ADVANCING TUBERCULOSIS CARE THROUGH VIDEO DIRECTLY OBSERVED THERAPY (VDOT)

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Preface

A central challenge in the fight against tuberculosis (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.[1,2] Poor treatment adherence has been linked to microbiologic failure, disease relapse and the emergence of drug resistance.[3,4]

In response, and in an effort to promote treatment completion, the Centers for Disease Control (CDC) and the World Health Organization (WHO) have advocated for directly observed therapy (DOT), wherein the ingestion of each dose is directly monitored.[1,5,6] In many areas, DOT is the current standard of care, though employing DOT in a patient-centered and efficient fashion can be challenging. Scheduling in-person DOT visits is logistically complicated, 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.[7,8]

To overcome these barriers, video-based DOT (vDOT) has been proposed as an alternative to in-person observation.[1,9,10] Herein, pill ingestion is monitored remotely via digital video capture. vDOT has been implemented using synchronous technologies, such as Skype and FaceTime,[11-14] as well as asynchronous ones, wherein recorded videos are uploaded and digitally stored for future review.[15] While both the CDC and WHO support the use of vDOT, data on the real-world implementation of vDOT remains

limited. To this end, we present two studies which broaden our understanding of vDOT by exploring its potential role in two distinct clinical settings, among two very different patient populations.

In Chapter 1, we present the results of a pragmatic, prospective, pilot implementation of vDOT at three TB clinics in Maryland, US. A mixed-methods approach is employed to assess (1) effectiveness, (2) acceptability and (3) cost. In Chapter 2, we extend the use of vDOT into a high TB burden, low resource setting, though a prospective, pilot implementation of vDOT in Pune, India.

Our work shows that vDOT may be a feasible and acceptable approach to TB treatment monitoring, both within the US and India. Further, vDOT may be associated with cost-savings within the US when compared to traditional in person DOT.

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Secondary Reader: Maunank Shah

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Chapter 1

Advancing patient-centered care in tuberculosis management: a mixed methods appraisal of video directly observed therapy (vDOT)

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SUMMARY

Video directly observed therapy (vDOT) is effective in diverse patient populations and represents an important tool in patient-centered tuberculosis (TB) care. Further, the implementation of vDOT is likely to result in cost-savings for TB clinics.

ABSTRACT

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

***Results*.**

Medication adherence on vDOT was comparable to that under in-person DOT (94% vs 98%, p=0.17), with a higher percentage of total treatment doses (inclusive of weekends/holidays self-administration) ultimately observed during the vDOT period (72% vs 66%, p=0.03). 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 $1,391 per patient, for a standard six 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 to in-person DOT. Video DOT may be cost-saving and should be considered as a component of individualized, patient-centered case management plans.

INTRODUCTION

Tuberculosis (TB) remains a global pandemic responsible for nearly two million deaths annually.[1] In the United States (US), 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 (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 US, DOT is now the standard of care, and 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 one 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, 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, provisions for DOT may impact provider prescribing practices. While updated TB guidelines advocate daily therapy (i.e. 7 days/week), our experiences suggest health departments commonly dose TB medications Monday to Friday (M-F, i.e. business days) only, or intermittently (i.e. 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 at 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 that 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. Firstly, we sought to understand feasibility and acceptability in broad patient populations, including those with previously poor adherence and drug-resistant disease. Secondly, we sought to assess effectiveness for observation of therapy, as well as costs. Finally, we sought to describe implementation challenges and successes, patient selection for vDOT, and 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 HIPAA-compliant mobile app, miDOT (emocha Mobile Health Inc.), for TB treatment monitoring, adherence support and case-management (see Supplement Figure 1). The study was carried out within three public health TB clinics in Maryland, USA, which 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 therapy were eligible for participation. Inclusion required patients be ≥18 year of age and to have ≥2 months of therapy remaining. All patients initiated TB therapy with in-person DOT, though could transition to vDOT at any point during their treatment course. The decisions to offer vDOT were made by non-conflicted health department clinicians, without explicit exclusion of non-English speakers, or those with multi-drug 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 day/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 day/week (M-F), with weekend (and holiday) self-administration, the latter not contributing to the overall dose target. While on vDOT, dosing frequency (i.e. 5 days/week versus 7 days/week) and whether to observe and count weekend doses towards an overall dose target was left to clinic discretion.

Patients were sent twice daily SMS reminders in the absence of submitted videos and were prompted to document side-effect prior to each submission (see Supplement 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 two 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 'expected' dose was defined by the TB clinic (usually omitting weekend and holiday self-administered doses) (see Supplement Figure 2). Given the goal of DOT is to observe all prescribed doses, as a second 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 analysis was 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 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 two 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 (see Supplement Table 5). To allow equal comparisons, final calculations were standardized to a six-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 costs of $50 per patient, per month (personal communication with 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 (e.g., type of staff conducting DOT, vehicle used and travel distance) and vDOT (e.g., range of software-associated costs from a high of $100 per patient per month to free, see Supplement 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 three received weekly rifapentine/INH for LTBI (Table 1). Ninety-three percent of patients were foreign born. Only three 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 was more frequent during the in-person period (100% vs. 76%, p=0.01). Overall, intermittent thrice weekly therapy was utilized less commonly on vDOT than during in-person (24% vs 16%, p=0.32). No patients received seven days of in-person DOT, though two were

transitioned to this schedule while on vDOT. Mean time on therapy for in-person DOT and vDOT was 12.2 and 19.2 weeks, respectively (p=.01).

Feasibility/effectiveness:

Measured *Adherence* was high irrespective of DOT strategy: median 98%(IQR 90-100) during in-person DOT and 94% (IQR 88-98) while on vDOT (p=0.17, Table 2). The median *observable fraction* (i.e. 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=0.03). Overall, only 15% of patients had more than 80% of total prescribed doses verified through observation during in-person DOT, compared to 36% during vDOT (p=0.01), a consequence of self-administered weekend and holiday doses.

Fifty-seven percent of patients had at least one rejected video (mean 1.8, range 0-11), representing 2.1% of all submitted videos (2,350). The two most commonly cited reasons for rejection were “Medication dose not visible” and “Poor video quality.”

A total of four patients traveled internationally while on miDOT, though continued to successfully submit videos. Two patients were transferred from health department care after permanently leaving the US prior to treatment completion (one to Liberia and one to Ivory Coast); both had been on vDOT for >16 weeks with an adherence of 72% and 87%, respectively, at the time of study exit. A single patient had vDOT discontinued prematurely after five 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 towards in-person DOT and vDOT. Twenty staff participated before vDOT implementation, and 16 post-implementation; Twenty-five 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=0.92).

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

Themes related to this preference for vDOT were common during interviews and focused on convenience and increased flexibility (Table 3 and Supplement 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, one 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 one 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 one 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 mobile phones to share private health information.

While an uncommon theme, one nurse manager discussed a fear of displacement among staff, stating "some DOT workers worry 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 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 Supplement.

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 $1,391, per person compared to using in-person DOT (Table 3).

Cost for in-person DOT was driven largely by labor. In our primary analysis, labor costs totaled $1,838, amounting to >90% of the overall DOT expenditure for a standard TB treatment course. Labor costs varied markedly in sensitivity analysis based on health care worker type (e.g., community health worker [CHW] versus registered nurse [RN]); overall we estimated total in-person DOT costs at $866 to $5,857.

For miDOT, we found 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 $1,000 per treatment course, compared to in-person DOT.

DISCUSSION

In our pragmatic mixed-methods implementation of treatment monitoring strategies at three 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 to exclusive usage of in-person DOT. Our study is unique compared to 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 DOT was logistically infeasible (e.g., complex schedules or travel where the alternative was self-administration) or represented a barrier to care (e.g., 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 to 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 had 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. Our study design did allow for within patient comparisons, but must be interpreted cautiously due to potential for time-varying confounders during, 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 to in-person DOT, given vDOT initiation later in the treatment course. Lastly, our study sample was based on clinic (and patient) discretion and 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 or 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 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 US. 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' towards treatment progress (i.e. 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 pre-specified 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 still accept a 5 day/week alternative "daily" schedule (for drug sensitive disease) acknowledging "there are no studies that compare 5 to 7 daily doses."[4] Given logistical constraints, many TB programs in the US utilize a hybrid treatment schedule, wherein 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 (i.e. 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 percent 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 days/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 two 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 towards 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 $1,000 per patient if implemented for a standard six month treatment course (versus 5x per week in-person DOT). When considering TB clinic costs and staffing overall, it is important to acknowledge that DOT represents one 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 also presented alternative perspectives noting vDOT allowed for increased time and attention to be directed toward other required activities (e.g., 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 feasibility, acceptability, and cost-savings in a previously unstudied environment and among a broader patient population, compared to prior studies.[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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Potential 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 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 use of miDOT or enrollment in the study was made by non-conflicted department of health clinicians and staff; M.S. recused himself from all data analysis but assisted with results interpretation.

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SUPPLEMENT

Description of miDOT platform

Upon opening the app, patients were automatically navigated through a series of windows which screened for side-effects, reviewed treatment regimen, and ultimately a video-capture interface where they recorded pill ingestion (Supplementary Fig 1). Any noted side-effects were automatically routed to the miDOT provider portal for follow-up. Twice daily text-message reminders were automatically sent in the absence of expected submissions by the software. Recorded videos were encrypted and stored within internal phone memory only until successful upload, after which they were automatically deleted . An encrypted transmission tunnel was used to access patient data from provider desktops (Figure 1). Given the asynchronous nature of miDOT, clinic staff were able to review submitted videos at any point following digital capture and transmission.

Supplemental Methods

Outcomes of interest

We considered two primary outcomes (Supplement Figure 2). *Adherence* was measured as the proportion of expected DOT ultimately completed, whether verified by in-person or video observation. *Observable fraction* considered the proportion total planned treatment doses (including weekend/holiday self-administered doses) observed (in-person or by video). For the latter measurement, 'observation' was defined loosely on vDOT to include accepted, rejected and unexpected videos.

Outcome ascertainment

For in-person DOT, dose administration was retrospectively abstracted from paper charts. During the miDOT phase, patient dosing was prospectively monitored via the miDOT system (provider web interface). All decisions regarding video classification (i.e. reject vs accept), were made by unbiased clinic providers. While the miDOT platform automatically tallies doses and calculates adherence, for accuracy (and as a check on the system) all miDOT dosing was abstracted to paper calendars and then tallied by hand.

Supplemental Results

Quantitative results

One MDR patient was included in our study cohort. This patient transferred into our jurisdiction mid- continuation phase (no injectable) and, given patient-specific needs, was started directly on vDOT 7x per week. She successfully completed therapy after 36 weeks of vDOT.

Qualitative results

Surveys and in-depth interviews were conducted with patients and staff, both before and after vDOT implementation. Interviews were transcribed verbatim and an open-coding strategy was utilized to identify salient themes. An inclusive list of themes is reported below (Supplement Table 3 and Table 4), with a subset, representing the most significant themes, presented in the primary manuscript.

Cost Analysis

Time motion studies

DOT workers were found to travel an average of 5.4 miles per day, though differences in population density and county size led to marked variability, with sites reporting daily travel anywhere between three and thirteen miles. Time per patient per day (inclusive of travel) also varied, ranging from 23 to 89 minutes, with 47 minutes used in our base-case.

Time spent, per patient, on DOT was much shorter during the miDOT period. Time motion studies showed a range of two to eight minutes per patient, with three minutes ultimately used in our base case.

Clinical variability

Significant heterogeneity was observed in the DOT delivery structure between health departments (see Supplement Figure 2). Each site had a nurse administrator overseeing one or more nurse case-managers, though the educational training/background of those conducting DOT ranged from that of a CHW, with no specific health training, to an LPN to an RN. CHWs were generally tasked only with DOT-related activities, while those with more robust clinical training (ex RNs) often had additional clinical roles such as latent tuberculosis (LTBI) screening, phlebotomy and vaccine administration (non-TB related). The average DOT caseload was 15, though ranged from as few as 3 to as many as 22. In terms of transportation, some sites

utilized government-owned vehicles, while others reimbursed staff of the usage of their own vehicles.

TABLES

Table 1 (1.1): Patient Characteristics

Variable	Number (percentage) (n=28)
Age, yr (median, IQR)	32 (23-49)
Female, n (%)	16 (57)
Foreign born, n (%)	26 (93)
Origin, n (%)	
United States	2 (7)
Africa	11 (39)
Latin America	8 (29)
South Asia	4 (14)
East Asia	2 (7)
Europe	1 (4)
Time in US, yr (median, IQR)[1]	5 (3-15)
Limited or no English[2], n (%)	7 (25)
Travel to TB endemic country within 5 years, n (%)	19 (67)
Highest level of education reached, n (%)[2]	
Grade school	3 (12)
High school	10 (38)
College	9 (35)
Post-graduate	4 (15)
Employment, n (%)	
Full-time	16 (57)
Part-time	7 (25)
Unemployed	5 (18)
Annual household income,[3] n (%)	
< $20,000	8 (36)
$20,000 - $49,999	9 (41)
$50,000 - $100,000	4 (18)
>$100,000	1 (5)
Substance use, n (%)[3,4]	
Tobacco	1 (4)
Alcohol	1 (4)
Illicit drugs	1 (4)
Comorbidities, n (%)	
HIV infected	2 (7)
Hypertension	2 (7)
Diabetes	1 (4)
History of malignancy	2 (7)
Taking daily (non-TB) medications, n (%)	6 (21)

Technology, n (%) Regular access to smartphone Required study phone[5]	 25 (89) 3 (11)
Tuberculosis type, n (%) Pulmonary Smear positive Smear negative Exclusively extrapulmonary Latent	 9 (32) 5 (18) 11 (39) 3 (11)
MDR disease, n (%)[6]	1 (4)

[1] Calculated for foreign-born individuals only, those reporting "less than one year" were considered to have been in US for six-months for statistical purposes
[2] Included six Spanish speakers and one Oromo
[3] Excludes those for which data unknown
[4] Represents three separate patients
[5] All three phones were returned at study completion in good working order
[6] Refers only to those treated for active TB. All LTBI patient received weekly rifapentine for 12 weeks.

Table 2 (1.2): Primary outcomes by DOT strategy

Variable	In-person DOT	vDOT	*P*
Adherence (%)[1] Median (IQR) Range	98 (90-100)	94 (88-98)	0.17
Observable Fraction (%)[2] Median (IQR)	66 (62-72)	72 (67-92)	**0.03**
Number (%) of patients with observable fraction greater than a target 80%	4 (15)	10 (36)	**0.01**
DOT schedule among active TB patients, n=25 (%)[3] 3x/wk DOT 5x/wk DOT 7x/wk DOT	 6 (24) 25 (100) 0 (100)	 4 (16) 19 (76) 2 (8)	 0.32 **0.01** 0.16
Treatment length, wks Mean ± SD Range	 12.22±6.5 0-26	 19.2±9.7 5-37	 **0.01**
Number of rejected videos Mean (SD) Range		 1.8 (2.4) 0-11	
Unexpected video submission Mean (SD) Range		 2.7 (5.3) 0-20	
Percent of patients reporting ≥1 side-effect via mobile platform (%)[4]		46	
Video length, sec Median, (IQR)		 48 (29-63)	
Video size, mb Median, (IQR)		 4.8 (1.4-5.8)	

[+] Only participants treated for active TB included (n=25).

[1] Percent of "expected" DOT doses (in-person or video) completed, excluding self-administered doses (i.e. weekends or clinic holidays). An additional, less stringent analysis was also conducted wherein "completed" vDOT was loosely defined to include both verified and rejected miDOT videos: in-person 98% (90-100) vs vDOT 96% (89-100), p=0.37.

[2] Percent 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 miDOT videos (verified, rejected, unexpected), though only one 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=0.22.

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

[4] The miDOT 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 (e.g. rash).

Table 3 (1.3): 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 7:30am and then I go to school … there is no time."
		vDOT increases access to transient patients	"When I was in Peru for two 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 … 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 5:00am."
		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 seven days a week [with vDOT], rather than five, 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 two hours, three 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 non-adherent in standard DOT. She was missing three or four doses a week ... we were going to quarantine this individual, but [we decided to] attempt video DOT, and ... for about a month or two [she] was nearly 100% adherent on a seven-day regimen of medicine on video DOT."

[+] Only subset of themes presented. For full list see Supplement Tables 3 and 4.
sDOT=standard DOT (i.e. in-person), vDOT=video DOT

Table 4 (1.4): Cost analysis of vDOT implementation

	DOT strategy	Equipment	Consumables	Labor[5]	Total	Incremental
DOT 5x per week	In-person DOT (range)	$175[1] ($0-$562)	$52[3] ($17-$907)	$1,838 ($869-$4,406)	$2,065 ($886-$5,875)	Ref
	vDOT (range)	$48[2] ($4-$136)	$495[4] ($0-$900)	$131 ($62-$413)	$674 ($66-$1,449)	-$1,391
DOT 7x per week	In-person DOT (range)	$175[1] ($0-$562)	$52[3] ($17-$907)	$2,573 ($1,217-$6,169)	$2,801 ($1,234-$7,638)	Ref
	vDOT (range)	$48[2] ($4-$136)	$495[4] ($0-$900)	$183 ($87-$578)	$726 ($91-$1,614)	-$2,075

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

[1] 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.

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

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

[4] Software estimates 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.

[5] 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.

Supplementary Table 1 (1.S.1): Staff opinions pre/post vDOT

Survey Question	**Pre-vDOT** (n=20)		**Post-vDOT** (n=16)		***p***
	Agree n (%)	Disagree n (%)	Agree n (%)	Disagree n (%)	
Patients can successfully complete TB treatment with self-administered therapy ONLY (i.e. DOT unnecessary)	2 (10)	18 (90)	0 (0)	16 (100)	0.16
DOT provides beneficial social support	19 (95)	1 (5)	16 (100)	0 (0)	.
vDOT is effective for monitoring patient adherence	17 (85)	3 (15)	15 (94)	1 (6)	0.16
sDOT provides improved adherence over self-administered	20 (100)	0 (0)	16 (100)	0 (0)	.
vDOT provides improved adherence over self-administration	14 (70)	6 (30)	16 (100)	0 (0)	**0.03**
sDOT is burdensome for patients	14 (70)	6 (30)	12 (75)	4 (25)	0.65
vDOT is burdensome for patients	0 (0)	20 (0)	1 (6)	15 (94)	.
vDOT is more convenient for patients than sDOT	15 (75)	5 (25)	14 (88)	2 (13)	0.56
sDOT can compromise patient privacy	8 (40)	12 (60)	10 (63)	6 (38)	0.16
vDOT can compromise patient privacy	2 (10)	18 (90)	2 (13)	14 (88)	0.32
Comfortable using computers for patient care	19 (95)	1 (5)[1]	15 (94)	1 (6)	1.00
Comfortable using smartphones for patient care	19 (95)	1 (5)[1]	15 (94)	1 (6)	.

sDOT=standard DOT (in-person), vDOT=video DOT

[+] A five point Likert scale was used. Agree/strongly agree and neutral/disagree/strongly disagree were grouped for the above reporting.

[++] Provider sample size varied pre/post vDOT implementation due to staffing turnover, with several staff members coming and going over the course of the study. Provider cohort included all those involved with DOT-related activities, including DOT-workers, nurse case managers and TB clinicians.

[1] Represents two separate staff members, though recorded response was "neutral" in both cases.

Supplement Table 2 (1.S.2): Patient opinions pre/post vDOT

Survey Questions	**Pre-vDOT** (n=25)		**Post-vDOT** (n=9)		***p***
	Agree n (%)	Disagree n (%)	Agree n (%)	Disagree n (%)	
DOT is helpful	15 (60)	10 (40)	6 (67)	3 (33)	0.10
Self-administration would be preferred	21 (84)	4 (16)	8 (89)	1 (11)	0.56
sDOT is inconvenient	15 (60)	10 (40)	7 (78)	2 (22)	0.32
Comfortable using a smartphone	23 (92)	2 (8)	8 (89)	1 (11)	.
Comfortable using a computer	18 (72)	7 (28)	6 (67)	3 (33)	0.32
Comfortable using video for DOT	23 (92)	2 (8)	7 (78)	2 (22)	0.32
vDOT is convenient[1]			8 (89)	1 (11)	
vDOT provides for autonomy[1]			7 (79)	2 (22)	
miDOT was easy to use			8 (100)	0 (0)	

sDOT=standard DOT (in-person), vDOT=video DOT

[+] A five point Likert scale was used. Agree/strongly agree and neutral/disagree/strongly disagree were grouped for the above reporting.

[++] The patient response rate declined post-vDOT due to frequent loss-to-follow-up beyond treatment completion. Notably, vDOT adherence did not differ between those completing and those not completing post-intervention qualitative assessment (adherence 89% vs 90%, p=0.92)

[1] All patients grouped under “disagree” responded “neutral” on the Likert scale

Supplementary Table 3 (1.S.3): Full list of staff themes from qualitative analysis

STAFF Themes

Theme	Subtheme	Illustrative quote
DOT efficacy	DOT is a necessary component of TB therapy	"DOT is absolutely necessary. I think without it, we'd have relapses right and left."
Impact of DOT on patients	sDOT can be burdensome for patients	"…some people have to go to school and waiting for the DOT provider … can be a problem. Sometimes they miss the bus."
	sDOT can cause emotional stress	"It's invasive. It's inconvenient. For some people, it's embarrassing or humiliating."
	Daily home visits with sDOT help some	"There are some people who like having that nurse come to their home … sometimes we're the only person they see throughout the course of the day."
	vDOT can be more convenient for patients	"[vDOT] frees the patient out to live a normal life. They don't feel like they are a prisoner in their home for nine months or a year."
DOT logistics	sDOT efficacy is limited by environmental factors	"…when there's power failure, or a weather state of emergency, or a traffic issue … we can't get to the patient … the medicine has to be self-administered … and we have to extend the length of patient's treatment."
	sDOT efficacy is limited by patient factors	"We've had several clients who do seasonal work … they leave at dawn and they don't get back home until dusk. My staff routinely works anywhere from 7:30-4:30, and so trying to do DOT is impossible."

	vDOT increases access to transient patients	"[vDOT] works very well with immigrant populations ... when they go back [to their home country], they can still do videos with us ... for countries in Africa like Liberia and Gambia it's very difficult to find a partner TB clinic ... but now we get to count those days because we see them."
	With sDOT travel can result in longer treatment courses	"A three day vacation. It's hard because you needs to have packs, and the packs are not counted. So the more days off, the more packs you have, the longer is your therapy."
Confidentiality	sDOT can violate patient privacy	"I've had people not want to meet at their house … because they don't want their neighbors or their families to know that they're being treated for TB."
	vDOT is more private than sDOT	"You can do [vDOT] in your car on the way to work. You can sit out in your driveway and do it. I think it's more private than having a nurse come to the house."
Impact of DOT on staff	sDOT is inconvenient for staff	"The DOT worker has to adjust his schedule according to the patient's schedule. Sometimes they have to get up very early or drive far distances."
	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 5:00am."
	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 seven days a week, rather than five, 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."
Decisions about DOT should be patient centered	vDOT good for those who travel	"I've had patients that have [traveled] to Vietnam, China, England, Holland, and Los Angeles in the past month. So if they have to travel, I think [vDOT] would be a good thing."
	vDOT may not work in those less tech savvy	"..for the folks ... still using ... older, outdated [phone] models, or that aren't familiar with how to use an app ... it may be a little foreboding."
	Some may prefer sDOT	"Some patients are lonely ... They won't want [vDOT]. They will say, 'Oh you know, I love her to come into my house. Oh, it's nice to see her.'"
	vDOT should not just be a reward for those with good adherence	"It's almost like [some view] video DOT [as] a prize for those that can show that they are going to be compliant. We nurses don't look at it that way ... If [it]feels like I can get better compliance from them by offering them the vDOT option, I would like to jump on board quicker."
	Some with poor adherence on sDOT may actually do better on vDOT	"We [had a] patient that was highly non-adherent in standard DOT. She was missing three or four doses a week ... we were going to quarantine this individual, but [we

		decided to] attempt video DOT, and ... for about a month or two [she] was nearly 100% adherent on a seven-day regimen of medicine on video DOT."
vDOT on clinic operations	vDOT may increase clinic capacity	"I don't have to spend two hours, three 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."
	vDOT costs not as high as feared	"Phones may not be as big of a cost as I thought it would be ... Most of our patients had a cell phone or an iPad … we've loaned out like two phones."
Technology	High community level access to smartphones	"We have a fair amount of foreign-born people from all walks of life, and I am always amazed at how far advanced everyone is with smartphones ... almost everybody has them, almost everybody uses them."
	vDOT platform easy to use	"I'm so surprised at how user-friendly the software is and how few technical issues we've had."
Concerns about vDOT	Patients taking different medications than prescribed	"When I'm there I'm putting the meds in the packet and I'm putting the contents of the packet into your hands but now I'm watching you. I don't have any control ... so many drugs that look similar"
	Patients gaming the system	"There is the possibility that the patient may be deceptive ... They may pretend to take it. And you have no assurance that they really took it or dropped it on their lap."

sDOT=standard DOT (i.e. in-person), vDOT=video DO

Supplementary Table 4 (1.S.4): Full list of patient themes from qualitative analysis

PATIENT Themes

Theme	Subtheme	Illustrative quote
DOT efficacy	DOT is a necessary component of TB therapy	"…when you start [treatment] … you're sick … but if you're talking nine months medication, by month three [or] four you feel great and you figure, "Oh, I don't need [medicine] anymore." But you do. So it's important that [treatment] be monitored."
	DOT is unnecessary	"… [the nurses] are making sure that I'm taking my medicines on time, but as a responsible adult, I can take it myself."
	Reminders could replace DOT	"I think if they just sent reminders, that would be fine … I would take the medicines."
Impact of DOT on patients	DOT can engender perceived stigma	"I feel a stigma for having tuberculosis …this [in-person] DOT arrangement, it … emphasizes that I have something that not so many people have … we tried first to have a person to come during my lunch break and it was just terrible."
	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]."

	vDOT can allay DOT-related stress	"When someone was next to me [for in-person DOT], I felt awkward … they were asking me a lot of things, it was stressful. When I got to use the app, it was way better. "
	sDOT acts as a treatment reminder	"[sDOT] is good, because sometimes I forget about my medication, but when someone comes to observe you, no problem."
	sDOT daily visits are appreciated by some	"I built a relationship with my duty officer. She's a very caring nice person, and I look forward to seeing her every day."
	vDOT can be more convenient for patients	"I prefer taking the medication during the night time. So [vDOT is] convenient because you can take it on your own time."
	vDOT preferred over sDOT	"I think [vDOT] is 100% better than the standard [DOT] … definitely better."
DOT logistics	sDOT efficacy is limited by patient factors	"[sDOT] just doesn't work. Like tonight, I work, I don't get off until 7:30am and then I go to school … there is no time."
	vDOT increases access to transient patients	"When I was in Peru for two 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 … just avoid taking videos in places where you can be viewed by others … we have control."
Treatment effects of vDOT	vDOT provided treatment support	"I liked that the application asked me about side-effects. I sometimes selected "nausea," and then someone would call …we would try different strategies, like trying to eat before taking the pills."
	vDOT able to shorten therapy	"[With vDOT] I was able to take meds in the Dominican Republic. Before I would have had to take [self-administered medication] packets, which are not observed and don't count … my treatment would have been three weeks longer."
	vDOT can improve treatment self-efficacy	"My ability to continue life in a very normal way [by using vDOT] made it easier to carry on with the treatment … the medication was hard … but because I was able to travel as I wished it was easier for me to follow the regimen."
Technology	High community level access to smartphones	"A smartphone is what everybody keeps in their hand all the time … no problem."
	Many patients are tech savvy	"Well, I use the internet … Facebook … and things like that … doesn't everyone?"
	The miDOT platform was easy to use	"You don't even have to be able to read English. Once they show you [how to use miDOT], its fine. You just follow the pictures."

sDOT=standard DOT (i.e. in-person), vDOT=video DOT

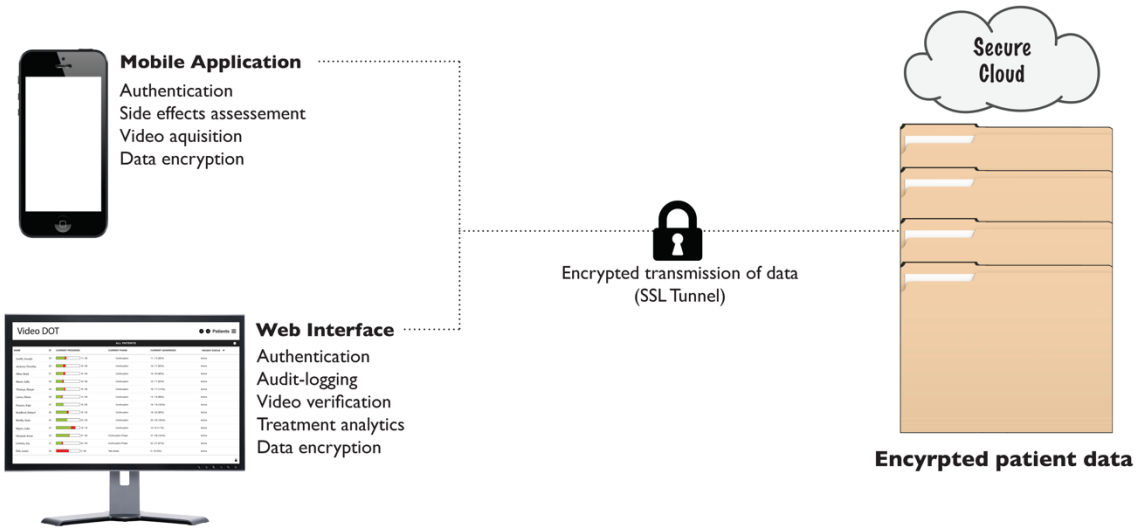
Supplementary Table 5 (1.S.5): Key parameters from cost analysis.

	Base-case	Low	High
Equipment[1]			
Economy car (DOH vehicle)	$16,400	$13,000	$35,000
Computer	$1,000	$600	$1,500
Smartphone	$250	$120	$770
Consumables[1]			
Mileage reimbursement (per mile)	$0.54	-	-
Gasoline (per gallon)	$2.20	$1.69	$2.35
Mobile data plan (per month)[2]	$32.50	$30.00	$50
Software (per patient month)[3]	$50	$0	$100
Labor (per hour)[4]			
Registered nurse (RN)	$38.13	$31.40	$44.85
Licensed practical nurse (LPN)	$30.21	$28.14	$39.06
DOT worker	$28.65	$18.23	$31.25

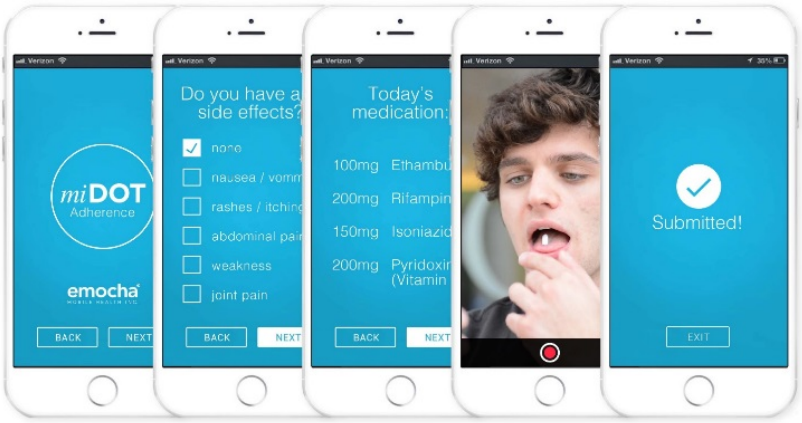
[1] Equipment and consumable costs were estimated through time-motion studies and publicly available commercial pricing.
[2] Reflects cost of data plans able to accommodate the minimum needs of the miDOT platform (2-3 GB per month).
[3] Estimates of miDOT platform costs were obtained through direct communication with emocha Mobile Health Inc.
[4] Hourly wage estimates were obtained through direct communication with TB clinic administrators and from general estimates provided by the US Bureau of Labor Statistics (https://www.bls.gov).

FIGURES

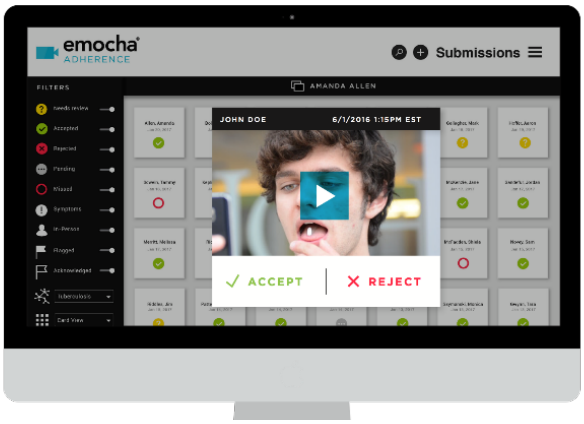
Figure 1 (1.1): Schematic of data acquisition and transmission on miDOT [emocha].



Supplementary Figure 1 (1.S.1): miDOT [emocha] platform

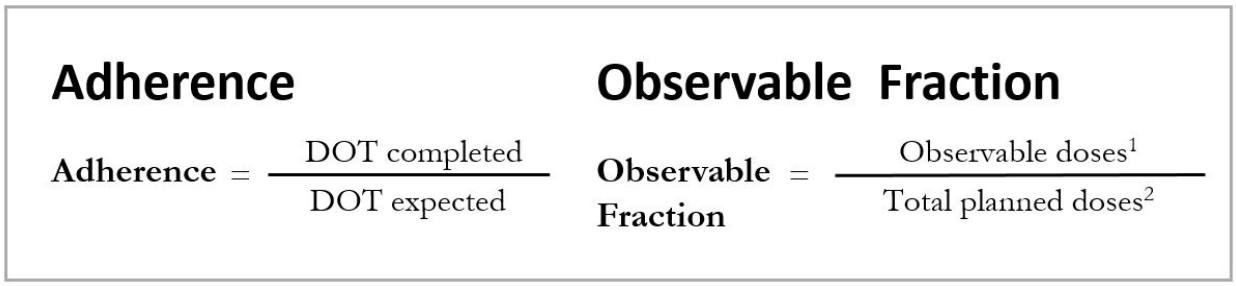


Patient facing



Provider facing

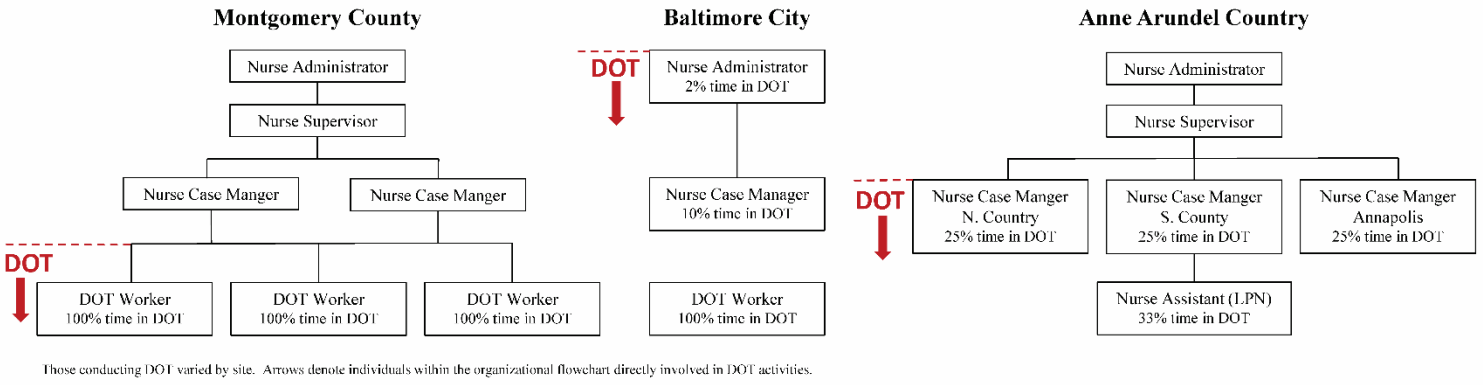
Supplementary Figure 2 (1.S.2): Treatment metrics



[1] Inclusive of all observed doses, either by video or in-person. Includes rejected and unexpected videos, the latter representing those submitted on days patient was not planned for observation, most often weekend videos submitted by those on M-F vDOT.
[2] Total number of planned doses, inclusive for weekend/holiday self-administered.

Supplementary Figure 3 (1.S.3): Site-specific variation in DOT implementation structure.

All staff listed below the dashed line were directly involved in DOT implementation. The educational training/background of those conducting DOT ranged from that of a community health worker (CHW), with no specific health training (all high school graduates), to a licensed practical nurse (LPN) to a registered nurse (RN). Across sites, those conducting DOT also varied in their location within the organizational hierarchy.



Those conducting DOT varied by site. Arrows denote individuals within the organizational flowchart directly involved in DOT activities.

Site specifics:

	Transportation	Average Case load (total)
Montgomery County	Department vehicle	4
Baltimore City	Personal vehicle (mileage reimbursement)	16
Anne Arundel County	Personal vehicle (mileage reimbursement)	15

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Chapter 2

Use of smartphone-based video directly observed therapy (vDOT) in tuberculosis care: a single arm, prospective, feasibility study

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Keywords. Video DOT; mHealth; tuberculosis; medication adherence; telemedicine; India

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ABSTRACT

Background.

India accounts for nearly one quarter of the global tuberculosis (TB) burden. Directly observed therapy (DOT), through in-person observation, is recommended in India, though implementation has been heterogenous due largely to resource limitations. Video DOT (vDOT) is a novel, smartphone-based approach which 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 a feasible, though little is known about the role it may play in resource limited, high burden settings.

Objective.

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 were enrolled. The median number of weeks on vDOT was 13 (11-16). Median *adherence* was 74% (IQR 62-84) and median *verifiable fraction* was 86% (IQR 74-98). Greater 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.

INTRODUCTION

Globally, tuberculosis (TB) is the leading cause of infectious disease-related mortality, responsible for 1.6 million deaths annually [1]. Incident TB is higher in India than anywhere in the world, with roughly 2.8 million cases, nearly 27% of the global TB burden, reported in 2017 [1]. To achieve positive treatment outcomes, adherence to TB therapy is critical [2, 3]. However, socioeconomic and health systems 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. It additionally emphasizes monitoring through directly observed treatment (DOT) [7]. Compared to 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 (though 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 (i.e. observing and documenting each prescribed dose) in the community is inconsistent and associated barriers can lead to treatment default [10-16].

More recently, video directly observed therapy (vDOT) has been introduced as a patient-centered alternative to in-person DOT. Herein, pill ingestion is monitored remotely via digital video capture. vDOT has been implemented using synchronous technologies [17-20], such as Skype and FaceTime, as well as asynchronous ones [21, 22], wherein 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 [21-28]. Further, two economic evaluations in the United States have suggested vDOT to be cost-savings over in-person DOT [21, 28]. These encouraging findings have led both the Centers for Disease Control (CDC) and the WHO to suggest vDOT as a viable alternative to in-person DOT [29-31].

While data on vDOT is becoming increasingly robust, vDOT has yet to be rigorously evaluated within low/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 [32, 33]. What's more, recent changes to the RNTCP guidelines have prioritized daily therapy (i.e. 7 days/week) over thrice-weekly therapy (i.e. 3 times/week), with DOT expected daily, a change which only 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, 34, 35].

To address this critical knowledge gap, we conducted a prospective pilot of vDOT in Pune, India. Specifically, we address 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 with the aim to assess its feasibility and acceptability within a resource-limited, high disease burden setting. The mobile app *emocha video DOT* (emocha Mobile Health Inc.; product formerly known as miDOT) was used for treatment monitoring and adherence support (Figure 1). emocha is HIPAA-compliant (i.e. meets internet security and privacy standards keeping with US HIPAA regulations) and allows for asynchronous vDOT (Figure 2). The study was conducted at the Dr. D.Y. 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 (IRB) at Johns Hopkins University in Baltimore, Maryland USA.

Participants

Dr. D.Y. Patil Medical College Hospital is a private hospital, which contains a government (public) TB treatment center (DOTS center) as a Public-Private Mix (PPM) initiative. Patients diagnosed and/or treated with TB at either Dr. D.Y. Patil or at local DOTS centers were eligible for the study. Inclusion required age $\geq$18, signed informed consent and $\geq$2 remaining months of TB therapy. Patients with multi-drug resistant (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, though many were assessed for eligibility mid-treatment. 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], though implementation is heterogenous and largely determined by local resources and patient preference [16] [personal communication Dr. Tushar Sahasrabudhe, 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, as well as a one-time incentive payment of Rs. 100 (~US $1.5) to cover travel expenses.

Study Procedures

Overall 35 patients based on convenient sampling method were selected for this study. All patients provided written informed consent and were allowed to withdraw from the study at any time. Demographic information and specifics related to each participants' medical history and TB diagnosis were collected using a standardized CRFs (case report forms). Data was subsequently entered into a digital database by study staff. During their first study visit, each participant was introduced to vDOT by a study staff member, who provided each with a unique username/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. Added training was provided on an as-needed basis.

Prior to formal enrollment, patients underwent a conditional one-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 (e.g. 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 or not 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.

Acceptability

To assess vDOT acceptability among patients a post-treatment survey was administered; a series of categorical and Likert-scale questions addressed 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 to 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

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 both technological barriers (e.g. inability to effectively use platform or poor cellular/WiFi

connectivity) as well as psychosocial ones (e.g. concerns regarding privacy). 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 years (IQR 24-42), 40% (10 of 25) were female and 72% (18 of 25) reported their local language as "Marathi." Most patients were low income with a monthly income less than INR 16000 (US ~$225). The majority of patients (88%, 22 of 25) had access to a smart phones and internet. Three patients (12%, 3 of 25) required the use of a study phone. Seventy-two percent patients (18 of 25) had pulmonary TB, while the remainder (28%) had extra pulmonary disease.

The majority of patients were initiated on vDOT during the continuation phase (80%, 20 of 25), with 20% (5 of 25) beginning during the intensive phase. The median number of weeks on vDOT was 13 (IQR 11-16), with a range of 9 to 23 weeks (Table 2). Eighty percent of patients (20 of 25) received daily (7x per week) therapy, while 20% (5 of 25) received an intermittent, thrice weekly (3x per week) regimen. No in-person DOT was documented either before or after implementation of vDOT. Overall, 60% (15 of 25) of patients reported at least one treatment-related side effect. The most commonly reported symptoms were the following: nausea/vomiting (8 of 15), abdominal pain (3 of 15) and itching (2 of 15).

Feasibility

Median *adherence* on vDOT was 74% (IQR 62-84) (Table 2). After including verbally verified doses (following unverifiable or incomplete videos), the median *verifiable fraction* was 86% (IQR 74-98). An average of 91 videos (SD ±53) were submitted per patient. The average number of rejected videos per patient was 1.6 (SD ± 2.4), with 56% (14 of 25) having no rejected videos at all. The most common reasons for video rejection were "poor quality of video" and "medication not fully seen." The median video length was 44 seconds (IQR 31-52), and associated with a median file size of 1.5 mb (IQR 1.1-1.7).

Acceptability

A total of 22 post-treatment surveys were completed. Three 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%.

Ninety one percent of surveyed patients described emocha as “easy to use” (Table 3). All patients (100%, 22 of 22) reported being able to record videos without difficulty and 95% (21 of 22) were able to upload without difficulty. Ninety one percent 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 (91%, 20 of 22) and preferred (91%, 20 of 22) over in-person DOT (Table 4). While 82% (18 of 22) felt vDOT would preserve patient privacy over in-person DOT, 18% (4 of 22) disagreed and felt in-person DOT would be more private.

Study coordinator notes were reviewed and summarized (Figure 4). Broadly, these notes revealed patient-level barriers impacting the successful implementation and utilization of vDOT (Figure 4). Included were psychosocial factors, such as the privacy concerns and stigma, as well as mental health barriers. Despite survey data suggesting that most were able to record and upload videos without issue, poor connectivity and cellphone-related challenges (e.g. SIM card malfunction) were noted in a few cases.

DISCUSSION

Our pilot study suggests that vDOT may be a feasible option for verification of medication adherence for TB patients in India. Among enrolled participants that 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, or *verifiable fraction*, increased to 86% (based on 1,722 submitted and reviewed videos), exceeding the adherence goal of >80% set forth by current treatment guidelines [29]. What's more, this degree of adherence is comparable to that described using vDOT in other settings, such as the USA, and advances current evidence supporting vDOT, as prior work has largely focused on implementation within resource rich settings [17, 21, 28, 36]. 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, thrice weekly therapy [14, 34, 35]. 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 six 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. Video DOT 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. Video DOT saves health care worker time and obviates the need for in-person visits to observe treatment [23]. For settings where home-visits are employed solely for DOT, vDOT may reduce costs and save time even further[19, 21, 28, 37, 38]. Video DOT may also have other previously unrecognized benefits related to infection control. Provisions for personal protective equipment (i.e., 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. Nevertheless, our study also highlights a need for patient training (e.g., *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, which requires patient to place an incomplete phone-call to a provided number at the time of pill ingestion [12, 34]. While 99DOTS may be a feasible means for basic adherence monitoring [39], vDOT has the distinct advantage of providing video confirmation of pill ingestion. It is also important to consider that the usage 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, which may further support treatment adherence. India recently rolled out a Direct Benefits Transfer (DBT) scheme, which encourages treatment adherence through the use of financial incentives (Rs. 500 per month while on therapy) [40, 41]. 99DOTS is currently being used as a mechanism to monitor treatment adherence, but is limited. For the reasons noted above, a more reliable, tamper-proof, means of adherence monitoring would be beneficial.

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, it's acceptability and feasibility in other parts of India remains unknown. Secondly, 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 pre-study adherence). On the other hand, our findings suggest that vDOT implementation could substantially improve adherence documentation, as compared to current practice. Through broader implementation, vDOT has the potential to enable enhanced accountability among TB clinics with regards to treatment adherence. Improvements in documentation would also increase the availability of high-quality data on TB treatment completion for public health reporting practices. Finally, whether vDOT is associated with improved patient outcomes compared to 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 technologic barriers related either to infrastructure (e.g. inconsistent cellular coverage) or inability/unease with smartphone operation. Further, despite the fact that we utilized 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. On the other hand, usage of a *run-in* 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 completing the *run-in*, and enrolling in the study, successfully finished therapy on vDOT.

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. Lastly, in other settings, such as the US, 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 [21].

Overall, our work has shown that despite socioeconomic and structural barriers, vDOT may be a feasible approach for treatment monitoring in India.

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We would like thank all those working hard to provide quality clinical care at D.Y. Patil and at the local DOTS centers throughout Pune. In particular, we thank Dr. Madhusudan Barthwal and Dr. Shailesh Meshram. We would also like to thank the team at emocha Mobile Health Inc. for providing technical support and leadership throughout the study. Specifically, we would like to thank Sebastian Seiguer JD MBA, Katrina Rios and Gorkem Sevic MSE.

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 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 use of miDOT or enrollment in the study was made by non-conflicted department of health clinicians and staff; M.S. recused himself from all data analysis but assisted with results interpretation.

Author Contributions

Study concept and design: M.S. Acquisition of data: S.A., S.B.H. S.A, D.J., T.S, S.M, M.B, A.K. Statistical analysis: S.A., S.B.H. Data interpretation: S.B.H, M.S., S.A. T.S. Drafting of initial manuscript: S.A., S.B.H. Manuscript revision: All authors.

Abbreviations

CDC: Centers for Disease Control and Prevention

DOT: directly observed treatment

MDR-TB: Multidrug-resistant tuberculosis

RNTCP: Revised National Tuberculosis Control Program

TB: Tuberculosis

vDOT: video directly observed therapy

WHO: World Health Organization

TABLES

Table 1 (2.1): Patient and disease characteristics

Variable			All patients (n=25)
Age, year (median, IQR)			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 (%)			
	>16,000		0 (0)
	8,000 – 16,000		13 (52)
	4,000 - 8,000		6 (24)
	2,000 – 4,000		0 (0)
	<2,000		6 (24)
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 (%) [a]			
	Alcohol		1 (4)
	Tobacco use		0 (0)
	Illicit drug use		0 (0)
Medical comorbidities, n (%) [a]			
	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)
TB category, n (%)			
	Pulmonary [b]		
		Smear positive	14 (56)
		Smear negative	4 (16)
	Exclusively extra pulmonary		7 (28)

[a] Categories not mutually exclusive, each out of 25 total participants.
[b] Pulmonary disease with or without extra pulmonary involvement.

Table 2 (2.2): Video DOT outcomes and data utilization

Variable		**vDOT (n=25)**
Adherence (%) [a]		
	Median (IQR)	74 (62-84)
Verifiable fraction (%) [b]		
	Median (IQR	86 (74-98)
Dosing frequency, n (%)		
	3x/wk DOT	5 (20)
	7x/wk DOT	20 (80)
Treatment phase at enrollment, n (%)		
	Intensive phase	5 (20)
	Continuation phase	20 (80)
Number of weeks on vDOT, median (IQR)		13 (11-16)
Total uploaded videos (n) [c]		1,722
Mean uploads per patient, mean (SD)		91 (53)
Number of rejected videos per patient		
	Mean (SD)	1-6 (2.4)
	Range	0-8
Video length, sec		
	Median (IQR)	44 (31-52)
Video size, mb		
	Median (IQR)	1.5 (1.1-1.7)

[a] Proportion of total prescribed doses completed under video observation. Of note, no in-person DOT was noted either before or after the implementation of vDOT.

[b] Proportion of total prescribed doses verified by any means. Verification included successful observation by video upload, as well verbal dose-confirmation (by phone or in-person) following the submission of an incomplete, or poor quality, video.

[c] Total video uploads across all patients over the length of the study. Composite of accepted videos + rejected videos + run-in phase videos.

Table 3 (2.3): Responses from patient agreeability survey

Survey questions: graded on a Likert scale	**Agree** n (%)	**Disagree** 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 five-point Likert scale was used. Agree/strongly agree and neutral/disagree/strongly disagree were grouped for the above reporting. Three patients declined participation. Study outcomes for those declining involvement were similar of the general study population; each patient completed >14 weeks on vDOT with an adherence $\geq$ 70%.

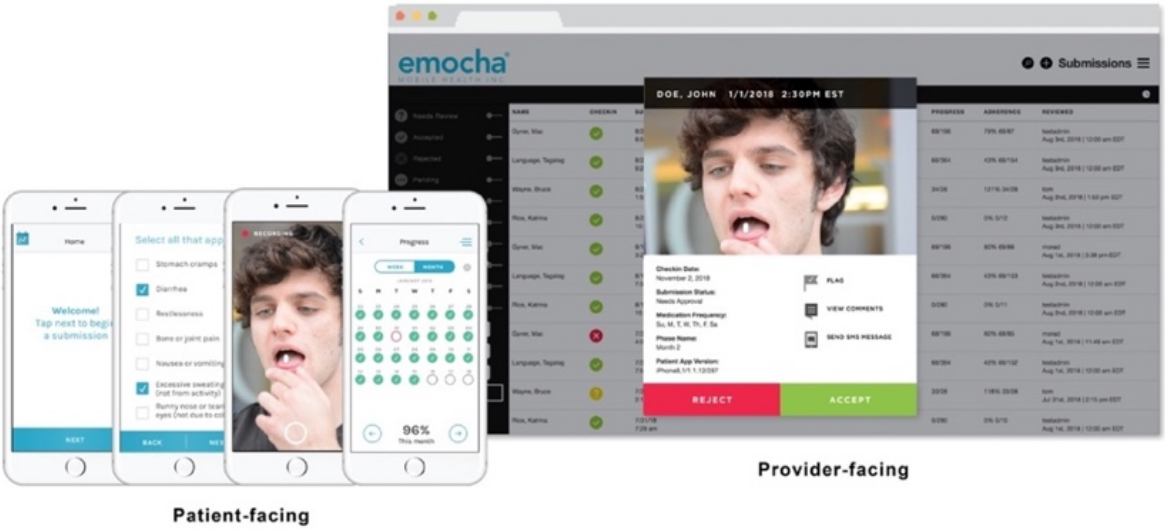
Table 4 (2.4): Responses from patient preference survey

Survey questions: categorical		**All patients** n (%)
Videos were most often uploaded using		
	WiFi at the clinic	0 (0)
	WiFi at home or other location	0 (0)
	Cellular data (3G/4G)	22 (100)
Which better preserves patient privacy? [a]		
	vDOT	18 (82)
	In-person DOT	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 DOT, either prior to enrollment or while on vDOT, was inconsistently performed and/or documented based on chart reviews. Answers referring to in-person DOT are therefore based on patients' perceptions of what in-person DOT would be like.

FIGURES

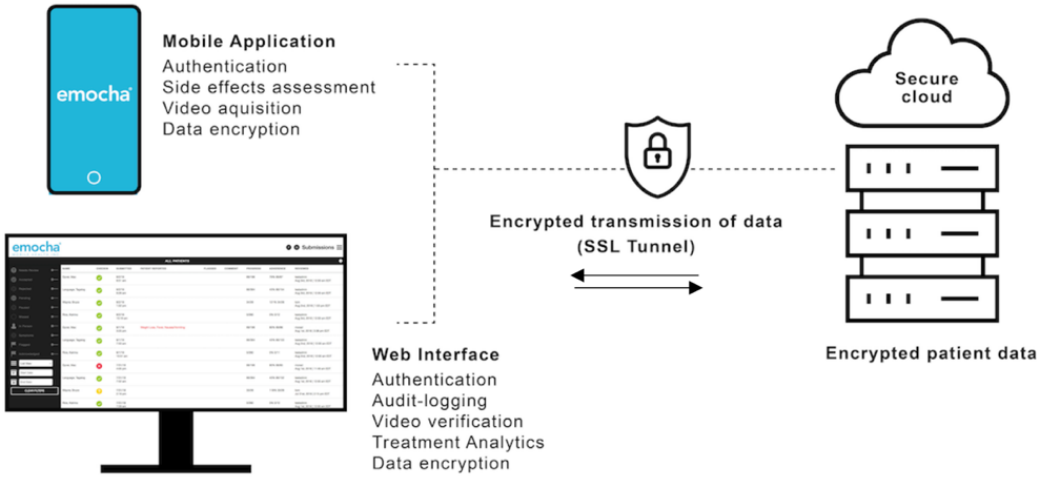
Figure 1 (2.1): The emocha [formerly miDOT] platform



The *patient-facing* portion of the platform (i.e. 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 pre-populated list). Through a calendar function, patients are able to review treatment progress and track adherence. Use of the software requires a camera-enabled device (tablet or smartphone), with at least intermittent access to WiFi 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 with internet access using an internet browser (e.g., Chrome, Firefox, or Microsoft Internet Explorer or Edge) and

is used by medical staff to review treatment videos. Given the system's asynchronous nature, submitted videos could can be reviewed at any time following digital capture and transmission. Through this interface providers are also notified of any patient-reported treatment side effects.

Figure 2 (2.2): Security and data flow on vDOT (emocha)



Video-capture occurs via the emocha app. Patient data is encrypted locally (within the smartphone) and uploaded (when internet available) immediately to a secure cloud storage site via an encrypted transmission tunnel. 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 (wifi or cellular data). Following transmission, videos are automatically wiped from smartphone memory. Encrypted patient data, therefore, remains 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.

Figure 3 (2.3): Study flow diagram

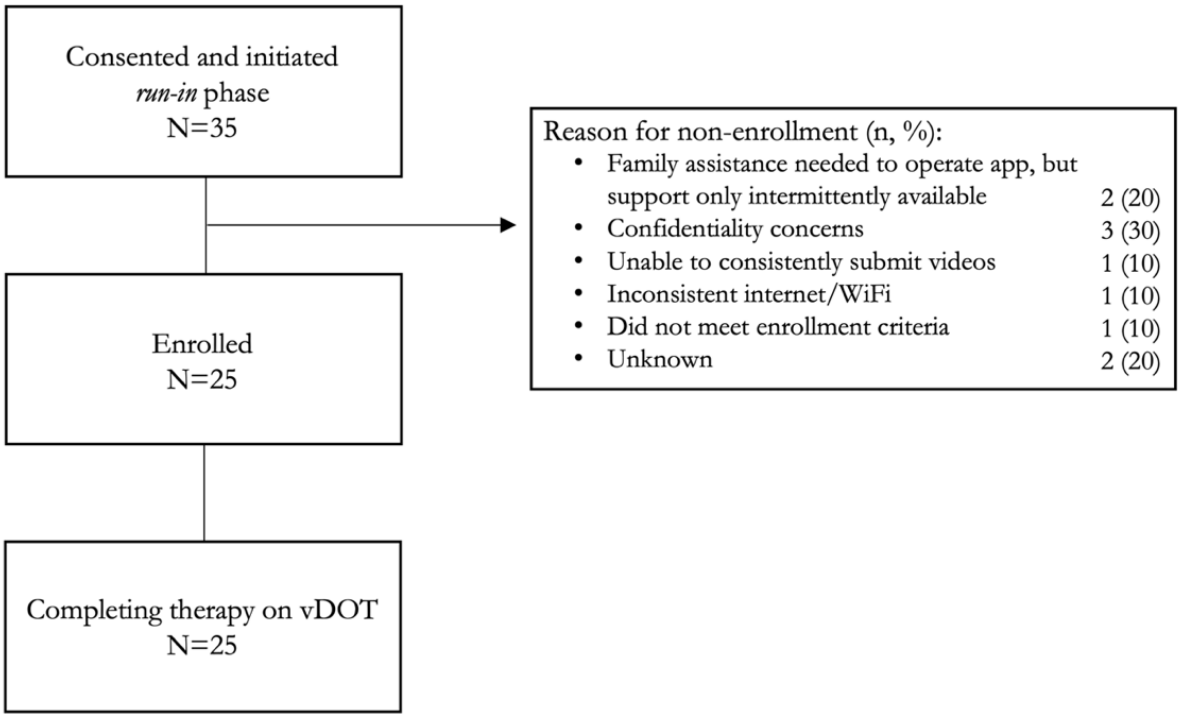


Figure 4 (2.4): Patient-level barriers to successful vDOT utilization.

As identified by study staff.

	Barrier to vDOT 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, though was 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 one-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, but 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 internet, I could not send videos."
	vDOT related challenges	"The registration process is 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 card	"I did not submit 'know your customer' (KYC) documents required for SIM verification. Hence my sim card was deactivated for some time … I was not able to send videos".

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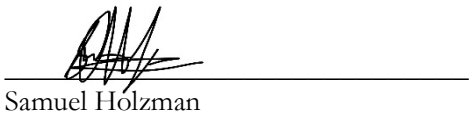
CURRICULUM VITAE



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Education and Training

Undergraduate	2001-2005	Honors Bachelor of Science, Brown University, *Providence, RI*
Masters	2016-2020	Masters of Science, Johns Hopkins Bloomberg Sch of Pub Health, *Baltimore, MD*
Doctoral	2008-2012	Doctor of Medicine, Icahn Sch of Med at Mount Sinai, *New York, NY*
Postdoctoral	2012-2015	Residency, Internal Med, Johns Hopkins Univ Sch of Med, *Baltimore, MD*
	2015-2018	Clinical Fellow, Infectious Diseases, Johns Hopkins Univ Sch of Med, *Baltimore, MD* Mentors: Maunank Shah, MD, PhD

Professional Experience

2006-2008	Field Director, Brown University, Internal Health Institute (IHI), *Tafuna, American Samoa*
2005-2006	Program assistant, Medical Practice and Policy, DIS, *Copenhagen, Denmark*

PUBLICATIONS:

Original Research [OR]

1. **Holzman SB**, Atre S, Sahasrabudeh T, Amike S, Jagtap D, Sayyad Y, Kakrani A, Gupta A, Mave V, Shah M. Use of smartphone-based video directly observed therapy (vDOT) in Tuberculosis care: single-arm, prospective feasibility study. *JMIR Form Res.* 2019. 3(3)
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3. **Holzman SB**, Zenilman A, Shah M. Advancing patient-centered care in tuberculosis management: a mixed methods appraisal of video directly observed therapy (vDOT). *Open Forum Infectious Diseases.* 2018. 5(4)
4. **Holzman SB**, Rastegar D. AST: A Simplified Tool for Managing Alcohol Withdrawal. *J Addict Med.* 2016. 10(3):190-5
5. Sanford E, **Holzman SB**, Haney R, Bertness M. Larval Tolerance, Gene Flow, and the Northern Geographic Range Limit of Fiddler Crabs. *Ecology.* 2006. 87 (11): 2882-94; study design, data collection, analysis, manuscript preparation

Case Reports [CR]

1. **Holzman SB**, Durso SC. Nutritional Deficiency and Acquired Ichthyosis. *J Gen Inten Med.* 2017. 32(10):1161-1162
2. Smith AJB, **Holzman SB**, Manesh RS, Perl TM. Gonococcal Conjunctivitis: A Case Report of an Unusual Mode of Transmission. *Pediatr Adolesc Gynecol.* 2017. 30(4):501-502; manuscript preparation

Media Releases or Interviews [MR]

1. Slabodkin G. Healthcare workers watch TB patients take meds with app. *HealthData Management.* May 8, 2018.

2. Smartphone App Keeps an 'Eye' on Daily Tuberculosis Therapy. Press Release, Johns Hopkins Medicine. April 26, 2018.

Published Curricula [PC], Learner Assessment Tools, Educational Evaluations, Assessment/Evaluation Instruments [PC]

1. **Holzman SB**, Workneh M, Stanton M. An Introduction to HIV/AIDS, Hepatitis C and Substance Abuse. Resident Guide. Comprehensive Care Practice, Johns Hopkins Sch of Med. 2014.

FUNDING

EXTRAMURAL Funding

PAST

2016-2018 T32 Postdoctoral Training Grant
T32AI007291-25
National Institutes of Health
Sara Cosgrove, MD, MS
Clinical Fellow in Infectious Diseases

2017 NTCA/NSTC Travel Award
Travel Scholarship
National TB Controller's Association / National Society of TB Clinicians
$1,500
Afforded opportunity to present at the society's national conference

2013 Tuition/Travel Scholarship
Summer Institute of Advanced Epidemiology and Preventative Medicine
Tel Aviv Sch of Public Health
$5,000
Supported participation in a vaccine development course

2009 Global Health Research Scholarship
Milton B. Rosenbluth Foundation
$5,000
Supported community-based research in Gorongosa, Mozambique

2004 Howard Hughes Undergraduate Research Fellowship
Howard Hughes Medical Institute
$3,500
Supported summer research

INTRAMURAL Funding

CURRENT

2016-present GTPCI ScM Tuition Scholarship Award
Graduate Training Program in Clinical Investigation
Johns Hopkins Bloomberg School of Public Health
$154,420 (over three years)
Full-tuition support as well as $2,500 for research-related expenses

PAST

2016-2017 EPIC Support for the Johns Hopkins Division of Infectious Diseases
Johns Hopkins Department of Medicine
$5,000
Provided hands-on support and system customization during EPIC roll-out

2014 Paul S. Lietman Global Health Travel Fellowship
Johns Hopkins Center for Global Health
$5,000
Supported TB research project in Mumbai, India

2014 Johns Hopkins Pyramid Grant

Johns Hopkins Center for Innovative Medicine
$1,000
Proposal to integrate patient photographs into the medical record

2010 Global Health Research Scholarship
Mount Sinai Center for Global Health
$5,000
Supported community-based research in Gorongosa, Mozambique

2009 Global Health Research Scholarship
Mount Sinai Center for Global Health
$5,000
Supported community-based research in Gorongosa, Mozambique

2003 Karen T. Romer Undergraduate Teaching and Research Award
Brown University
$3,500
Supported summer research

CLINICAL ACTIVITIES

Certification

Medical, other state/government licensure

2016-present Medical license, Maryland, D82383
2016-present DEA registration, FH6626292

Boards, other specialty certification

2020 Infectious Diseases (anticipated)
2015 Internal Medicine (ABIM)
2013 USMLE Step 3, 250
2011 USMLE Step 2 CK, 243/83; USMLE Step 2 CS pass
2010 USMLE Step 1, 239/99

EDUCATIONAL ACTIVITIES

Teaching

Classroom instruction

Feb 2018 Faculty mentor, medical students, Micro Workshop, Johns Hopkins Sch of Med
Feb 2018 Small group leader, medical students, Clinical Microbiology, Johns Hopkins Sch of Med
Feb 2017 Small group leader, medical students, Global Health TIME Course, Johns Hopkins Sch of Med
Nov 2016 Clinician preceptor, medical residents, Infectious Disease AM Report, Johns Hopkins Bayview

Mentoring

Post-doctoral mentees

2018-2019 Christopher Prater, MPH candidate

ORGANIZATIONAL ACTIVITIES

Editorial Activities

Journal peer review activities

2017-present American Journal of Tropical Medicine and Hygiene
2016-present Open Forum Infectious Diseases
2016-present Journal of General Internal Medicine

Professional Societies

National Tuberculosis Controllers Association (NTCA), member
Infectious Disease Society of America (IDSA), member
American Medical Association (AMA), member
Society of General Internal Medicine (SGIM), member

Sigma XI, Scientific Research Honor Society

RECOGNITION

Awards, Honors

2017 Dr. Joseph Pergolizzi Award for Clinical Research, *Johns Hopkins Bloomberg School of Public Health*
2008 Seymour L. Kaplan Scholarship Foundation, Scholarship for Academic Excellence
2006 James Kidwell Prize in Genetics and Population Biology, *Brown University*

Invited Talks

JHMI/Regional

Sep 2018 "Tuberculosis diagnostics." Johns Hopkins Bloomberg School of Public Health. *Baltimore*, MD
Apr 2018 "What's new in TB?" Federal Training Centers Collaborative. Association of American Medical Colleges. *Washington, D.C.*
Apr 2018 "Tuberculosis for the primary care doctor." Grand rounds. Baltimore Medical Systems. *Baltimore, MD*
Nov 2017 "Directly Observed Therapy." CDC Regional Tuberculosis Training. Rutgers Global Tuberculosis Institute. *Baltimore, MD*
Sep 2017 "Video DOT: Can we bring directly observed therapy to HIV care? Association for Nurses in AIDS Care. *Baltimore, MD*
Jun 2017 "Implementation of Video Directly Observed Therapy in Maryland." Center for TB Research Annual Scientific Meeting. Johns Hopkins Hospital. *Baltimore, MD*
Jan 2017 "Drug Resistant Bacteria: The rise of antimicrobial resistance and the decline of novel therapeutics." Icahn Sch of Med at Mount Sinai, *New York, NY;* InFocus2: Curriculum on Global Health

National

May 2017 "Employing Geospatial Methods to Target Patients at High-risk for Latent Tuberculosis." Tuberculosis Epidemiologic Studies Consortium, Centers for Disease Control, *Atlanta, GA*

International

Oct 2009 "Obesity, Diabetes and Efforts to Reduce the Burden of Noncommunicable Disease in American Samoa." Micronesian Medical Symposium. *Guam, USA*

OTHER PROFESSIONAL ACCOMPLISHMENTS

Oral/Podium Presentations [abstracts that were both presented orally and published]

May 2017 **Holzman SB**, Shah M. "Feasibility, Acceptability and Cost of Video Directly Observed Therapy in Maryland." National TB Controllers Association. *Atlanta, GA*
Mar 2017 **Holzman SB**, Chapman S, Rios KC, Shah M. **"**Implementing Mobile Health for Tuberculosis Care in Sydney: Experience with video directly observed therapy." Australasian Society for Infectious Diseases. *Sydney, Australia*
May 2015 **Holzman SB**, Rastegar D. "AST: A Simplified Tool for Managing Alcohol Withdrawal." Society of General Internal Medicine. *Toronto, Canada*
Aug 2010 **Holzman SB**, Hahn S, Stephens L, Mutemba M, Hennig N. "Human-Elephant Conflict as a Major Ecohealth Concern in Communities within the Buffer Zone of Gorongosa National Park, Mozambique." EcoHealth: International Association for Ecology and Health, *London, England*
Aug 2010 Hahn S, Stephens L, **Holzman SB**, Mutemba M, Hennig N. "Deforestation as a Major Ecohealth Concern in Communities within the Buffer Zone of Gorongosa National Park, Mozambique." EcoHealth: International Association for Ecology and Health, *London, England*

Posters

May 2015 **Holzman SB**, Banka R, Udwadia Z. "Bedaquiline, a New Weapon in an Old Fight." American College of Physicians. *Boston, MA*

May 2015	Liebowitz J, Lee K, Shenderov E, **Holzman SB**. "Profound Pernicious Anemia Causing Pancytopenia and Elevated Lactate Dehydrogenase." American College of Physicians. *Baltimore, MD.*
Apr 2015	**Holzman SB**, Udwadia Z, Gupta A. "Exploring Drug-Resistant TB and Novel Therapeutics in Mumbai, India." Global Health Day, Center for Global Health at Johns Hopkins Univ. *Baltimore, MD*
Nov 2010	Hahn S, Stephens L, **Holzman SB**, Hennig N, Anadaraja N. "Integrating Population, Health, and the Environment: Connecting community reproductive health concerns with health interventions in the context of conservation." American Society of Tropical Medicine and Hygiene. *Atlanta, GA*

Leadership

2013-2015	Program representative, Johns Hopkins House Staff Council, *Baltimore, MD*
2013-2015	Founding member, Bayview Global Health Interest Group, Johns Hopkins Univ, *Baltimore, MD*
2011-2012	Committee member, Admissions Committee, Icahn Sch of Med at Mount Sinai, *New York, NY*
2009-2012	Student rep, Arnold Inst for Global Health, Icahn Sch of Med at Mount Sinai, *New York, NY*
2011	Clinical skills mentor, peer-to-peer support, Icahn Sch of Med at Mount Sinai, *New York, NY*

Community Services

2013-2015	Patient advocate and founding member, Hopkins/International Rescue Committee Collaborative Engagement Initiative, Johns Hopkins Bayveiw Medical Center, *Baltimore, MD*
2010-2012	Founder, ENGAGE: The student-teen self-efficacy partnership, Icahn Sch of Med at Mount Sinai, *New York, NY*
2008-2012	Junior Clinician, East Harlem Health Outreach Partnership, *East Harlem, NY*
2008-2009	Diabetes educator, Reach OUT!, Boriken Neighborhood Health Center, *East Harlem, NY*