methods for improving patient care. http://bit.ly/2Hxnvwu

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Introduction

The End TB Strategy envisions a world free of tuberculosis (TB): zero deaths, disease and suffering due to TB by 2035 [1]. Nonadherence to treatment remains a major obstacle to TB control because it reduces cure rates, prolongs infectiousness and contributes to the emergence of acquired multidrug-resistant strains [2–5]. Nonadherence to treatment is a challenge particularly in sub-Saharan Africa, where TB rates can be as high as 800 per 100 000, yet resources for healthcare delivery are limited [1]. Adherence support and monitoring interventions improve TB treatment outcomes compared to unsupervised, self-administered treatment [5, 6]. Innovative approaches to improve care and prevention must be explored in order to make the goals of the End TB Strategy a reality [7].

Directly observed treatment (DOT) is a standard strategy that was established to ensure adherence to treatment in the early 1990s but proper implementation has proved difficult to achieve worldwide [6, 8]. In sub-Saharan Africa, the practice of DOT is limited by a severe shortage of healthcare workers coupled with weak public health systems in which most TB programmes operate [9, 10]. Previous studies in Uganda showed that only 16% of TB clinics implemented DOT properly due to a shortage of health workers [11]. Furthermore, only 63% of DOT workers consistently supervised treatment [12] whereas 26% of patients did not properly adhere to their prescribed treatment [13]. Community-based strategies to enhance the implementation of DOT have utilised volunteers, family members or patient peers as treatment supporters. However, the success of such DOT models remains limited by reliance on the efforts of unpaid workers [14, 15]. Studies show that nonadherence can be due to forgetfulness, a false perception of wellbeing, drug side-effects, stigma, long distances to health facilities coupled with long waiting times [16–21]. Novel alternative approaches that address these gaps are urgently needed.

In 2015, the World Health Organization established a Global Task Force on Digital Health for TB to support the development of digital health innovations to improve care and prevention [22, 23]. In 2017, video directly observed therapy (VDOT) was endorsed as an alternative to DOT for monitoring treatment where possible [7]. VDOT enables the patient to use a smartphone to record videos of their daily pill intake without face-to-face interactions with the health providers. VDOT can overcome the limitations of in-person DOT at the patient and health system levels. For example, VDOT studies have shown that the distance barrier is mostly eliminated [24–26], patients have greater autonomy to choose when and where to take their medications [25, 27], the costs of travel are minimised [24, 28], and providers can support a higher number of patients, thus increasing the health system efficiency [24, 29].

Previous studies in high-income [26, 27, 30–32] and low-income countries [9, 33] have reported high adherence and patient satisfaction with VDOT. One study from Kenya showed the promise of digital health interventions for supporting TB treatment success [34]; however, no published studies exist on the use of VDOT in Africa. The aim of this study was to determine the feasibility and acceptability of VDOT for monitoring and supporting treatment adherence in the Ugandan context.

Materials and methods

Study setting

Uganda is a unique setting for testing and adopting VDOT because it is classified as a high-burden country for TB and HIV, with an estimated 80 000 new TB cases each year according to the national prevalence survey [35]. By March 2018, the number of mobile phone users had increased to 24.8 million, representing a 71% cellular penetration rate, mostly concentrated in the cities [36]. Kampala City, Uganda's capital, is residence to ~25% of TB patients. The TB Control Program is responsible for providing free diagnosis, treatment and case management services to all patients. Adherence monitoring and support are delivered mostly through community-based DOT by designated treatment supporters. The treatment supporters can be trained community health volunteers, family members or friends. TB medications are provided free of charge and patients are expected to return to the health clinics for monthly prescription refills until they complete the 6–8-month regimen for drug-susceptible disease.

Study design

We conducted a pilot prospective single-arm cohort study that included patients with active TB attending an outpatient clinic supported by the Uganda National TB Program in Kampala City. Eligible patients were 18–65 years old with confirmed drug-susceptible TB and had ⩾3 months remaining to complete TB treatment. Patients were excluded if they had confirmed multidrug-resistant TB, or a documented cognitive, visual or motor disability that would interfere with recording videos. Patients were also excluded if they did not have access to electricity to charge a smartphone. Consecutive patients presenting at the clinic were invited to participate regardless of smartphone ownership (figure 1). Sample size determination was guided by pragmatic parameters such as cost and human resources. The main objective of the pilot was to determine feasibility and not to test a hypothesis; therefore, no power calculations were performed.

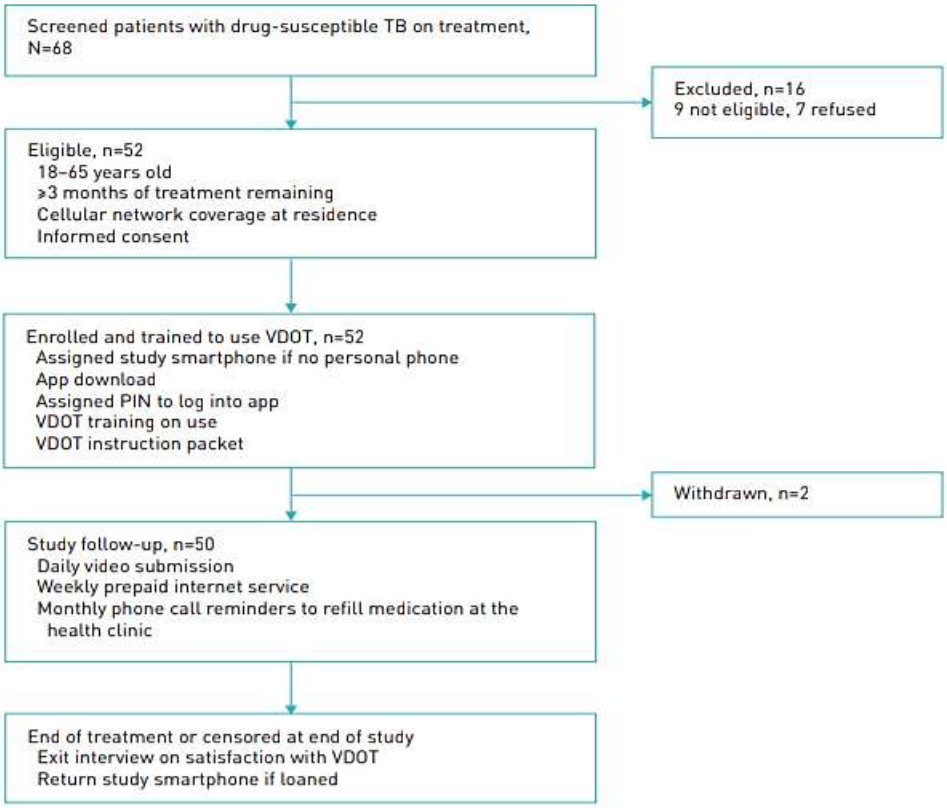

FIGURE 1 Flow diagram of video directly observed therapy (VDOT) procedures. TB: tuberculosis; PIN: personal identification number.

Description of VDOT System

Treatment monitoring was performed using an asynchronous VDOT. This involved a smartphone application (app) that enabled patients to record videos while swallowing each dose of medication and upload them to a secure cloud server to be accessed and viewed later by health workers. A detailed description of the app is published elsewhere [27, 32]. The app worked with an Android (Google LLC, Menlo Park, CA, USA) or iOS (Apple Inc., Cupertino, CA, USA) smartphone and time-stamped videos were automatically sent by the app through third- or fourth-generation (4G) cellular networks or Wi-Fi. The app prevents videos from being viewed, edited or deleted by users on the smartphone, thus ensuring confidentiality and fidelity of the videos. After successful upload, the videos are automatically deleted from the smartphone. Participants used either their own smartphone or were loaned a 4G smartphone by the study. Cellular internet data charges were prepaid weekly at ~US$1.00 and sent directly to the participants' phone to ensure videos would be sent in a timely manner.

Study participants received automatic daily short text reminders 1 h before the scheduled medication doses and 1 h after only if a video was not received. Trained research staff logged into an internet-based, password-protected client management system to watch the uploaded videos and document whether they observed the pills being swallowed. A predefined protocol adapted from the TBeDOT toolkit published by the US Centers for Diseases Control and Prevention was followed [37]. If a video was not sent within 24 h, the research staff followed up with the participant by a phone call to ascertain if a medication dose was taken and to report reasons for failing to send the video, and provided necessary support.

Study enrolment procedures

Clinic nurse providers at the study site invited consecutive patients to participate in the VDOT pilot. Two trained research staff screened prospective participants for eligibility and enrolled them into the study.

After the informed consent process and documentation, participants received VDOT training conducted in English or Luganda, and lasting ~30 min. The participants were allowed to practice logging into the app using an assigned personal identification number, recording and submitting videos, and to ask questions. Participants received a packet with written instructions on how to use the VDOT app and a "pill mat" to help them organise their pills before making their videos. During follow up, retraining was provided to participants as needed in cases of difficulties with navigating the app.

Data collection and follow-up

A baseline interview was administered to collect information about participants' sociodemographics, phone ownership, previous experience with technology including smartphone, internet, taking photos or videos, and frequency of use in the last 3 months. Additional clinical information about date of diagnosis, duration on treatment and other medications was collected from the clinic records. Study participants returned to the clinic for their routine monthly visit to refill prescriptions, and for evaluation at 2, 4 and 6 months, per the standard of care. Exit interviews were conducted at the end of the observation period to evaluate satisfaction with VDOT and difficulties with using the VDOT system.

Ethical considerations

The study was approved by the institutional review boards at the University of Georgia, Athens, GA, USA (approval number STUDY00004974), and the Higher Degrees, Research and Ethics Committee at Makerere School of Public Health, Kampala (approval number 562) in Uganda. Participants provided written informed consent in their preferred language, either English or Luganda. Participants were reimbursed for an equivalent of US$3.00 at baseline and follow-up to cover travel expenses that were related to VDOT visits.

Statistical analyses

We reported baseline summary statistics including means, standard deviations, medians, interquartile ranges and percentages with 95% confidence intervals. Experience with using phone functions was assessed using a Likert scale from 1 to 10 (1: not all comfortable; 10: very comfortable) then responses were collapsed into three groups (8–10: very comfortable; 4–7: somewhat comfortable; 0–3: not comfortable) or not applicable if a person did not use the feature. The primary outcome was adherence measured as the fraction of expected doses observed (FEDO) through VDOT. FEDO has also been used in prior studies [32] because it allows for standardisation of adherence measurement when there are unequal observation periods across participants who are enrolled after initiating treatment. Doses were only counted as "taken" if the research staff observed all pills being swallowed in the video. In a secondary analysis, we evaluated differences in FEDO by sex, age, phone ownership and duration of observation. We also calculated the total observed and unobserved doses reported as self-administered treatment. Other outcomes included reasons for missed videos and participant satisfaction with VDOT at exit of the study. Data were analysed using STATA/SE 15.1 software (StataCorp, College Station, TX, USA).

Results

Participants' baseline characteristics

Between May and December 2018, 68 patients were invited to participate, of whom nine were ineligible and seven refused. Of those who refused, two men did not have time or interest, one male student was attending boarding school where cell phones were prohibited, one woman could not record herself for religious reasons and three younger women needed to seek permission from family members who had provided them with the cell phones but never returned. Two female participants were withdrawn within 1 week of enrolment (one developed a mental illness and the other was a caregiver of a very sick child). 50 participants were included in the final analysis.

28 patients (56%) were male and the mean age was 31 years (range 19–50 years). Most (96%) owned cell phones and 35 (70%) owned smartphones. The VDOT app was installed on the personal smartphones of 21 (42%) patients and 29 (58%) used loaned study phones. Detailed baseline characteristics of study participants are shown in table 1.

Participants' baseline experience with mobile phone technology

Nearly half (42%) of patients used a social networking site daily, 44% accessed the internet using a cell phone daily and 44% had used WhatsApp (Facebook Inc., Menlo Park, CA, USA). Overall, 78% were very comfortable making and receiving phone calls, 70% with texting messages, 72% with taking pictures and 50% with recording videos with the cell phone (results not shown).

TABLE 1 Baseline characteristics of video directly observed therapy (VDOT) study participants (N=50)

Sex	
Female	22 (44%)
Male	28 (56%)
Age years mean (range)	31 (19–50)
Resides in Kampala	
Yes	22 (46%)
No	28 (54%)
Highest level of education attained	
None/primary, 0–7 years schooling	14 (28%)
Secondary, 8–14 years schooling	21 (42%)
Tertiary/university, >14 years	15 (30%)
Employment status	
Unemployed	10 (20%)
Formal employment	22 (44%)
Self-employed	18 (36%)
Monthly income USD# median (IQR)	80.8 (27–135)
HIV status	
Positive	14 (28%)
Negative	36 (72%)
Patient owned a cell phone	
Yes	48 (96%)
No	2 (4%)
Patient owned a smartphone	
Yes	35 (70%)
No	15 (30%)
Other household members owned cell phones	
None	13 (26%)
1–2 people	28 (56%)
⩾3 people	9 (18%)
Study-provided smartphone used for VDOT	
Yes	29 (58%)
No	21 (42%)

IQR: interquartile range. #: US$1~3700 Uganda Shillings.

Access to TB services, and concerns and preferences related to treatment at baseline

Most participants (54%) travelled by public transportation to the clinic and 34% experienced some difficulty with transportation (table 2). The mean cost for a round trip to the TB clinic was less than US $2.00, with a self-reported median travel time one-way of ~30 min and a waiting time of 15 min. Patients expressed concerns about family members (36%) and neighbours or friends (50%) learning about their TB status. 82% of patients preferred phone calls as a way of communicating with the health providers.

Adherence with VDOT and reasons for missed video submission

Cumulatively, 5150 videos were expected from participants during the study period and 4231 (82.2%) were received. The mean period of observation was 103 days (range 14–208 days). The median FEDO was 85% (table 3). Median FEDO did not differ significantly by sex, age group, or by phone status or phone use (loaned or personal) for VDOT. However, median FEDO significantly differed by duration of follow-up ($p<0.05$); the longer the duration, the higher the FEDO (figure 2).

Of the 919 missed videos, 541 (58.8%) represented doses that were not observed *via* video but were reported as self-administered treatment. The top three reasons reported by patients for missing video submission were phone malfunction (32%), dead phone batteries (24.2%) and possible technical problems with VDOT app (11%). Additional reasons for missed videos are shown in table 3.

Participants' experiences with VDOT at exit of study

Overall, most participants favoured the use of VDOT for treatment monitoring. 98% were satisfied with using VDOT and 88% found VDOT easy to use while all participants said they would recommend it to other patients (table 4). More than half of the patients reported that they rarely or never experienced

TABLE 2 Baseline access to tuberculosis (TB) services, and concerns and preferences related to treatment (N=50)

Usual transportation taken to TB clinic	
Taxi/bus	27 (54%)
Motorcycle, boda-boda	19 (38%)
Other, *e.g.* personal car/walked	4 (8%)
Cost for round-trip to TB clinic USD#	1.35 (0.81–2.16)
Time to reach TB clinic min	30 (20–60)
Time spent at TB clinic min	15 (10–20)
Experienced some difficulty with transportation to TB clinic	
Yes	17 (34%)
No	33 (66%)
Taking other non-TB medications daily	
Yes	14 (28%)
No	36 (72%)
Concerns about VDOT study¶	
No concerns	48 (96%)
Keeping the smart phone secure	1 (2%)
Money to pay for internet data	1 (2%)
Do not know how to use smartphone	1 (2%)
Concerned about family finding out about TB status or treatment	
Yes	18 (36%)
No	31 (62%)
Missing data	1 (2%)
Concerned about friends, neighbours, schoolmates or workmates finding out about TB status or treatment	
Yes	25 (50%)
No	14 (28%)
Do not know	11 (22%)
Preferred method(s) of communication with TB provider¶	
Phone call	41 (82%)
Text message	9 (18%)
In person	7 (14%)
Preferred method of TB treatment monitoring	
VDOT	45 (90%)
In-person DOT	1 (2%)
No preference	4 (8%)

Data are presented as n (%) or median (interquartile range). VDOT: video directly observed therapy; DOT: directly observed therapy. #: US$1~3700 Uganda Shillings; ¶: data sum to >50 as multiple responses were permitted.

problems with the VDOT app or the cellular network while uploading videos. The majority (80%) shared their VDOT experience with family members and 38% with friends or workmates.

Discussion

We found that VDOT was feasible and acceptable for monitoring TB treatment adherence in Kampala, Uganda, which is a high-burden setting. To our knowledge, there is no published study on the use of VDOT in this urban setting. Patients successfully recorded and submitted a high fraction of the expected videos to the VDOT system. Moreover, patients using VDOT were able to submit videos 7 days a week, including weekends, providing a more complete picture of medication dosing than the standard in-person DOT, which typically covers a 5-day period. A few prospective participants refused to enrol in VDOT for lack of time or needing to seek permission from other family members. We identified some technical challenges with smartphones and uncharged batteries leading to missed video submissions, but most participants were satisfied with using VDOT. These results are consistent with previous studies [27, 30–32, 38] and add to the evidence base that supports digital health as a promising intervention for supporting TB treatment in African settings [34].

In Uganda, adherence estimates, as measured by TB treatment completion rates, range from 67% to 77% according to the TB Control Program and health sector performance reports [39, 40]. In our study, the median FEDO of 85% using VDOT was similar to 88.4% reported by a study in Vietnam [9]. In contrast, a lower adherence of 74% was reported from a recent study in Kampala among patients attending two

TABLE 3 Adherence to video directly observed therapy (VDOT) and reasons for missed video submission (N=50)

Time under VDOT intervention days mean (range)	103 (14–208)
Total expected videos under VDOT	5150
Cumulative total videos received	4231 (82.2%)
Self-administered doses reported without videos	541 (10.5%)
FEDO with VDOT median (IQR)	85% (66%–94%)

Reasons for missed videos	Patients reporting	Videos missed
Phone malfunction	30	293 (32.0%)
Phone battery not charged	38	223 (24.2%)
VDOT app errors	13	97 (11.0%)
Ran out of TB medications	17	49 (5.3%)
Reported lack of internet connection	11	48 (5.0%)
Location not convenient or no private place to record	9	48 (5.0%)
Phone stolen#	7	37 (4.0%)
Took medication but forgot to record video	6	35 (3.8%)
Failed to use VDOT app, needed retraining	3	30 (3.3%)
Travelled to a place with no electricity	5	31 (3.4%)
No reasons specified	4	28 (3.0%)
Total		919 (100%)

FEDO: fraction of expected doses observed; IQR: interquartile range; TB: tuberculosis. #: five personal and two study phones.

public TB clinics using standard DOT [13]. Other studies of VDOT in the USA, Mexico, Belarus and the UK showed adherence ranging from 77% to 98% among TB patients [26, 27, 31, 32]. The differences in adherence results between our pilot study and other VDOT studies could be explained by variations in technological infrastructure and population samples. To ensure nonadherence was addressed in a timely manner, the research staff assessed actual medication doses swallowed even when videos were not submitted. Importantly, we accounted for an additional 10% of doses that were self-administered,

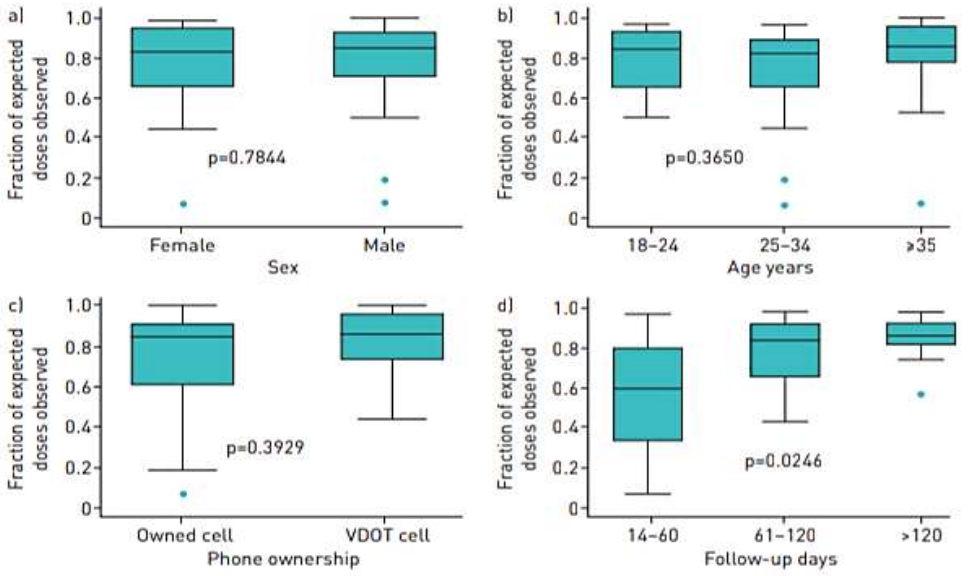

FIGURE 2 Boxplots of fraction of expected doses observed stratified by a) sex, b) age, c) phone ownership and d) follow-up duration. p-values based on Kruskal-Wallis test for comparison of medians. VDOT: video directly observed therapy.

TABLE 4 Participants' reported experiences using video directly observed therapy (VDOT) at exit of the study

Patient satisfaction with VDOT process	
How satisfied were you with your TB treatment monitoring using VDOT?	
Satisfied	49 (98%)
Dissatisfied	1 (2%)
Would you recommend VDOT to other TB patients?	
Yes	50 (100%)
Overall, how easy/difficult did you find the VDOT process?	
Easy	44 (88%)
Difficult	6 (12%)
If you had to redo the TB treatment, would you choose in-person DOT or VDOT?	
VDOT	49 (98%)
No preference	1 (2%)
In-person DOT	0 (0%)
How often did you take TB medication while away from home?	
Never	22 (44%)
Rarely	18 (36%)
About half the time or more	8 (16%)
About less than half the time	2 (4%)
How important was it for you to be able choose the time of day that you took your medications using VDOT?	
Very important	45 (90%)
Somewhat important	4 (8%)
Not at all important	1 (2%)
Experience with VDOT app	
How often did you have problems using the VDOT application?	
Never	17 (34%)
Rarely	11 (22%)
Less than half the time	13 (26%)
Half the time or more	9 (18%)
How often did poor cellular network reception cause you problems uploading videos?	
Never	19 (38%)
Rarely	17 (34%)
Less than half the time	9 (18%)
Half the time or more	5 (10%)
Patient perception of privacy and using VDOT	
Did you share your VDOT experience with family members?	
Yes	40 (80%)
No	10 (20%)
Did you ever share your VDOT experiences with your friends, neighbours, classmates or co-workers?	
Yes	19 (38%)
No	31 (62%)
Were you ever concerned someone would see you using the VDOT app on the cell phone?	
Yes	23 (46%)
No	27 (54%)
Did you ever fail to record a video because you were worried someone was watching you?	
Yes	9 (18%)
No	41 (82%)
What did you perceive about confidentiality of VDOT *versus* DOT?	
VDOT is more confidential	39 (78%)
VDOT is less confidential	1 (2%)
No difference between VDOT and DOT	3 (6%)
Don't know	7 (14%)

TB: tuberculosis; DOT: directly observed therapy.

potentially increasing the estimated overall adherence to 92%. When using VDOT, the follow-up process could inherently improve patient–provider interactions and engagement beyond the routine observation [9].

The World Health Organization has updated TB treatment guidelines to include the use of digital health interventions such as VDOT as alternatives to in-person DOT when operational conditions are appropriate for healthcare providers and patients [7]. The baseline experiences with cell phones and the

use of internet among participants show that this patient population was comfortable with the technology providing insights into future readiness for digital health interventions in Uganda. With the rapid expansion in mobile network coverage and smartphone ownership in resource-limited settings, such interventions are poised to become more feasible and scalable [41]. A key question that must be answered is: what will it cost to implement digital technologies? A study evaluating potential cost and impact of digital technologies for supporting TB treatment in high-burden settings projected up to 58% in cost savings when using medication monitors and video observed therapy [42]. But more studies on cost and cost-effectiveness of mobile technology interventions are needed to inform the local programme context. A preliminary cost analysis of the implementation of our VDOT pilot study is underway.

Stigma and privacy issues when using digital technologies in TB management are potential concerns that must be carefully considered [43]. In our study, patients reported that they were concerned about their family members, friends or neighbours finding out about their TB status, which could suggest underlying fear of being stigmatised. TB-associated stigma is a social determinant of health and has negative impacts on individuals including delays in seeking care, delays in TB diagnosis and nonadherence to treatment [44]. In relation to privacy, 18% of participants reported that they failed to record videos because of fear of being seen by someone. However, 78% perceived VDOT as more confidential than in-person DOT. In a similar VDOT study in California, USA, Garfein *et al.* [32] found comparable results, of 8% and 98% respectively, on the same issues. Although the evidence is limited, these findings may suggest that patients perceived using VDOT as more private as it relates to their TB status. This is consistent with a mixed-methods study by Wade *et al.* [38] in which most respondents felt that the videophone service improved patients' privacy.

For future adoption and scale-up of VDOT, TB programmes should address the main reasons that prevented video submission. For example, use of solar power banks or solar-powered smartphones could become future solutions to the problem of dead phone batteries. Phone malfunctions might have been due to the lower quality of cheap personal smartphones. TB programmes may need to set minimum requirements of the devices to be used for VDOT interventions. Despite some technological challenges, most participants were satisfied with using VDOT, suggesting that the benefits might have outweighed the difficulties faced from the patients' perspective. Previous studies indicate that a high level of patient satisfaction with services generally predicts high levels of adherence to TB treatment [45].

Our pilot results may not be generalised to the whole of Uganda because we used a convenience sample of participants at an urban TB clinic; nonetheless, we gained preliminary insights about feasibility of using of VDOT. Self-selection could have biased the results towards overestimation of adherence in our study. Due to limited resources, we did not evaluate important clinical outcomes such as sputum culture conversion and cure. However, it is reasonable to assume that better adherence should result in improved clinical outcomes. We cannot draw conclusions about effectiveness of VDOT since there was no control group. Therefore, comparative studies to evaluate efficacy of VDOT are logical next steps. Implementation research is needed to further understand potential barriers and facilitators for adoption or effective scale-up of digital health intervention in the context of local TB programmes.

Conclusions

VDOT was feasible and acceptable as a method of monitoring and supporting adherence among patients receiving TB treatment in urban Uganda. A relatively large proportion of the missed videos were due to technical malfunctions rather than a loss of patients' motivation to submit their videos of medication intake. Evaluating the implementation process of digital technologies in comparative studies is an important next step in strengthening TB patient care in low-resource settings [46].

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MAJOR ARTICLE

Advancing Patient-Centered Care in Tuberculosis Management: A Mixed-Methods Appraisal of Video Directly Observed Therapy

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Background. Directly observed therapy (DOT) remains an integral component of treatment support and adherence monitoring in tuberculosis care. In-person DOT is resource intensive and often burdensome for patients. Video DOT (vDOT) has been proposed as an alternative to increase treatment flexibility and better meet patient-specific needs.

Methods. We conducted a pragmatic, prospective pilot implementation of vDOT at 3 TB clinics in Maryland. A mixed-methods approach was implemented to assess (1) effectiveness, (2) acceptability, and (3) cost. Medication adherence on vDOT was compared with that of in-person DOT. Interviews and surveys were conducted with patients and providers before and after implementation, with framework analysis utilized to extract salient themes. Last, a cost analysis assessed the economic impacts of vDOT implementation across heterogeneous clinic structures.

Results. Medication adherence on vDOT was comparable to that of in-person DOT (94% vs 98%, $P = .17$), with a higher percentage of total treatment doses (inclusive of weekend/holiday self-administration) ultimately observed during the vDOT period (72% vs 66%, $P = .03$). Video DOT was well received by staff and patients alike, who cited increased treatment flexibility, convenience, and patient privacy. Our cost analysis estimated a savings with vDOT of $1391 per patient for a standard 6-month treatment course.

Conclusions. Video DOT is an acceptable and important option for measurement of TB treatment adherence and may allow a higher proportion of prescribed treatment doses to be observed, compared with in-person DOT. Video DOT may be cost-saving and should be considered as a component of individualized, patient-centered case management plans.

Keywords. mHealth; medication adherence; telemedicine; tuberculosis; video DOT.

Tuberculosis (TB) remains a global pandemic responsible for nearly 2 million deaths annually [1]. In the United States, previously reported declines in incident disease have stagnated in recent years [2, 3].

A central challenge in the fight against TB is overcoming the barriers presented by TB therapy itself. Side effects are common, and treatment courses are long, extending well beyond a year in some cases of drug-resistant disease [4, 5]. Poor treatment adherence has been linked to microbiologic failure, disease relapse, and the emergence of drug resistance [6, 7].

In response, and in an effort to promote treatment completion, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have advocated for directly observed therapy (DOT), wherein the ingestion of each dose is directly monitored [4, 8, 9]. Programmatic uptake of DOT has been widespread. Within the United States, DOT is now the standard of care, and is even codified into law in many states [10].

Despite broad policy support, more recent studies looking at the effectiveness of DOT on treatment outcomes have been mixed, likely owing to heterogeneous approaches to implementation [11–13]. Nonetheless, current treatment guidelines, including that from the CDC, continue to underscore the importance of DOT, but now emphasize its role as just 1 component of a multifaceted approach to case management and treatment support [4, 14]. Further, "To be consistent with the principles of patient-centered care, decisions regarding the use of DOT must be made in concert with the patient" [4]. As such, DOT implementation must account for patient-specific needs, and should ideally couple observation of pill ingestion with strategies for adherence support.

Employing DOT in a patient-centered fashion can be challenging. Scheduling in-person DOT visits is logistically complicated and resource intensive (for patients and TB programs) and can increase both patient- and program-level costs. In some individuals, logistical barriers and perceived stigma related to DOT have led to feelings of humiliation, loss of control, and stress [15, 16]. In some situations, DOT requirements may therefore represent a barrier to adherence. What's more,

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provisions for DOT may impact provider prescribing practices. While updated TB guidelines advocate daily therapy (ie, 7 days/week), our experiences suggest that health departments commonly dose TB medications Monday through Friday (M–F, ie, business days) only, or intermittently (ie, 3 days/week), in an effort to facilitate in-person DOT.

To overcome these barriers, video-based DOT (vDOT) has been proposed as an alternative to in-person observation [4, 14, 17]. Early in 2017, the CDC released a toolkit for the implementation of vDOT within TB programs [18]. However, given the limited experience with vDOT, the guideline cautions against its use in complex patients, including those with "adherence issues," "language barriers," and "multi-drug resistance," and acknowledges the need for operational research. This approach, however, may restrict usage in those with complex treatment factors who could potentially benefit most from the added flexibility provided by vDOT.

As such, we designed a pilot implementation study to address several gaps in our current understanding of vDOT implementation [19–27]. We utilize a mixed-methods approach to evaluate (1) feasibility, (2) accessibility, and (3) costs when implemented under real-world conditions. First, we sought to understand feasibility and acceptability in broad patient populations, including those with previously poor adherence and drug-resistant disease. Second, we sought to assess effectiveness for observation of therapy and costs. Finally, we sought to describe implementation challenges and successes, patient selection for vDOT, and the impact of heterogeneities in clinic structure.

METHODS

Overview

We conducted a pragmatic, prospective pilot implementation study. Our objective was to assess the feasibility, acceptability, and cost of vDOT utilizing a Health Insurance Portability and Accountability Act (HIPAA)-compliant mobile app, miDOT (emocha Mobile Health Inc.), for TB treatment monitoring, adherence support, and case management (Supplementary Figure 1). The study was carried out within 3 public health TB clinics in Maryland that service a mixed urban/suburban population. Protocols were approved by the ethics committees at Johns Hopkins University, the Baltimore City Health Department, and the Maryland Department of Health.

Study Population

All adult patients receiving active TB treatment or short-course isoniazid/rifapentine-based latent TB (LTBI) therapy were eligible for participation. Inclusion required that patients be ≥18 years of age and have ≥2 months of therapy remaining. All patients initiated TB therapy with in-person DOT, though they could transition to vDOT at any point during their treatment course. The decisions to offer vDOT were made by nonconflicted health department clinicians, without explicit exclusion of non-English speakers or those with multidrug-resistant disease or poor prior adherence. Patients interested in utilizing vDOT provided written informed consent, and those without access to a smartphone were provided one by the study.

TB Treatment

Treatment decisions were clinic-directed according to Maryland state and CDC guidelines, regardless of DOT modality [4, 28]. Under these guidelines, drug regimens generally rely on either daily or intermittent (3 days/week) dosing. While studies have not compared the efficacy of 5 vs 7 doses per week, under DOT, both regimens were referred to as "daily" [4]. Each clinic defined treatment completion and success based on ingesting a set number of target doses. Any missed doses were added to the end of therapy, extending treatment duration. At baseline, for daily dosing, TB clinics combined in-person DOT 5 days/week (M–F) with weekend (and holiday) self-administration, the latter not contributing to the overall dose target. While on vDOT, dosing frequency (ie, 5 days/week vs 7 days/week) and whether to observe and count weekend doses toward an overall dose target were left to clinic discretion. Patients were sent twice-daily SMS reminders in the absence of submitted videos and were prompted to document side effects prior to each submission (see the Supplementary Data for more on miDOT specifics). All patient data, servers, and transmissions were encrypted to protect patient privacy, and the app automatically deleted videos from the smartphone upon transmission (Figure 1).

Feasibility and Effectiveness

We assessed 2 primary outcomes, acknowledging a lack of consensus definition on measurement of adherence and differences in programmatic practices related to "expected" doses. The first was *treatment adherence*, or the proportion of "expected" DOT (in-person or video) that was successfully completed, in which the "expected" dose was defined by the TB clinic (usually omitting weekend and holiday self-administered doses) (Supplementary Figure 2). Given that the goal of DOT is to observe all prescribed doses, as a secondary measure, we calculated the *observable fraction*, or the proportion of total doses (inclusive of weekends, holiday, or other "self-administered" doses) completed under observation (either in-person or by video). All patients received case management per routine at each TB clinic site irrespective of DOT modality; this generally included case management phone calls or visits following missed doses or reported side effects.

Differences pre/post–vDOT implementation were evaluated using paired t tests, though our study was not powered, nor specifically intended, to detect between-group differences. All analyses were conducted in STATA 14.

Acceptability

Qualitative research methodology was employed to explore participant and staff perceptions of in-person and vDOT. All clinic staff (DOT workers, case managers, clinicians) and enrolled patients

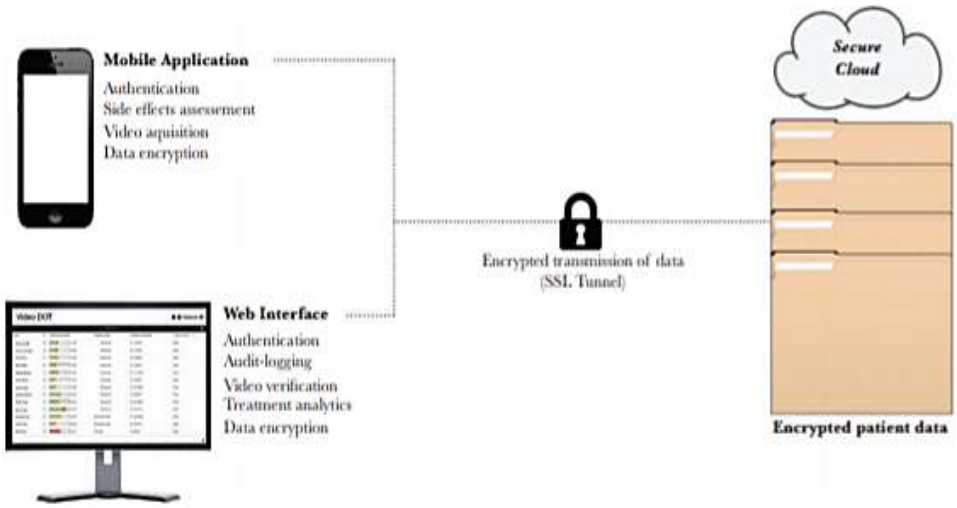

Figure 1. Schematic of data acquisition and transmission on miDOT.

were approached to complete surveys and in-depth interviews pre/post–vDOT implementation; a separate informed consent was used, and patients could enroll in the study without participation in the qualitative component. All interviews were digitally recorded and transcribed verbatim. Each transcription was reviewed by 2 study members, and an iterative, open-coding strategy with framework analysis was employed to identify salient themes [29].

Cost

A cost analysis was conducted using time motion studies and an ingredients-based approach in which unit costs for labor, equipment, and consumables were multiplied by quantities required for in-person DOT and vDOT (Supplementary Table 5). To allow equal comparisons, final calculations were standardized to a 6-month treatment course (daily therapy) for drug-sensitive TB; based on clinic practices, primary analysis was standardized to a M–F dosing strategy, with a secondary analysis comparing 7-day/week therapy.

In base case analysis, we incorporated costs for a licensed practical nurse (LPN) utilizing a Department of Health (DOH)–owned vehicle for community-based, in-person DOT. For vDOT, the base case scenario incorporated costs of a program-provided smartphone (and associated data costs) and an estimated commercial software cost of $50 per patient per month (personal communication, emocha).

Sensitivity analysis was conducted to evaluate variations in consumable, labor, and equipment costs with consideration of programmatic heterogeneity in the implementation of in-person DOT (eg, type of staff conducting DOT, vehicle used, and travel distance) and vDOT (eg, range of software-associated costs from a high of $100 per patient per month to free) (Supplementary Figure 3).

RESULTS

A total of 28 patients were enrolled and treated between March 2016 and August 2017. Of these, 25 received active TB therapy and 3 received weekly rifapentine/isoniazid (INH) for LTBI (Table 1). Ninety-three percent of patients were foreign born. Only 3 patients (11%) required use of a study phone for vDOT. Thirty-nine percent had extrapulmonary disease, consistent with regional and national epidemiology [30, 31].

Among active TB patients prescribed "daily" therapy (at any point during their treatment), a dosing strategy of DOT 5 times/week (M–F) with weekend self-administration was the most common observation strategy regardless of DOT modality, though it was more frequent during the in-person period (100% vs 76%, $P = .01$). Overall, intermittent thrice-weekly therapy was utilized less commonly on vDOT than during in-person (24% vs 16%, $P = .32$). No patients received 7 days of in-person DOT, though 2 were transitioned to this schedule while on vDOT. The mean times on therapy for in-person DOT and vDOT were 12.2 and 19.2 weeks, respectively ($P = .01$).

Feasibility/Effectiveness

Measured *adherence* was high irrespective of DOT strategy: median 98% (interquartile range [IQR], 90–100) during in-person DOT and median 94% (IQR, 88–98) while on vDOT ($P = .17$) (Table 2). The median *observable fraction* (ie, proportion of all prescribed doses observed) was statistically lower during the in-person DOT period (in-person, 66% [62%–72%]; vs vDOT, 72% [67%–92%]; $P = .03$). Overall, only 15% of patients had more than 80% of total prescribed doses verified through observation during in-person DOT, compared with 36% during vDOT ($P = .01$), a consequence of self-administered weekend and holiday doses.

Table 1. Patient Characteristics

Variable	No. (%) (n = 28)
Age, median (IQR), y	32 (23–49)
Female, No. (%)	16 (57)
Foreign born, No. (%)	26 (93)
Origin, No. (%)	
United States	2 (7)
Africa	11 (39)
Latin America	8 (29)
South Asia	4 (14)
East Asia	2 (7)
Europe	1 (4)
Time in United States, median (IQR),[a] y	5 (3–15)
Limited or no English,[b] No. (%)	7 (25)
Travel to TB endemic country within 5 y, No. (%)	19 (67)
Highest level of education reached, No. (%)	
Grade school	3 (12)
High school	10 (38)
College	9 (35)
Postgraduate	4 (15)
Employment, No. (%)	
Full-time	16 (57)
Part-time	7 (25)
Unemployed	5 (18)
Annual household income,[c] No. (%)	
<$20 000	8 (36)
$20 000–$49 999	9 (41)
$50 000–$100 000	4 (18)
>$100 000	1 (5)
Substance use,[c,d] No. (%)	
Tobacco	1 (4)
Alcohol	1 (4)
Illicit drugs	1 (4)
Comorbidities, No. (%)	
HIV infected	2 (7)
Hypertension	2 (7)
Diabetes	1 (4)
History of malignancy	2 (7)
Taking daily (non-TB) medications, No. (%)	6 (21)
Technology, No. (%)	
Regular access to smartphone	25 (89)
Required study phone[e]	3 (11)
Tuberculosis type, No. (%)	
Pulmonary	9 (32)
Smear positive	5 (18)
Smear negative	11 (39)
Exclusively extrapulmonary	
Latent	3 (11)
MDR disease,[f] No. (%)	1 (4)

Abbreviations: IQR, interquartile range; MDR, multidrug-resistant; TB, tuberculosis.

[a]Calculated for foreign-born individuals only, those reporting "less than 1 year" were considered to have been in the United States for 6 months for statistical purposes.

[b]Included 6 Spanish speakers and 1 Oromo.

[c]Excludes those for whom data were unknown.

[d]Represents 3 separate patients.

[e]All 3 phones were returned at study completion in good working order.

[f]Refers only to those treated for active TB. All LTBI patients received weekly rifapentine for 12 weeks.

Fifty-seven percent of patients had at least 1 rejected video (mean, 1.8; range, 0–11), representing 2.1% of all submitted videos (2350). The 2 most commonly cited reasons for rejection were "Medication dose not visible" and "Poor video quality."

A total of 4 patients traveled internationally while on miDOT, though they continued to successfully submit videos. Two patients were transferred from Health Department care after permanently leaving the United States prior to treatment completion (1 to Liberia and 1 to Ivory Coast); both had been on vDOT for >16 weeks with adherence of 72% and 87%, respectively, at the time of study exit. A single patient had vDOT discontinued prematurely after 5 weeks due to an adherence of 63% (on 7 days/week of DOT); the patient had been on in-person DOT for 17 weeks prior to vDOT, expressed an interest to return to her prior routine of in-person DOT, and successfully completed therapy with an adherence of 100%.

Acceptability

All staff and patients were approached to explore attitudes toward in-person DOT and vDOT. Twenty staff members participated before vDOT implementation, and 16 post-implimentation; 25 patients were included before vDOT, with 10 providing post-treatment feedback. vDOT adherence did not differ between patients completing and those not completing post-intervention qualitative assessment (adherence, 89% vs 90%; $P = .92$).

At baseline, nearly all staff members felt that in-person DOT provided beneficial social support (95%), and only a few (10%) considered self-administered therapy to be sufficient alone (Supplementary Tables 1 and 2). Both staff (95%) and patients (92%) were comfortable using smartphones from the outset. Following the intervention, all surveyed patients felt that the miDOT platform was "easy to use" and preferred it over in-person DOT.

Themes related to this preference for vDOT were common during interviews and focused on convenience and increased flexibility (Table 3; Supplementary Tables 3 and 4). Both patients and staff commented on the limitations of in-person DOT when managing complex schedules. Speaking to the impact of foreign travel, 1 staff member noted, "We try to arrange jurisdictional coverage during [travel] times, but if it's outside the country, you really can't."

Another prominent theme was the impression that in-person DOT threatened patient privacy. This concern appeared to be driven by the public optics of daily visits (at home/work) from DOH staff. In speaking to this concern, 1 patient stated, "Sometimes they meet me…at work…. I'm afraid I'll be seen." The added flexibility provided by vDOT seemed to allay these fears. As 1 nurse commented, "You can do [vDOT] in your car on the way to work. You can sit out in your driveway and do it…. It's more private than having a nurse come to the house." Notably, no patients or staff raised concerns regarding data security with the use of mobile phones to share private health information.

Table 2. Primary Outcomes by DOT Strategy

Variable	In-Person DOT	vDOT	*P*
Adherence,[a] median (IQR), %	98 (90–100)	94 (88–98)	.17
Observable fraction,[b] median (IQR), %	66 (62–72)	72 (67–92)	.03
No. (%) of patients with observable fraction greater than a target 80%	4 (15)	10 (36)	.01
DOT schedule among active TB patients (n = 25),[c] %			
3x/wk DOT	6 (24)	4 (16)	.32
5x/wk DOT	25 (100)	19 (76)	.01
7x/wk DOT	0 (100)	2 (8)	.16
Treatment length, wk			.01
Mean ± SD	12.22 ± 6.5	19.2 ± 9.7	
Range	0–26	5–37	
No. of rejected videos			
Mean (SD)		1.8 (2.4)	
Range		0–11	
Unexpected video submission			
Mean (SD)		2.7 (5.3)	
Range		0–20	
Patients reporting ≥1 side effects via mobile platform,[d] %		46	
Video length, median (IQR), sec		48 (29–63)	
Video size, median (IQR), mb		4.8 (1.4–5.8)	

Abbreviations: DOT, directly observed therapy; IQR, interquartile range; TB, tuberculosis; vDOT, video directly observed therapy.

Only participants treated for active TB included in = 25).

[a]Percentage of "expected" DOT doses (in-person or video) completed, excluding self-administered doses (ie, weekends or clinic holidays). An additional, less stringent analysis was also conducted wherein "completed" vDOT was loosely defined to include both verified and rejected mDOT videos: in-person 98% (90%–100%) vs vDOT 96% (89%–100%), *P* = .37.

[b]Percentage of total planned doses (inclusive of weekend/holiday self-administered) that were observed (in-person or video). For vDOT, "observation" was loosely defined to include all forms of uploaded mDOT videos (verified, rejected, unexpected), though only 1 video was counted for a given dosing day. An additional, stricter analysis was also conducted wherein, for vDOT, "observation" referred only to verified videos: in-person 66% (62%–71%) vs vDOT 70% (63%–90%), *P* = .22.

[c]Total number of regimens exceeds sample size (n = 25, active TB only) as some participants had >1 dosing frequency during their therapy.

[d]The mDOT video system prompts patients to indicate side effects prior to video submission using checkboxes on the mobile app, with positives resulting in an automatic provider alert. The most common symptom reported was abdominal pain, followed by weakness. Other reported side effects included nausea/vomiting, rash, sores on lips/mouth, joint pain, yellowish skin or eyes, and other. Of note, some patients digitally captured side effects during the video recordings (eg, rash).

While an uncommon theme, 1 nurse manager discussed a fear of displacement among staff, stating, "Some DOT workers worry that video DOT will take their jobs." At the same time, she went on to highlight the ability of vDOT to maximize clinic resources, noting, "[vDOT] actually helps because a lot of the time we're short [staffed and] when you have this.... You don't want your workers running around the streets all day." Further, it was noted that DOT workers could take on larger patient panels and spend more individual time face to face with those remaining on in-person DOT. Additional comments and themes can be found in the Supplementary Data.

Cost Analysis

In our primary analysis (observation 5 days/week for a 6-month course), we projected that vDOT implementation would lead to an incremental cost-savings of $1391 per person compared with using in-person DOT (Table 3).

Cost for in-person DOT was driven largely by labor. In our primary analysis, labor costs totaled $1838, amounting to >90% of the overall DOT expenditure for a standard TB treatment course (Table 4). Labor costs varied markedly in sensitivity analysis based on health care worker type (eg, community health worker [CHW] vs registered nurse [RN]); overall, we estimated total in-person DOT costs at $866 to $5616.

For vDOT, we found that costs were driven by consumables, namely estimated software ($0–$100 per month) and data costs. In our base case, consumable costs totaled $495 ($0 to $900), comprising two-thirds of net treatment costs. Labor costs were low, totaling only $131 ($62–$413) and accounting for <20% of overall costs ($674). At the highest estimates of consumable costs ($900), driven by a monthly charge of $50 for data and $100 for software, vDOT was still associated with a cost-savings of roughly $1000 per treatment course, compared with in-person DOT.

DISCUSSION

In our pragmatic mixed-methods implementation of treatment monitoring strategies at 3 separate public health TB clinics in Maryland, we found broad patient and staff acceptability of vDOT, with similar adherence and an increased proportion of prescribed doses confirmed through observation. Our economic evaluation suggests potential cost-savings with vDOT, when compared with exclusive usage of in-person DOT. Our study is unique compared with prior evaluations of vDOT in its broad patient inclusion criteria, allowing for a real-world assessment and insights related to vDOT implementation. In-depth interviews with patients and staff revealed that TB programs considered vDOT a preferred option for patients in whom in-person

Table 3. Subset of Themes from Qualitative Analysis

Theme	Subtheme	Representative Quote
Patient		
Impact of DOT on patients	sDOT can be burdensome for patients	"I'm about to start a class, and the class…doesn't really match the time that I have to be here to take the pill.… I won't be able to do the class, and I need the class more than I need [DOT]."
	sDOT can cause emotional stress	"In-person DOT had an emotional impact on me; it was stressful. It made me resent [the treatment team]."
DOT logistics	sDOT efficacy is limited by patient factors	"[sDOT] just doesn't work. Like tonight, I work, I don't get off until 7:30 AM, and then I go to school.… There is no time."
	vDOT increases access to transient patients	"When I was in Peru for 2 months, the system worked perfectly. Sometimes I even used it outside of the city or at the beach."
	vDOT increases access to those with complicated work schedules	"I have very long working hours.… It's not possible for me to meet with a DOT nurse.… With video DOT, I could continue with my work and still take the medicine."
Confidentiality	sDOT can violate patient privacy	"When somebody has to come to your house driving that [DOH] car, coming in…the whole neighborhood's going to look and start asking questions."
	vDOT is more private than sDOT	"With [vDOT], we can control [the] setting we are in.… It's in your hand[s].… Just avoid taking videos in places where you can be viewed by others.… We have control."
Provider		
Impact of DOT on staff	vDOT convenient for staff	"Especially for people who have to get up very early in the morning to go to work, [vDOT] saves us from having to…be at their house at 5:00 AM."
	vDOT may threaten livelihood	"The only rumor that I'm hearing is that some of the DOT workers are thinking that [vDOT] is going to take their jobs."
Treatment effects of vDOT	vDOT able to shorten therapy	"For patients who aren't [home] during our normal hours, video DOT…is much more effective.… They can dose anytime during the daytime as long as they have their phone available…and they're still getting a counted dose.… We can actually count that dose towards their end goal as an observed dose, and their treatment is shortened by several days."
	vDOT allows for observed therapy 7x per week	"The ability to do 7 days a week [with vDOT], rather than 5, is really kind of uncharted territory.… We don't actually know whether people are taking their medicines over the weekends, and a lot of programs don't even prescribe weekend packs, which when you think about it is sort of odd."
vDOT on clinic operations	vDOT may increase clinic capacity	"I don't have to spend 2 hours, 3 hours in the morning driving all over and around the county. It frees me up time-wise enormously. I can see more patients in my office."
Decisions about DOT should be patient centered	Some with poor adherence on sDOT may actually do better on vDOT	"We [had a] patient that was highly nonadherent in standard DOT. She was missing 3 or 4 doses a week.… We were going to quarantine this individual, but [we decided to] attempt video DOT, and…for about a month or 2 [she] was nearly 100% adherent on a 7-day regimen of medicine on video DOT."

Abbreviations: DOT, directly observed therapy; sDOT, standard directly observed therapy (ie, in-person); vDOT, video directly observed therapy.

"Only a subset of themes presented. For the full list, see Supplementary Tables 3 and 4.

DOT was logistically infeasible (eg, complex schedules or travel where the alternative was self-administration) or represented a barrier to care (eg, stigma). Program managers reported that associated time- and cost-savings allowed task-shifting with redistribution of limited clinic resources. Overall, our results suggest that vDOT is able to more effectively measure TB treatment adherence (including weekends and holidays), compared with in-person DOT, and can be successfully integrated into patient-centered, individualized case management plans that result in high rates of adherence and treatment success.

Our study has several important limitations. Given current TB case rates, our sample size was modest, and we were not powered to identify small changes in adherence. Nonetheless, we found improvements in the "observable fraction" of prescribed doses with vDOT, and our study is strengthened by in-depth qualitative and cost analyses that will help guide future larger-scale public health implementations. We did not assess for clinical end points, such as sputum conversion or disease relapse. While our study design allowed for within patient comparisons, these data must be interpreted with caution given the potential for time-varying confounders, such as medication adherence, which is known to decline as patients feel better and undergo treatment fatigue [32]. These factors could have reduced the observed vDOT adherence compared with in-person DOT, given vDOT initiation later in the treatment course. Lastly, our study sample was based on clinic (and patient) discretion and was not randomized; as such, our conclusions may not apply to all patients indiscriminately. Nonetheless, we included a range of TB patients, from the latently infected to those with extrapulmonary disease, and did not exclude patients based on prior adherence. Furthermore, it is important for TB programs to consider that while observation of pill ingestion may facilitate measurement of adherence, it is not the sole determinant of one's adherence; reported adherence and treatment outcomes may therefore differ according to how DOT services are integrated into broader case management strategies. At our study sites, all patients continued to receive dedicated case management and other adherence support interventions per routine, irrespective of DOT modality (particularly after missed doses or reported side effects). As such, our quantitative and qualitative

Table 4. Cost Analysis of vDOT Implementation

	DOT Strategy	Equipment	Consumables	Labor[f]	Total	Incremental
DOT 6x per week	In-person DOT (range)	$175[b] ($0–$562)	$52[c] ($29–$648)	$1838 ($869–$4406)	$2065 ($898–$5616)	Ref
	vDOT (range)	$48[d] ($4–$136)	$496[e] ($0–$900)	$131 ($62–$413)	$674 ($66–$1449)	−$1391
DOT 7x per week	In-person DOT (range)	$175[b] ($0–$562)	$72[c] ($40–$907)	$2573 ($1217–$6169)	$2820 ($1234–$7638)	Ref
	vDOT (range)	$48[d] ($4–$136)	$495[e] ($0–$900)	$183 ($87–$578)	$726 ($91–$1614)	−$2094

Abbreviations: DOT, directly observed therapy; vDOT, video directly observed therapy.

[a]Cost are per patient and calculated for a standard 6-month treatment course.

[b]Base case assumes a Health Department vehicle (economy class) used to treat 15 patients per year, annualized over the expected lifespan of the vehicle. In the sensitivity analysis, we varied the number of patients treated annually and calculated alternative pricing structures, including ones wherein health care workers utilized a personal vehicle and received mileage reimbursement.

[c]Base case assumes a program-provided smartphone and dedicated clinic computer. The sensitivity analysis incorporates the scenarios wherein a patient phone/data are used for vDOT (ie, no clinic cost incurred).

[d]Miles traveled was estimated from discussions with clinic managers, DOT workers, and through evaluation of monthly gas and mileage reimbursements logs. Range incorporates fluctuations in gas price and variability in the distance between patients.

[e]Software estimates were provided directly by emocha Mobile Health Inc., with the base case assuming a flat monthly rate of $50 per patient per month. The low-end estimate assumes free software and a patient-provided data plan, while the high-end accounts for variable data costs and a flat monthly software fee of $100 per patient. Commercial pricing may vary.

[f]Base case assumes an LPN conducting DOT activities. Time spent per patient was calculated as an average of that observed through time motion studies. The low range assumes a community health worker and the lowest possible estimates of time per patient. The high range assumes an RN (highest salary) and uses the highest possible estimate for time spent per patient. Note, labor cost is calculated based on the time required specifically for DOT activities.

results provide support for the promotion of individualized case management plans and argue against a "one size fits all" strategy for providing treatment support and treatment monitoring.

Overall, our study provides needed insights on key aspects of vDOT usage related to patient selection, implementation, effectiveness, and costs. We found that many patients were ultimately enrolled because of social factors thought to preclude, or at least impact, the ability to conduct in-person DOT. For example, several patients were able to have treatment observation and adherence measurements using vDOT while traveling outside of the United States. Such examples have practical implications. In most public health TB programs, prior to vDOT implementation, such doses (taken under self-administration) would not have "counted" toward treatment progress (ie, would need to be made up), ultimately prolonging treatment.

Beyond facilitating early recognition of poor adherence or side effects, DOT also has other critical roles in promoting successful TB control. In the absence of a biological marker for disease cure, TB programs base treatment completion on a prespecified number of treatment doses [4]. When applied consistently, DOT therefore serves as a key method to measure adherence and represents a mechanism to track treatment progress. In this regard, our study highlights an important consideration in adherence measurement and dosing frequencies. Current treatment guidelines have placed increasing emphasis on daily (7 days/week) therapy, though they still accept a 5-day/week alternative "daily" schedule (for drug-sensitive disease), acknowledging that "there are no studies that compare 5 to 7 daily doses" [4]. Given logistical constraints, many TB programs in the United States utilize a hybrid treatment schedule, wherein a regimen of 5 days of DOT (M–F) is coupled with self-administered weekend doses; some programs omit weekend doses altogether. Self-administered weekend (or holiday) doses are generally not applied to the overall treatment dose count or adherence calculations (ie, they are not "expected" and are not "made up" if missed). In effect, with current practices, "in-person DOT" is only able to measure 5 of 7 (71%) prescribed weekly doses.

We therefore a priori chose to report a related metric, the observable fraction, to quantify the true percentage of prescribed doses, inclusive of weekend self-administration, that could be measured through observation (in-person or video). Prior to the study, we assumed that clinics would move away from intermittent dosing regimens, in favor of 7-day/week therapy upon transition to vDOT. Ultimately, we did see a significant 8% increase in the observable fraction upon transition to vDOT; however, the absolute fraction was only 76% (vs 68% with in-person DOT). This result stemmed from the fact that only 2 participants had their monitoring frequencies increased to 7 days/week on vDOT, likely a result of entrenched provider practices. For example, some clinics explicitly instructed patients not to submit weekend videos, while others actively rejected any such submissions. Our study demonstrates the need to adapt clinic workflows to this new monitoring approach, as vDOT ultimately enables the expansion of treatment monitoring to 7 days/week and eliminates the need for self-administered doses. This increase in the number of observable doses is likely to reduce overall treatment duration by eliminating the need to make up extra doses related to self-administered or unobserved doses (under the assumption that programs only count observed doses toward treatment progress).

Finally, our study provided the first in-depth cost analysis of asynchronous vDOT. We found marked heterogeneity across health departments, both in terms of staffing and the operational implementation of in-person DOT. Despite this diversity, we estimated vDOT to save programs at least $1000 per patient if implemented for a standard 6-month treatment course (vs 5 days per week in-person DOT). When considering TB clinic costs and staffing overall, it is important to acknowledge that DOT represents 1 of several TB treatment– and case management–related activities. During our in-depth interviews, a single CHW expressed concerns about

being displaced by this new technology; such considerations need acknowledgment during implementation. However, several staff members also presented alternative perspectives noting that vDOT allowed for increased time and attention to be directed toward other required activities (eg, contact investigations, patient counseling, and social support). In an era of increasing responsibilities and limited funds, maximizing staff potential is often a necessity.

Overall, our study contributes to the growing literature on usage of alternative modalities for TB treatment monitoring and expands on prior efforts by demonstrating the feasibility, acceptability, and cost-savings in a previously unstudied environment and among a broader patient population [20–23]. By using a rigorous mixed-methods implementation science approach, our results identified and highlighted several important considerations related to patient selection, treatment frequency, and measurement of adherence that will guide policy makers and TB programs considering vDOT implementation. Importantly, our findings suggest the need for flexible, individualized case management plans that consider patient needs while achieving public health goals.

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Conflicts of interest. Dr. Shah is one of the inventors of the miDOT technology. Under a license agreement between emocha Mobile Health Inc. and the Johns Hopkins University, Dr. Shah and the university are entitled to royalties on the technology described in this article. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. To mitigate any potential conflicts of interest, all clinical decision-making regarding the use of miDOT or enrollment in the study was made by nonconflicted Department of Health clinicians and staff; M.S. recused himself from all data analysis but assisted with interpretation of results.

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Lampiran Artikel 9

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Early View

Original article

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

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ABSTRACT

Introduction

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

Methods

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

Results

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

Discussion

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

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

INTRODUCTION

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

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

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

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

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

METHODS

Study design

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

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

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

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

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

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

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

Procedure - DOT

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

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

Procedure - VOT

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

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

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

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

Sample

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

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

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

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

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

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

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

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

Outcomes and analysis

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

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

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

RESULTS

Primary Outcome: Adherence

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

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

Table 3: Regression of Primary and Secondary Outcome Measures

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

Standard errors in parentheses

Model: Column 1: Linear regression with standard errors clustered at the patient level; Columns 4, 6 and 7: Linear regression with heteroskedasticity robust standard errors. Columns 2, 3, 5, 8 and 9: Logistic regression with heteroskedasticity robust standard errors, coefficients show odds ratios.

Coefficients are omitted when they predict success perfectly/are collinear.

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

Secondary Outcomes (Figure 2)

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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Figure 1: Consort Flow Diagram

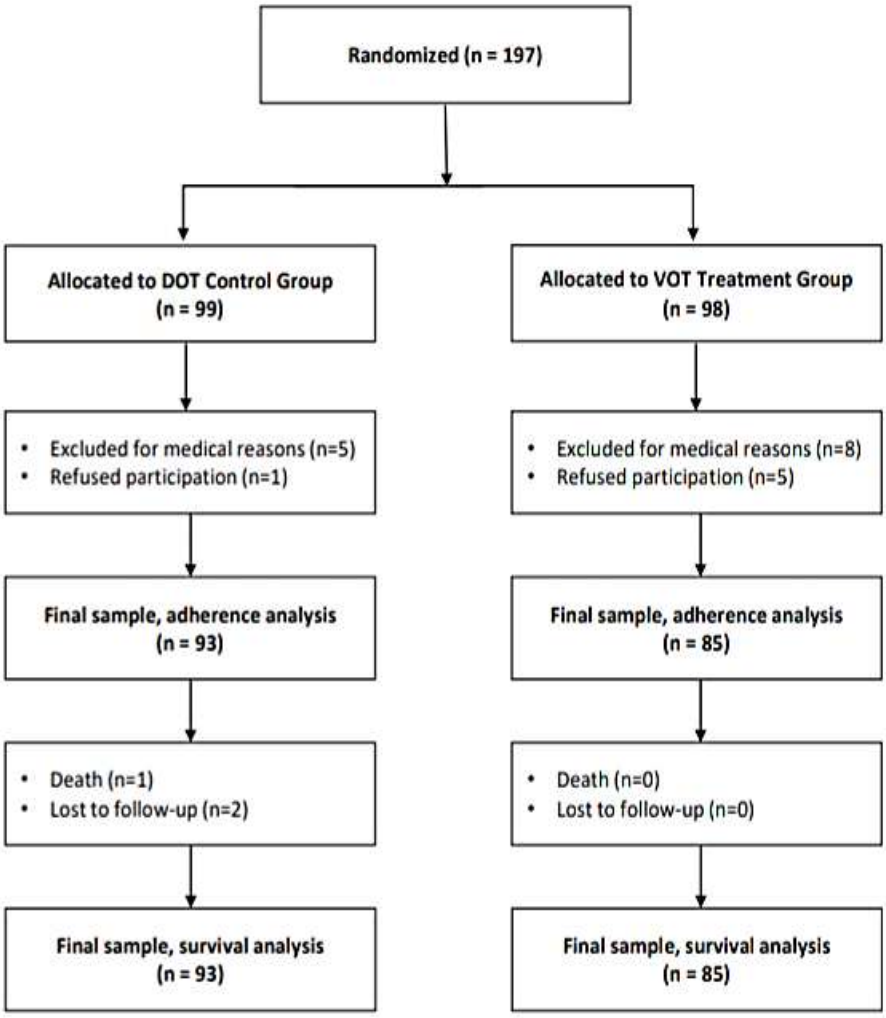
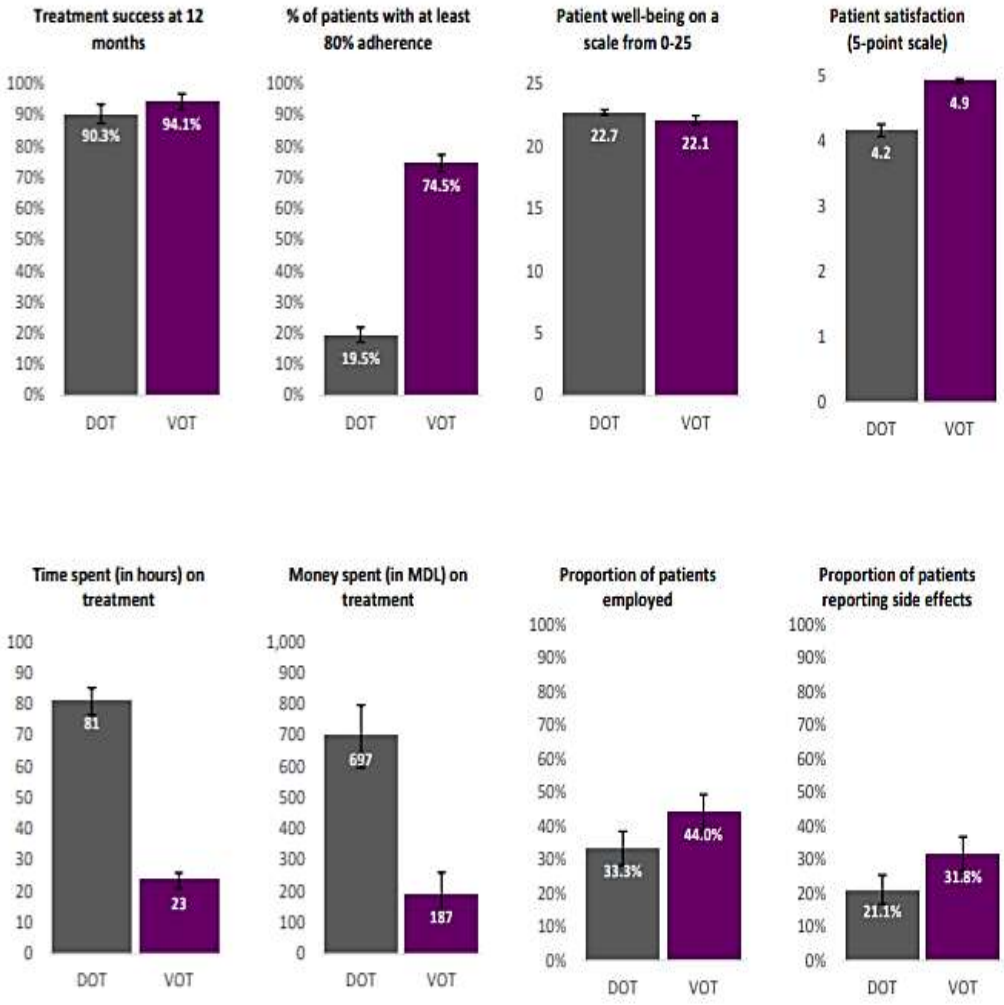


Figure 2: Summary of Secondary Outcomes



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

Table S4: Regression of Satisfaction Outcomes

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

Standard errors in parentheses

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

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

Baseline Questionnaire

- Last Name _____ First name(s) _____ UID number _____
- Sex ☐M ☐F Polyclinic _____ Are you currently employed? ☐Y ☐N
- Access to a desktop computer, tablet or mobile phone that is internet enabled? ☐Y ☐N
- Do you have at least 4 months of care remaining? ☐Y ☐N
- Problem drug use ☐Y ☐N
- Alcohol misuse ☐Y ☐N
- Currently homeless ☐Y ☐N
- Currently in prison ☐Y ☐N
- Injectable drug regime ☐Y ☐N

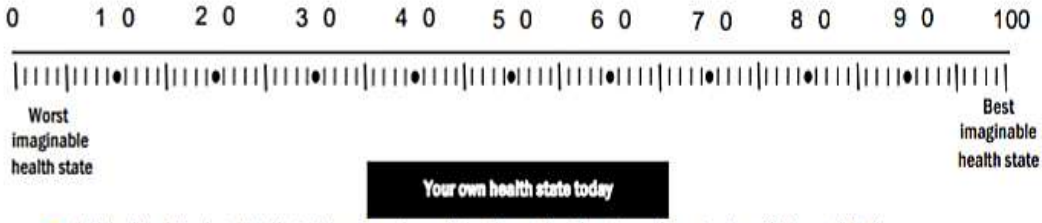
- Please go through the following statements and circle the box that best describes your thoughts and feelings over the last two weeks:

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

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

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

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



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

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

IVth Month - Questionnaire on health and welfare

Suggested revisions by BIT, 23rd January 2017

Part A – For all patients (DOT and VOT)

A.1 General Information:

A.1.1 Date of interview:

A.1.2 Code:

A.1.3 Treatment: ☐ VOT

☐ DOT

A.1.4 Gender: ☐ F

☐ M

A.1.5 Polyclinic:

A.1.6 Are you presently employed? ☐ Yes

☐ No

A.2 Wellbeing & satisfaction

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

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

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

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

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

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

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

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

A.3 Time use and cost

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

Transport cost

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

Travel time

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

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

_____

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

_____

Time spent on treatment

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

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

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

Part B – Only for the VOT patients

Code:

B.1 Device

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

	PC
	Tablet
	Mobile phone
	Other, specify: _____

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

	PC
	Tablet
	Mobile phone
	Other, specify: _____

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

	I borrowed a tablet
	I used my own device

B.2 Comparison VOT - DOT

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

	VOT (M-Health)
	DOT (polyclynic)

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

	VOT (M-Health)
	DOT (polyclynic)

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

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

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

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

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

Lampiran 10

Original Paper

Using Video Technology to Increase Treatment Completion for Patients With Latent Tuberculosis Infection on 3-Month Isoniazid and Rifapentine: An Implementation Study

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Abstract

Background: Since January 2013, the New York City (NYC) Health Department Tuberculosis (TB) Program has offered persons diagnosed with latent TB infection (LTBI) the 3-month, once-weekly isoniazid and rifapentine (3HP) treatment regimen. Patients on this treatment are monitored in-person under directly observed therapy (DOT). To address patient and provider barriers to in-person DOT, we piloted the use of a videoconferencing software app to remotely conduct synchronous DOT (video directly observed therapy; VDOT) for patients on 3HP.

Objective: The objective of our study was to evaluate the implementation of VDOT for patients on 3HP and to assess whether treatment completion for these patients increased when they were monitored using VDOT compared with that using the standard in-person DOT.

Methods: Between February and October 2015, patients diagnosed with LTBI at any of the four NYC Health Department TB clinics who met eligibility criteria for treatment with 3HP under VDOT (V3HP) were followed until 16 weeks after treatment initiation, with treatment completion defined as ingestion of 11 doses within 16 weeks. Treatment completion of patients on V3HP was compared with that of patients on 3HP under clinic-based, in-person DOT who were part of a prior study in 2013. Furthermore, outcomes of video sessions with V3HP patients were collected and analyzed.

Results: During the study period, 70% (50/71) of eligible patients were placed on V3HP. Treatment completion among V3HP patients was 88% (44/50) compared with 64.9% (196/302) among 3HP patients on clinic DOT ($P<.001$). A total of 360 video sessions were conducted for V3HP patients with a median of 8 (range: 1-11) sessions per patient and a median time of 4 (range: 1-59) minutes per session. Adherence issues (eg, >15 minutes late) during video sessions occurred 104 times. No major side effects were reported by V3HP patients.

Conclusions: The NYC TB program observed higher treatment completion with VDOT than that previously seen with clinic DOT among patients on 3HP. Expanding the use of VDOT may improve treatment completion and corresponding outcomes for patients with LTBI.

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KEYWORDS

computer-assisted therapy; directly observed therapy; mobile phone; telemedicine; videoconferencing

Introduction

In 2015, the World Health Organization, a leading public health organization, published an agenda that outlines the strategic direction to promote the integration of digital health concepts into tuberculosis (TB) prevention and care activities [1]. One digital health product identified that supports their strategy is the use of electronic observation of treatment [1]. In the United States, the use of video to remotely monitor patient treatment for active TB is rapidly growing [2]; however, the use of technology to monitor adherence to preventive treatment for latent TB infection (LTBI) has not been widely documented [3].

Nearly a quarter of the world's population is infected with TB and, left untreated, many are at risk of progressing to active TB disease [4]. An important component of the US Centers for Disease Control and Prevention's (CDC) TB elimination strategy is to expand efforts to treat individuals diagnosed with LTBI using shorter treatment regimens [5]. In 2011, CDC began recommending the use of a shorter treatment regimen, a 3-month, once-weekly regimen of isoniazid and rifapentine (3HP) under directly observed therapy (DOT), for treatment of LTBI in otherwise healthy individuals aged ≥12 years and in HIV-infected patients not taking antiretroviral medications [6,7].

In 2013, the New York City (NYC) Department of Health and Mental Hygiene (DOHMH) began offering 3HP at its TB clinics and found that treatment completion increased from a baseline of 34% with 9 months of isoniazid (9H) to 65% with 3HP [8], but it was still lower than the 82% treatment completion observed in the 3HP clinical trial [9]. Stennis et al attributed the lower than expected treatment completion to the inconvenience associated with the DOT requirement [8]. Patients in this study were treated with 3HP under in-person clinic DOT. Furthermore, among patients who chose a non-3HP treatment, 96% reported the clinic DOT requirement and 77% reported concerns about taking time away from work, child care, or other responsibilities for clinic visits as reasons they did not choose the 3HP regimen [8].

In the United States, DOT is the standard of care for monitoring patients on treatment for active TB disease, particularly those who are infectious, to ensure adherence to medication [10]. DOT requires substantial public health resources and generally is not the standard of care for patients on treatment for LTBI, a noninfectious form of TB. DOT involves trained workers observing patients ingest each dose of medication throughout the duration of treatment. DOT requires patients to either go to a clinic or have DOT workers visit patients' homes or other locations to observe medication ingestion [11]; this can be inconvenient and disruptive for patients [12,13]. Several TB programs have explored the use of videoconferencing to remotely monitor patients on treatment for active TB, known as video DOT (VDOT). These programs have reported better or equal rates of treatment completion compared with those with in-person DOT while providing a more convenient and flexible option for patients [2,12,14-16]. VDOT uses videoconferencing software to allow patients and staff to communicate remotely via smartphones, tablets, or desktop computers. An NYC study found VDOT to be a feasible alternative to in-person DOT while improving the treatment adherence and maximizing health department resources [12]. However, to date, only one published instance known to the authors has reported using VDOT to monitor patients on treatment for LTBI [3].

To improve treatment completion for patients on 3HP, the NYC DOHMH piloted the use of live-videoconferencing technology to conduct weekly DOT observations for patients on 3HP (V3HP). The intent of the V3HP pilot was to alleviate barriers to DOT to improve treatment completion among patients started on the 3HP regimen. The objectives of this evaluation were as follows: (1) to determine the feasibility of using VDOT on patients prescribed 3HP and assess resources required to implement; (2) to compare treatment completion of patients in the V3HP pilot with previously measured 3HP treatment data; and (3) to describe challenges encountered during the pilot implementation.

Methods

Integration of Video Directly Observed Therapy for Treatment of Latent Tuberculosis Infection

For the V3HP implementation study, NYC DOHMH adapted the existing videoconferencing software, educational and enrollment materials, and protocols used in the previous NYC 3HP and VDOT pilot experiences [8,12]. Clinic staff received in-service training and job aids for assessing patient eligibility and referring patients to the V3HP pilot. Three nonclinical staff were trained to perform observations for V3HP, even though one performed nearly all of the observations. In addition, staff were trained in the installation and operation of the software and basic troubleshooting. Furthermore, staff were trained in documentation procedures for monitoring patients in the implementation study.

Study Population

Eligible patients treated for LTBI with 3HP between February and October 2015 at any of the four NYC Health Department TB clinics and who met NYC DOHMH eligibility requirements for VDOT [12] were offered participation in V3HP. The diagnosis of LTBI and the prescription of 3HP were left to the discretion of providers. The eligibility for V3HP included the possession of a smartphone, tablet, or computer with videoconferencing capability; patients' willingness to use their personal devices for VDOT sessions; access to a reliable internet connection; and agreement to a VDOT schedule. Participants were followed through the completion of treatment or up to 16 weeks from treatment initiation, whichever came first. Eligible minors were enrolled at the provider's discretion if parental consent was obtained. Patients and guardians of minors signed a DOT agreement, which included the use of videoconferencing for observation sessions and acknowledgment of personal responsibility for costs incurred due to the use of personal devices and data service. Patients ineligible for or refused V3HP were still able to be treated with 3HP with in-person clinic DOT at any of the Health Department TB clinics but were excluded from the implementation study.

V3HP patients were prescribed medication, as per CDC guidelines [7], monthly at one of the four Health Department TB clinics. Patients returned to the clinic for monthly follow-up evaluation and medication refills. During these monthly visits, patients had the option of taking their medications in-person in lieu of their weekly VDOT sessions.

Process Conducting Video Sessions

3HP patients were assigned to a VDOT worker who contacted the patients to verify enrollment eligibility, schedule weekly video observation sessions, remotely assist the patients in installing the Health Department-approved videoconferencing software, and test the stability of the internet connection similar to the process in a prior NYC study [12]. During each observation session, the VDOT worker logged into the videoconference at the scheduled time using a conference identifier unique to each patient and waited for the patient to log in. Observation sessions were conducted using NYC's standard VDOT practice [12], which includes a VDOT worker asking patients at the beginning of each session if they experienced any side effects since their previous dose, and if no side effects were reported, patients were observed ingesting all prescribed medications. Patients reporting or experiencing any side effects during VDOT sessions were asked to return to the clinic or were contacted by a provider to determine the course of action. Patients were observed through the completion of therapy. No additional follow-up was performed after treatment completion or 16 weeks after treatment initiation.

Patients who failed to log in within 5 minutes of their scheduled appointment were contacted by the VDOT worker via telephone. If patients could not be reached within 30 minutes of the appointment time, a voicemail or short message service (SMS) text message was left requesting the patient to call the worker to reschedule. In addition, SMS text messaging was used to remind patients of their appointment but was used only after obtaining patient approval in accordance with the NYC DOHMH policy. The VDOT worker would attempt to call patients the following day if they had not returned the original phone call. Treatment outcomes, issues with completing VDOT observations, and other evaluation variables were documented in a V3HP database by the VDOT worker following all successful and failed VDOT sessions.

Data Collection

Patient demographics, treatment outcomes (ie, treatment completion), and information on monthly clinic visits and clinic DOT were obtained from the TB clinic's electronic medical record system. Treatment outcomes were categorized as follows: treatment completion (ie, completion of treatment using 3HP on VDOT), lost (ie, unable to locate after treatment initiation), refused treatment, switched treatment types, discontinued due to side effects per physician advice, and other (eg, moved). Duration of the VDOT observation sessions, outcomes of the sessions, issues encountered during sessions, and other comments pertinent to therapy sessions or failed attempts to contact patients were obtained from the V3HP database. Issues encountered during the sessions were captured as predefined codes and free text by the VDOT staff.

Definitions

Patients were considered to have completed treatment successfully if they received at least 11 doses of 3HP within 16 weeks of treatment initiation. Issues were categorized into adherence, medical, and technical. Adherence issues consisted of 4 subcategories as follows: patient lateness (defined as >15 minutes late to a scheduled session); patient lateness for more than a day; missing or lost medications; and unapproved self-administered doses. Medical issues were included if patients reported side effects to a VDOT worker or other clinical staff or if they were documented in the electronic medical record. Technical issues were subdivided into the following 3 categories: DOHMH error, including health department computer or phone connection errors, videoconference software crashes, and audio or visual hardware malfunctions; patient equipment error, including connection difficulties, software errors, and hardware errors; and patient knowledge, including inability to operate phone or software and misunderstanding of observation requirements for VDOT.

Analysis

The characteristics and treatment outcomes of patients in the V3HP implementation study were compared with those of 3HP patients on in-person clinic DOT who were part of an earlier NYC study implemented from January to November 2013 [8]. Participants for both studies were enrolled at NYC Health Department clinics and were included if they met the following criteria: patients being treated for LTBI; those aged ≥12 years; males or nonpregnant, nonnursing females; HIV-uninfected or -infected individuals who were not on highly active antiretroviral medications, and patients who could be contacted via telephone in case of a missed DOT visit. The significant differences in demographics and treatment outcomes between patients on 3HP with VDOT and those on clinic DOT were calculated using Pearson's chi-square or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

This implementation study was considered a public health program evaluation activity, not research, and, therefore, it did not meet the criteria to undergo review by the NYC DOHMH Institutional Review Board. Furthermore, this project was reviewed and approved at the CDC as program evaluation activity.

Results

Treatment Outcomes

From February to October 2015, 70% (50/71) of patients who initially agreed to V3HP were placed on VDOT. Among the V3HP patients, 88% (44/50) completed their treatment on 3HP under VDOT (Figure 1); 6% (3/50) of the additional patients completed treatment after switching to a non-3HP treatment regimen following 1-2 VDOT sessions. Of 3 patients who did not complete treatment, 2 patients opted to discontinue the treatment after experiencing headache and dizziness, respectively; 1 patient moved out of the jurisdiction after completing a single VDOT session and was referred for follow-up in the other jurisdiction. Furthermore, 21 patients

who initially agreed to V3HP subsequently did not start on V3HP for various reasons (Figure 1).

There were few differences in patient demographics between V3HP patients and patients in the prior NYC 3HP study who were monitored under clinic DOT, although a higher proportion of V3HP patients were recently exposed to an infectious TB patient (Table 1). Treatment completion for V3HP patients was higher than that for 3HP patients on clinic DOT (44/50, 88%, vs 196/302, 64.9%; $P<.001$) [8].

Video Directly Observed Therapy Sessions

Of 549 3HP treatment doses ingested by 50 V3HP patients, 65.6% (360/549) were observed under VDOT, 30.4% (167/549) doses were observed in the clinic by staff, and 4.0% (22/549) were self-administered. Patients had a median of 8 VDOT (range: 1-11) sessions. In addition, 42 patients completed 3HP treatment with 12 doses of medication and 2 patients received physician approval to discontinue therapy after 11 doses. Session times were captured for 95.8% (345/360) of VDOT sessions. The median session time was 5 (range: 1-59) minutes.

Figure 1. Outcomes of patients on 3-month, once-weekly treatment with isoniazid and rifapentine referred for video directly observed therapy (DOT; V3HP). MD: medical doctor.

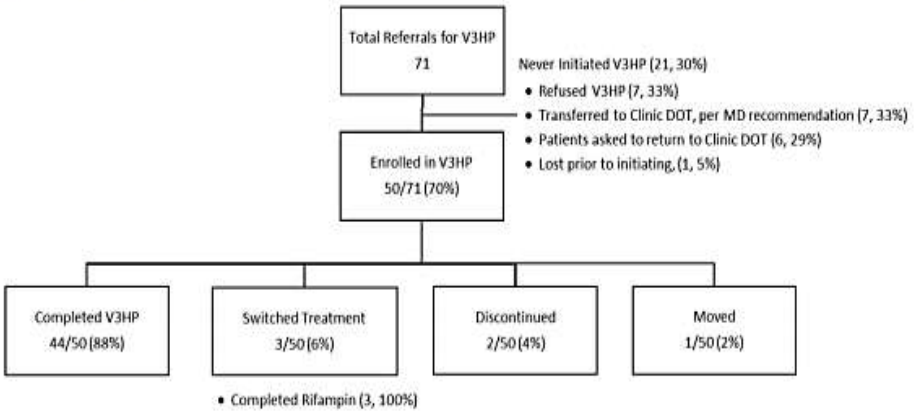

Table 1. Characteristics and treatment outcomes of patients on 3-month, once-weekly treatment with isoniazid and rifapentine (3HP) on clinic directly observed therapy (DOT; January to November 2013) versus video directly observed therapy (VDOT; February to October 2015) in New York City.

Characteristic	3HP Clinic DOT (n=302)	3HP VDOT (n=50)	*P* value[a]
Male sex, n (%)	154 (51.0)	25 (50.0)	.90
Age (years), median (interquartile range)	33 (22-45)	33.5 (25-46)	.51
US born, n (%)	70 (23.2)	7 (14.0)	.15
HIV status, n (%)			.33
Positive	1 (0.3)	0 (0.0)	
Negative	161 (53.3)	32 (64.0)	
Unknown	140 (46.4)	18 (36.0)	
Tuberculosis risk category, n (%)			.02[b]
Population Risk	187 (61.9)	27 (54.0)	
Medical Risk	56 (18.5)	8 (16.0)	
Contact to an active TB case	42 (13.9)	15 (30.0)	
Other	17 (5.6)	0 (0.0)	
Treatment outcomes, n (%)			.001[b]
Completed Treatment	196 (64.9)	44 (88.0)	
Did Not Complete	106 (35.1)	6 (12.0)	

[a]*P* value calculated using the Pearson's chi-square or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.
[b]Significance at $P<0.05$.

Table 2. Issues encountered during the implementation study (n=205).

Issue type	Value, n (%)
Adherence	104 (50.7)
Unapproved self-administer	12 (11.5)
Patient misplaced or forgot meds	5 (4.8)
Patient late >1 day	15 (14.4)
Patient late >15 minutes	72 (69.2)
Technical	75 (36.6)
Health department related	29 (38.7)
Patient equipment	43 (57.3)
Patient knowledge	3 (4.0)
Medical	26 (12.7)

Textbox 1. Justifications for self-administered doses of 3-month, once-weekly isoniazid and rifapentine (3HP) regimen (n=22).

Unapproved self-administered justifications (n=12)

- Unable to reach patient. Self-administered prior to the callback: 6.
- The patient was to be observed in the clinic. The patient self-administered instead: 2.
- Technical issue. The patient self-administered rather than awaiting troubleshooting: 2.
- Administered prior to initial contact by the pilot staff: 1.
- The patient went on vacation without prior notice and did not have a video-enabled device: 1.

Approved self-administered justification (n=10)

- Administrative or holiday closure of office. Unable to schedule alternate time with the patient: 3.
- Technical issue. The patient thought observation was underway, but the video was nonfunctional: 3.
- Physician excused absence
  - Patient overseas and unable to connect: 3
  - Patient away on a meditation: 1

A total of 205 issues were encountered during the V3HP pilot among 47 patients (Table 2); 76.6% (157/205) occurred during 149 unique VDOT sessions. The remaining issues were side effects reported in-person during monthly clinic follow-ups, problems resulting in clinic DOT visits, and instances where patients self-administered medication was not under observation. Of all the issues, 50.7% (104/205) were related to patient adherence, including 12 instances where patients self-administered treatment without prior physician or program staff approval (Textbox 1). There were 26 medical issues, most of which were reported within the first 6 doses of medication (n=20). Of 37.1% (76/205) technical issues identified, a majority resulted from patient equipment errors (n=43). Health Department-related equipment errors (n=29) typically occurred in the beginning of the pilot and earlier in patients' treatment course.

Discussion

Principal Considerations

This implementation study examined over 300 VDOT sessions among 50 patients on 3HP. Our analysis found that the 3HP treatment completion for patients in the implementation study increased compared with that in a prior NYC study that offered 3HP with clinic DOT (196/302, 64.9%, vs 44/50, 88%). Our evaluation supports the inclusion of VDOT to improve the completion of therapy with 3HP. Although patient nonadherence was prominent during the pilot period, with nearly half of the scheduled VDOT sessions having some form of adherence issue, the implementation study still demonstrated that staffing needs were minimal to account for the variable rescheduling time for monitoring nonadherent patients and providing reminders calls and SMS text messages when patients were late. In this implementation study, a single VDOT worker managed all observation sessions for 50 patients. Furthermore, technical issues did not prohibit the continuation of the observation sessions and the completion of treatment. This suggests that VDOT can successfully monitor patients on 3HP using minimal health department resources while offering an effective alternative for treating LTBI that removes some of the barriers to treatment completion.

In spite of these circumstances, the occurrence of patients self-administering doses remained low. A variety of causes resulted in self-administered doses, including nearly half that

were approved absence by a physician or NYC staff (Textbox 1). The occurrence of self-administered doses is anticipated, and the minimal unexcused absence adds to its acceptability as an option for patient-centered care.

A recent clinical trial by Belknap et al found that in the United States, 3HP under self-administration was noninferior to 3HP under DOT [17]; however, further evaluation is needed under program settings. Therefore, the wider use of VDOT for monitoring patients on 3HP may contribute toward efforts to more rapidly reduce TB in the United States by increasing treatment completion and preventing disease.

Strengths and Limitations

This V3HP implementation study was successfully implemented in NYC by integrating two existing programs—VDOT for monitoring patients on treatment for active TB and the 3HP short-course treatment regimen, recommended to be administered with DOT [8,12]. Staff experienced with the two initiatives were consulted to inform the implementation plan, and the few technological issues encountered were easily resolved because staff could quickly identify and address problems. The V3HP pilot required one staff person working part-time to conduct the VDOT sessions for all 50 patients enrolled during the 8-month pilot period. Furthermore, we found that patients were willing to use their own phones for VDOT sessions, a potential cost saving for health departments. However, additional evaluations including cost-effectiveness analyses comparing VDOT with in-person DOT or self-administered treatment would help quantify the value to TB programs.

This pilot also had a number of limitations. One limitation was the use of data from a prior study as the comparison group. While there were few differences between the study population for the V3HP pilot and the previous 3HP study, the V3HP pilot did enroll a greater proportion of high-risk patients with recent contact to someone with active TB disease; these high-risk individuals may have been more motivated to adhere to treatment and could have impacted treatment completion. In addition, the 2-year time difference between the previous study and the current V3HP pilot may have given clinicians an increased level of comfort in offering 3HP and less likely to discontinue the treatment because of mild or anticipated side effects. No other programmatic changes were identified between the two time periods that could have impacted the clinic population and influenced treatment completion among V3HP patients.

Enrollment in the program also presented several limitations. First, patients had to be available for VDOT sessions during limited business hours (ie, between 8:00 AM and 4:30 PM), so patients who preferred to take their medications in the early morning, late evening, or weekend could not participate. Patients opting for clinic DOT had a wider window of time to receive their weekly dose because several NYC Health Department TB clinics offer weekend and evening hours. Use of asynchronous video technology (technology that can record and timestamp video) could alleviate the scheduling constraint of live-video DOT [18]. Second, not only did patients have to use their own videoconferencing-enabled devices, but their devices also had to be compatible with the videoconferencing software approved by the DOHMH, and they were required to demonstrate the ability to use the software. Patients having a device may represent a population more inclined to accept treatment and complete through the use of video monitoring. Providing additional software options or loaner devices may make the supervision of treatment more convenient for patients and reach a wider population. Finally, patients still had to travel to the clinic for monthly follow-up visits to receive their medication. Aside from being a deterrent to patients who may not want to have to return to the clinic to receive medication, this may also have had a positive effect on treatment completion. However, as participants were able to receive medications in-person during those visits, this decreases the number of opportunities for VDOT observations. It likely accounted for the median of 8 DOT sessions per participant; the remaining observations were likely performed in-person. Further evaluation would be necessary to assess treatment completion when the number of clinic visits is reduced.

Additionally, as eligibility for and offering of 3HP is not collected as part of the program practice, the data were not available for analysis; this limits our ability to quantify the acceptance of 3HP and whether VDOT potentially increased its acceptance among patients. While there was a high proportion (21/71, 30%) of patients who did not start on V3HP, it is uncertain how these missing data affect the treatment outcome. Thus, additional studies are needed to assess DOT monitoring preferences for LTBI.

Concurrent to the pilot, a policy change in the NYC TB clinics preferentially offered another short-course treatment regimen, 4 months of daily rifampin, as an alternative to 3HP for the treatment of LTBI, which could have impacted the enrollment into the pilot. Furthermore, a shortage of rifapentine interrupted providers from offering 3HP for approximately 2 months. The overall impact of this shortage is difficult to determine because the shortage was initially not reported, but clinicians may have been aware and restricted their offering of the regimen. These events prevented the analysis to determine whether the treatment initiation with 3HP increased with VDOT. However, in taking a patient-centered approach to care, several treatment options may give patients alternatives to achieve better outcomes. Additional analysis is needed to determine whether preferentially offering of multiple short-course treatment regimens increases treatment initiation for LTBI as well as treatment completion.

Conclusions

This evaluation shows that the use of VDOT with 3HP for the treatment of LTBI is feasible and could be integrated into the current NYC LTBI treatment practice with minimal disruption to staff time and training. Treatment completion of patients on 3HP for LTBI increased with the use of VDOT. VDOT addressed some of the barriers to in-person DOT for patients with LTBI. Programs looking to implement 3HP for the treatment of LTBI should consider evaluating the use of VDOT. Further research is necessary to assess the use of VDOT for patients on treatment with 3HP compared with self-administration in a programmatic setting. Additionally, it may be worth exploring the expansion of the use of

asynchronous videoconferencing technology, thereby further reducing the intrusiveness of DOT.

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Conflicts of Interest

None declared.

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