

Digital Adherence Technologies for TB: Translating Surveillance to Care

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Abstract

Digital adherence technologies (DATs) have been deployed in India and are being scaled nationally with the goal of improving TB medication adherence and treatment outcomes. The governing principle of DATs is rooted in historical models of care that equated patient surveillance with care delivery in the treatment of TB. These forms of care delivery have evolved from directly observed therapy (DOT) to modern, sophisticated technology-enabled models of digital surveillance. The impact of this form of surveillance on patient adherence, outcomes, or any other dimensions of well-being is unknown and remains to be studied. Yet, the political economy of modern technologies render digital surveillance as an obvious solution to be taken up by governments for disease management. Here, the first large-scale implementation of the digital adherence surveillance models in India is examined in order understand the justifying rationale and the exact mechanism through which digital surveillance is translated to care for the TB patient.

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Part 1: Historical Models of Care

The TB Epidemic

Tuberculosis (TB) is the leading infectious cause of death globally from a singular infectious agent (*Mycobacterium tuberculosis*), with 10 million people falling ill with the disease.⁽¹⁾ In 2018, 1.5 million people died from TB despite the existence of effective drug treatments since the 1940s.⁽¹⁾ Current guidelines for treatment for drug-susceptible TB consist of a 6-month regimen of four drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide, with an estimated treatment success rate of 85% globally. Treatment regimens for drug-resistant TB, require more complex, expensive, highly toxic regimens with a treatment duration of 18-24 months,⁽²⁾ and a treatment success rate of 56% globally.⁽¹⁾

The burden of tuberculosis (TB) in India is the highest in the world and persists despite of over 55 years of TB control and care delivery. India has the world's highest incidence of TB, with 2.8 million cases annually, and accounts for more than a quarter of the global TB burden, with an estimated half a million people dying of the disease each year.⁽¹⁾ India also has the largest burden of multi-drug-resistant TB (MDR-TB) among all countries, with almost 150,000 cases every year. In contrast, the United States reports a little over 9,000 cases of TB in the entire country each year-- about the same as the number of cases reported in only 3 months of just one Indian urban city of Patna, belonging to one of the poorest states in India.⁽¹⁾

The inability to save patients from a curable disease for which effective treatment has long been available-- requires a transformation in how patients are being perceived and cared for. In recent years, India has taken several critical steps to position itself as a leader in TB care. The Government of India's National Strategic Plan for TB Elimination 2017-2025⁽³⁾ details and ambitious agenda with targets that would create a historic achievement for the country.

TB in Postcolonial India

The long-standing link between social and structural determinants and incidence of TB was made undeniable through the daily suffering of millions of tuberculosis patients of colonial India who lived in dismal social conditions- and the half a million that died annually from the disease. These conditions included unsanitary environments and housing, overcrowding with multiple individuals sleeping in small rooms, absence of light or ventilation, low consumption of milk and meat, and poor overall food security.⁽⁴⁾ Colonial practices of industrialization, urbanization, and migration to cities with poor sanitation and housing-- increased incidence and mortality rates.⁽⁵⁾

Tuberculosis control in colonial British India was primarily led by voluntary efforts of medical missionaries and regional physicians. The Tuberculosis Association of India was established in 1939 by local physicians and missionaries to undertake the prevention and treatment of tuberculosis. Convenings and conference of the members of the Association in 1939 revealed a fundamental understanding of tuberculosis as a disease of poverty, manifested through overcrowding and malnourishment and various social determinants.⁽⁴⁾ In November 1946, at the dawn of Indian independence, the Technical Advisor of the Tuberculosis Association of India at a Tuberculosis Workers' Conference in Delhi, emphasized the large gap in resources and facilities to treat TB patients and declared the training health workers to deliver care as essential in urban settings. Similarly, in 1947, the Honorary Secretary to the TB Association of Madras state attributed the disease to poverty and diets of limited nutritional value.⁽⁴⁾ The colonial state therefore, although non-interventionist and relying on philanthropic associations for care delivery, understood TB to be a social disease and constructed campaigns that addressed these

structural barriers, a framework that would come to be dissolved in the immediate years of post-colonial India.

The post-independent, post-colonial state of 1947 dramatically shifted the nation's non-interventionist stance to one with nationalist rhetoric and nationalist anxiety. In 1948, just over a year after independence, India became the first developing country to sign an agreement with the International Tuberculosis Campaign (ITC) and served as an important demonstration site for the BCG vaccination initiative.⁽⁶⁾ With a focus on eradication, BCG became the “technology” that could surpass the structural barriers of disease. Techno-centric frameworks came to see TB as less of a social disease and rather “ a public health and medical administrative problem.”⁽⁷⁾ The international convergence around biomedicine and technological solutions,⁽⁸⁾ with India becoming a special geography of interest, allowed the state to circumvent the structural problems of poverty and disease. Tuberculosis control subsequently became a medium for the reconstruction of British India through technological and economic planning.

Sanatorium to Self-Administered Treatment

The 1940s and 1950s witnessed a dramatic shift in TB management due to the materialization of chemotherapy, thereby shifting TB patient management from one of long-term hospitalization or sanatorium care to an outpatient model known as ambulatory-care or domiciliary treatment, whereby treatment could be self-administered at home instead of a hospital setting.⁽⁹⁾ The first randomized controlled trial in India, called the Madras Study, was organized with agreements across a newly independent India, the World Health Organization, and the British Medical Research Council in order to compare the efficacy of sanatorium-based

care versus ambulatory care. ⁽¹⁰⁾ This shift was not driven by a rationale of patient-centric care but an economic rationale, given that the low availability of hospitals could not accommodate the high burden of TB.(9)

“In India, as in most under-developed countries, the tuberculosis problem is aggravated by an acute shortage of sanatorium beds. The number of active cases of tuberculosis in the country has been estimated at 2 1/2 million, but only 23 000 tuberculosis beds are available. In these circumstances great importance attaches to the possibility of applying mass domiciliary chemotherapy as a substitute for sanatorium treatment in cases of pulmonary tuberculosis. The findings of the present study, based on a comparison of the two types of treatment over a period of 12 months, show that despite the manifest advantages of sanatorium care--rest, adequate diet, nursing and supervised medicine-taking--the merits of domiciliary chemotherapy are comparable to those of sanatorium treatment, and that it would therefore be appropriate to treat the majority of patients at home, provided an adequate service were established.”⁽¹¹⁾

Sanatorium-based treatment had prevailed since the early 1900s. The dimension of “care” in sanatorium treatment was acknowledged to be highly effective in the form of exposing the body to healthy food with balanced diets, completed rest from physical activity, open air, regular physician interactions, and effective drugs in the right quantities. Ambulatory care models, however, sent patients back to slums, overcrowded conditions, significantly less rest, and poor diet. The Madras Trial revealed these stark contrasts between then sanatoria-based care and ambulatory care--or absence thereof-- that returned patients to these strains of poverty. Yet, the Madras Trial ultimately concluded that the circumstances of poverty had little effect in achieving bacteriological quiescence. The conclusion drawn from the study was that successful treatment

of patients at their homes need not await an increase in a the standard and quality of living, and that mass treatment could begin as soon as drugs become available without the need of social support. ⁽¹²⁾ The trial in effect rendered the delivery of care for patients across dimensions of nutrition, housing, sanitation, and social security irrelevant and postulated that the association between tuberculosis and poverty could be addressed through technological intervention.

The methodology of the first randomized controlled trial in India had tremendous consequences that shaped global framing of care delivery for TB. The design of a scientific trial embedded within controlled social and economic conditions proved the trial to be unrealistic. Patients were carefully pre-selected to be the ones most likely to be “co-operative” with the study exercising significant social control over patients in ensuring compliance. Patients in the study were “educated, advised, and indoctrinated that if they miss treatment, they will pay dearly for it.” ⁽¹⁰⁾ Financial incentives, behavioral incentives, and extensive follow-up of patients to retain them in care were critical to the study but ultimately ignored in favor of a view that care delivery in the form of social support was not required.

With the embrace of antibiotics and ambulatory models as the effective strategies for cure, the Madras Study signaled the end of sanatoriums globally, with the important consequence of shifting the frameworks of TB care. Because the problem of tuberculosis turned into a problem of individual patients and their likelihood of “compliance” to long-term therapy, it followed that “care” delivery would take the form of ensuring this compliance. Surveillance of treatment therefore became the equivalent of care, and the governing principle of the public health response to TB. The move to domiciliary treatment increased the need to find ways of surveilling patients and obtaining information on the regularity of drug-taking during treatment. Studies highlighted the problem of irregular patient adherence to treatment in ambulatory care

models.⁽¹³⁾ Patients were reported to be non-compliant to treatment despite intensive monitoring efforts of self-administered treatment including urine tests to verify patient intake of anti-TB medication, pill counts during clinic visits, and unannounced home visits.^(9, 13) The study portrayed the “unreliable” patient who could not be entrusted to self-administer medication for the required duration of the illness.⁽¹⁴⁾

Direct Observation of Therapy

It is from this narrative that the concept of directly observed therapy (DOT) emerged, whereby TB patients were required to travel daily to DOT centers to access medication-- and to be observed swallowing each dose of anti-TB medication by a healthcare provider or healthcare worker.⁽¹⁴⁾ The first model of this supervised care was illustrated by William Fox in India, whereby TB patients were asked to travel up to 5 miles to clinics six days a week without transportation support in order to access treatment --for the sole purpose of being physically observed by a health care provider in the swallowing of pills.⁽⁹⁾ DOT subsequently became the new standard of care for India and entrenched into public health systems as a central dimension of care delivery.

Fox implemented this DOT model in the 1950s in the city of Madras, where the majority of TB patients and communities were poor.⁽⁹⁾ Working in a country that was just emerging from colonial dependency, Fox’s primary objective was to use the Indian context to learn lessons that could be applied to developed countries. He explained that "Long term daily supervised administration can be organized under special circumstances, *even in developing countries.*"⁽⁹⁾

It is within this context that the first model of directly observed therapy was conceived as a standard for Tuberculosis care. Fox’s work directly influenced parallel work in the ambulatory

care models being delivered in Hong Kong and the USA throughout the 1960s.⁽⁹⁾ The model was widely promoted and integrated into state, federal, and local health policy by the 1990s in both developing and developed nations.⁽¹⁴⁾

Although this mandate to ‘supervise’ placed an economic and social burden on patients, the ethical debate on such models paradoxically was not focused on these aspects of care or care delivery. The debate on DOT was not about why or how patients could cope with state-mandated care models, but rather *who* should be targeted for the administration of DOT.⁽¹⁵⁾ The central argument was that DOT was acceptable only in cases where patient has demonstrated non-compliance and therefore behaving in way that posed a threat to public health.⁽¹⁵⁾ The public health, legal, and ethical frameworks claimed that this form of care delivery stigmatized the most vulnerable patients (the non-compliant) in both rhetoric and application by stating that patients should not be presumed “guilty until proven innocent.”⁽¹⁶⁾

These frameworks of care had adverse effects on patients that were not immediately foreseen. It ensured that the most vulnerable groups (who faced the most significant structural barriers to adherence and therefore became non-compliant) faced the highest burden to treatment access with the requirement of DOT. Prior to the work of Fox, care delivery was being driven by models that sought to identify patient characteristics that would be predictive of non-compliance.⁽⁹⁾ The advantages of such models included an early association of structural and social barriers to non-compliance, leading to early identification and care delivery to high-risk patients. Early identification as an output of predictive model had the benefit of developing a care system that was preventive rather than reactive and adapting solutions to underlying reasons for nonadherence. However, the ethical frameworks criticized these models with the position that such stereotypes about a person’s socio-economic status (such as being poor or homeless) were

offensive.⁽¹⁶⁾ The ethical framework required that these patients first demonstrate noncompliance. “Objective evidence of noncompliance would be required under the significant risk standard.”⁽¹⁵⁾

In addition to monitoring of patient compliance to therapy, the DOT-based care delivery model had a significant impact on the quality of medication therapy itself. The model forced the shift from daily regimen (where patients took medications daily) to that of intermittent therapy (where patients took medication thrice a week). This shift in therapy, which involved biological and pharmacological consequences for patients, was primarily driven by the fact that it made DOT supervision easier and reduced the burden of daily observation. This was a critical example of how surveillance became the governing principle of TB care. Preservation of the principle of surveillance and ease through which it could be administered dictated the terms of treatment. The argument for DOT therefore formed the foundation of a care delivery model that centered on thrice-weekly regimen, which placed patients at higher risk of poor treatment outcomes if they were non-compliant. Intermittent therapy became entrenched into the Indian national standards of TB care for almost sixty years. Studies as recent as 2018 have since demonstrated that a daily anti-TB regimen is superior to a thrice-weekly regimen in terms of clinical outcomes and controlling the emergence of rifampicin resistance.⁽¹⁷⁾

Community-based DOTS

Supervision of treatment through a DOT model proved to be too resource intensive for high TB burden settings with weak health systems such as India. Studies documented the challenges for patients to visit clinics daily for supervision. DOT added transportation costs and consultation fees as well indirect costs such as time lost in traveling and waiting for treatment.⁽¹⁸⁾

In this backdrop of limited feasibility in implementing DOT and increasing patient burden, policy makers looked to community-based DOT model as an alternate form of care delivery.⁽¹⁹⁾

The rationale was that “Organized community groups, peer groups, chosen members of the community, and family members all have the potential to act as supervisors to ensure completion of treatment and hence cure.”⁽¹⁸⁾

One interpretation of this shift is that the state placed the burden of non-compliance back to patients and communities without the provision of support, essentially withdrawing from care delivery. The co-opting of family and community support systems into state-led delivery of care can be argued as a policy shift of convenience. What existing care structures were already in place prior to a protocolized community-based DOT model? How did families cope with TB as an illness without state support? Why is it assumed that families and community members can become caregivers without taking on an additional burden?

The impact of DOT and subsequent decentralized models of community-based DOT on patient outcomes have been studied over time with mixed findings. A 2007 review found a small benefit from community-based DOT that was supervised at home by family members or community health workers as compared to self-administered treatment in the form of higher treatment success. No such benefit was identified in outcomes of patients administered DOT at a clinical facility.⁽¹⁸⁾ Two randomized controlled trials (RCT) found no significant difference between treatment at a DOT clinic as compared to DOT delivery by a family member or community health worker, concluding that different DOT strategies were not having an impact on health outcomes.⁽¹⁸⁾

Digital Adherence Technologies

Several rationales emerged that justified the government use of videos, tablets, and phones to transition the DOT strategy into the technology era. First, ongoing studies raised concerns that DOT was burdensome for patients, challenged patient autonomy, and had limited effectiveness in improving treatment outcomes.⁽²⁰⁻²²⁾ Second, the implementation of DOT proved difficult in high-burden and diverse settings such as India without significant investments in human resource infrastructure. Daily observation of a 6-9 month regimen for DS-TB and 18-24 month regimen for DR-TB across an estimated 2 million patients a year proved nearly impossible to execute, even within robust infrastructure. DOT therefore primarily existed in principle and on paper but was rarely implemented by local health systems.⁽²²⁾

Third, an increasing body of literature emerged illustrating that irregular adherence to TB therapy significantly increased the risk of death, relapse, and drug resistance^(23, 24)—even more so than previously understood. Studies indicated that TB patients with “very irregular” adherence exhibited a TB recurrence rate of 25%, almost 3 times higher than patients with “regular” adherence.⁽²³⁾ TB drug therapy was therefore subsequently described as being “unforgiving,” whereby a relatively small number of missed doses could result in a significant loss of drug efficacy and risk poor clinical outcomes.⁽²⁵⁾ A biomedical framework therefore emphasized that the daily intake of every single dose was more important than ever before, justifying the potential use of more intensive and consistent surveillance as part of standards of care.

An articulated need for better surveillance by the biomedical community combined with the insufficient capacity of government health systems to execute human surveillance led to a natural emergence of digital adherence technologies (DATs). Similar to the techno-centric fixes that characterized decision-making in the 1950s and 1960s, DATs allowed governments to

respond to the failure of DOT and the ongoing rise of drug resistance in India --by again circumventing the need to address social and structural barriers. Similar to the nationalist anxiety of a newly independent India, a nationalist desire to project modernity in the era of technology enabled a quick acceptance of DATs without reflection on how such models translated to patient care. Similar to the strategic importance assigned to India in the 1950s and 1960s to demonstrate the feasibility of a model to other developing countries, India again emerged as a strategic local and global market of focus for DATs.

Maintaining the governing principle of “surveillance as care,” various types of DATS were designed in technology markets to monitor adherence. For example, simple SMS-based models reminded patients to take their medication or allow a two-way SMS where the patient can indicate to the system that he or she had taken a dose. The most commonly deployed DAT in India was 99DOTS, whereby patients were provided TB medications in blister packs wrapped in a custom envelope. When the patient opened a blister tab to access a dose, a hidden and unpredictable phone number was revealed on the back of the blister, prompting the patient to make a toll-free call to a national monitoring platform to indicate a dose taken. Other technology designs used digital pillboxes with visual and audio reminders that prompted the patient to take their daily medication at the set time. The open-closing of the box lid subsequently sent a signal to the national monitoring platform that a dose was taken. In a third technology option called video DOT (VDOT), patients used a smartphone to send a daily short video of themselves consuming the medication in real time. The video was uploaded to the national monitoring platform to indicate a dose was taken for that day. In the fourth option of e-compliance, patients were asked to provide a fingerprint on a tablet that served as a biometric record of dose taken for the day. More complex and costly DAT designs were developed for developed countries. These

included ingestible sensors with microchips embedded within the TB medication dose. Once the dose is consumed, the interaction with the patient's gastric fluid transmits a signal to smartphones and servers.⁽²⁶⁾

Patient-Centered & People-Centered Care

The failure to cure a treatable disease in the 21st century combined with impending TB elimination targets inevitably led to some reflection by various TB actors on definitions of care models and how they have shaped policies. Early concepts of “patient-centered” care called on healthcare providers to understand the social context in which a patient resides rather than viewing them as a manifestation of pathology in order to design care models that deal with the disruptive nature of illness.⁽²⁷⁾ This conceptualization of “patient-centered” care was reinvigorated and again interrogated in order to better shape care models into national TB policies. In the context of modern TB care, the consensus around the principles of patient-centered care was guided by four key attributes:^(28, 29) (i) Care models should see and value the patient as a whole, possessing multiple needs shaped by the context of his or her physical, cognitive, and psychological functioning; ii) Care should be individualized, reflecting each patient's unique needs, preferences; (iii) Care should be empowering, recognizing patients as active consumers; and (iv) Care should be respectful, encouraging informed decision-making and self-determination.⁽³⁰⁾

In the context of a patient-health care worker relationship, the practice of patient-centered care involved engaging and working with the patient to understand his/her moral and emotional concerns to find common ground on the nature of the problem and jointly reach a mutual agreement on the management of the illness. At the health system level, patient-centered care required coordinated input from other sectors and services to ensure continuity of care is

achieved with active patient engagement in the process.⁽³⁰⁾ The concept of ‘people-centered care’ emerged more recently with the distinction of going further to develop not only an understanding of what defines the patient but also his or her social and economic environment. It also extended the concept of patient-centeredness to include not only the affected patient but also their families and communities.⁽³⁰⁾

The terminology of patient-centered and person-centered care became part of national TB policy frameworks in rhetoric. Although intended to fundamentally re-think care delivery, the longstanding surveillance principles that governed care models merely co-opted the language as a label to safeguard their intended purpose. The use of “patient-centered” care as a descriptive label prevented or at least gave pause to an otherwise easy critique of digital surveillance.

Differentiated Care

The mechanism through which DAT surveillance translated to patient-centered care was not simple and required a sophisticated and nuanced explanation. It’s important to note that DAT emerged as a reaction to the limitations of DOT implementation, not to the underlying principles that governed DOT itself. In this regard, the DAT model was more “patient-centric” in that it did not require patients to go to a different location or be supervised by another person to confirm that pills were swallowed. It enabled patients to report their adherence to health systems through engaging with the technologies from the comfort of their own home or workplace. A second interpretation of adopting a patient-centric model was that it empowered patients by providing them multiple options of technologies, thus giving patients choice. Neither of these rationales, however, questioned the governing principle of surveillance as care, only that surveillance was not sufficiently efficient or conducive for both health systems and the patient.

The fundamental principle that DAT-enabled digital surveillance claimed was that of “differentiated care.” In contrast to DOT, whereby all patients were required to be observed, DATs enabled health systems to distinguish adherent patients from non-adherent patients in order to triage and escalate the latter for further care. Once non-adherent patients were identified through DATs, healthcare workers could ideally work with patients to understand reasons for non-adherence with the provision of individualized care based on patient needs. The shortage of healthcare workers in a high burden country made this a more efficient model of care delivery, where patients that needed more care could be provided more care. DATs also compiled detailed patient dosing histories through daily technology signals over the treatment duration period. This level of granular and detailed adherence information in theory could also guide clinicians and healthcare workers to better develop individualized counseling and intervention support for these patients.

DAT-enabled surveillance provided the resources and technological infrastructure for the identifying of non-adherence. However, the effectiveness of a differentiated care model ultimately relied on the challenge of effectively addressing the primary reasons for non-adherence including nutrition, mental health, stigma, alcohol and substance abuse and other factors that were recognized as critical over a century ago. The infrastructure to deliver these services was the status quo. DAT care models, therefore, can potentially be more efficient surveillance tools but don’t provide a mechanism for significantly improving quality of care. The DAT-enabled patient triage model is also designed to work in a status-quo environment of limited human workforce that is not sufficient to deliver high-quality care for all patients, arguably re-framing differentiated care as “rationing of care.”

Part 2: Publishable Paper

Introduction

Regimens for treating Tuberculosis (TB) are long in duration, ranging from six to nine months for drug-susceptible TB and up to 18-24 months for drug-resistant TB¹. Irregular adherence to TB therapy is known to increase the risk of death, relapse, and drug resistance¹. Globally, directly observed therapy (DOT) has been the standard of care for TB adherence management, where patients take their TB medication in front of a DOTS agent. However, this model is often burdensome and resource-intensive; challenges patient autonomy by insisting on patient ‘observation’; and treats all patients the same with uniform monitoring²⁶.

To address these limitations, various digital adherence technologies (DATs) have been deployed globally to enable remote monitoring of patient adherence, including i) 99DOTS, a mobile call-based monitoring system; ii) Medication Event Reminder Monitor (MERM), a visual and audio alarm-enabled digital pillbox; and iii) videoDOTS (VOT), a mobile video-based reporting system.²⁶ All DATs were integrated with the Indian national TB platform Nikshay, enabling the remote observation of daily DAT signals as a proxy to medication adherence. DAT models enable “differentiated care,” whereby non-adherent patients can be identified through DAT signals and escalated for further intervention and care.

Single deployment of these technologies has been piloted in India with the learning that no single DAT is suitable for all patients. For example, patients without daily access to a mobile phone cannot engage with 99DOTS and patient occupations and lifestyles may prefer alternative models. In May 2019, the Central TB Division of India launched the Integrated Digital Adherence Technology Initiative (IDAT), the first initiative to introduce all three digital technologies (99DOTS, MERM, and VOT) into TB health systems.

IDAT protocol required that patients and healthcare providers jointly determine the appropriate DAT to be assigned to the patient based on the minimum requirements needed to engage with the technology (i.e. regular access to a mobile phone, network connectivity, etc) and patient preferences. Patient escalation protocols required healthcare workers to follow-up with patients via calls for patients with 3-6 consecutive missed doses (as indicated by missed DAT signals) and a home visit for 7 or more consecutive missed doses.

We conducted a mixed-methods study of TB patients in India enrolled IDAT in order to understand factors affecting optimal IDAT implementation and the potential of an IDAT model to influence TB medication adherence.

Methods

We conducted a mixed-methods study to assess the implementation of IDAT in eight districts across the three Indian states of Gujarat, Karnataka, and Haryana. The states were selected for high, intermediate, and low implementation strength respectively based on factors of supply chain infrastructure, ratio of patients to healthcare workers, private sector engagement, and monitoring capacity.

The quantitative sample enrolled 12,100 patients enrolled in the national TB platform Nikshay in the selected geographies between May 15, 2019, and February 29, 2020, and assigned one of the three DATs at treatment initiation. The qualitative study comprised of 64 semi-structured patient interviews and three health worker focus group discussions (FGDs) with a total of 26 participants. The patient sample was drawn from the state of Gujarat with a purposeful sampling of patients that represent diverse experiences with DATs. The health worker FGDs

were conducted in the states of Gujarat and Karnataka with health workers who were trained and engaged in IDAT for a minimum of 1 month at the time of the FGD.

Informed consent was taken for patient interviews and focus group discussions by reading aloud consent statement by an interpreter in the state's local language and obtaining verbal consent to the interviews, note-taking, and audio-recordings of the interview. A copy of the consent statement with contact information for follow-up questions was left with each respondent.

The quantitative portion of the study used Nikshay programmatic data for descriptive analysis. The primary outcome measure was technology-derived adherence, a continuous measure defined as the number of doses taken over the prescribed treatment duration period. Linear regression was used to evaluate systems, technology, demographic, and clinical factors associated with technology-derived adherence. Quantitative analysis was conducted in Stata version 16. The qualitative analysis was conducted through an inductive, thematic approach that analyzed interview data to create categories representative of participant responses. The content of transcribed interviews was coded with the data management software, Dedoose version 8. A codebook was developed then piloted on a subset of interviews to ensure consistency, followed by the iterative development of categories to identify themes supported with content evidence for each category.

Results

A cohort of 12,100 TB patients is described across 8 districts and 3 states (Table 1). Patients notified into the national TB platform Nikshay from May 15, 2019, and February 29, 2020, and assigned one of three DATs were selected for analysis. Patient distribution across the

three states of Gujarat, Karnataka, and Haryana was 8,294 (68.6%), 3,131 (25.9%), and 675 (5.6%), respectively. Distribution across 99DOTS, MERM, and VOT was 11,036 (91.2%), 876 (7.2%), and 188, (1.6%) respectively. 4,931 (40.8%) patients were between the ages of 26-45, and a majority of 7,700 (63.6%) were male. 9,592 (79.3%) patients were initiated on treatment in the public sector. 2,239 (18.5%) were registered as retreatment cases and 3,391 (28.0%) as extrapulmonary cases. 527 (4.7%) were co-infected with HIV, and 876 (7.7%) had diabetes.

Table 1: Characteristics of TB patients assigned DATs: May 15, 2019 – Feb 29, 2020 (n=12,100)

	N	%
State		
Gujarat	8,294	68.6%
Karnataka	3,131	25.9%
Haryana	675	5.6%
Sector		
Public	9,592	79.3%
Private	2,508	20.7%
Technology		
99DOTS	11,036	91.2%
MERM	876	7.2%
VOT	188	1.6%
Gender		
Male	7,700	63.6%
Female	4,391	36.3%
Transgender	9	0.07%
Age		
1-25	4,001	33.1%
26-45	4,931	40.8%
46-60	2,100	17.4%
>60	1,068	8.8%
HIV Positive	527	4.7%
Diabetes Positive	876	7.7%
Site		
Pulmonary	8,709	72.0%
Extrapulmonary	3,391	28.0%
Type		

New	9,747	80.6%
Retreatment	2,239	18.5%
MDR	114	0.94%

Figure 1 indicates the median and interquartile range (IQR) of technology-derived adherence across the three technologies and the three states. Within-technology variation is observed across geographies. Median 99DOTS adherence was 56.5% in Gujarat, 22.0% in Karnataka, and 24.0% in Haryana. Median MERM adherence was 56.8% in Gujarat, 67.3% in Karnataka, and 67.9% in Haryana. Median VOT adherence was 14.3% in Gujarat and 10.8% in Haryana. Figure 2 plots the same measure of technology-derived adherence over time.

Figure 1: Median/ IQR technology-derived adherence, by technology and state (n=12,100)

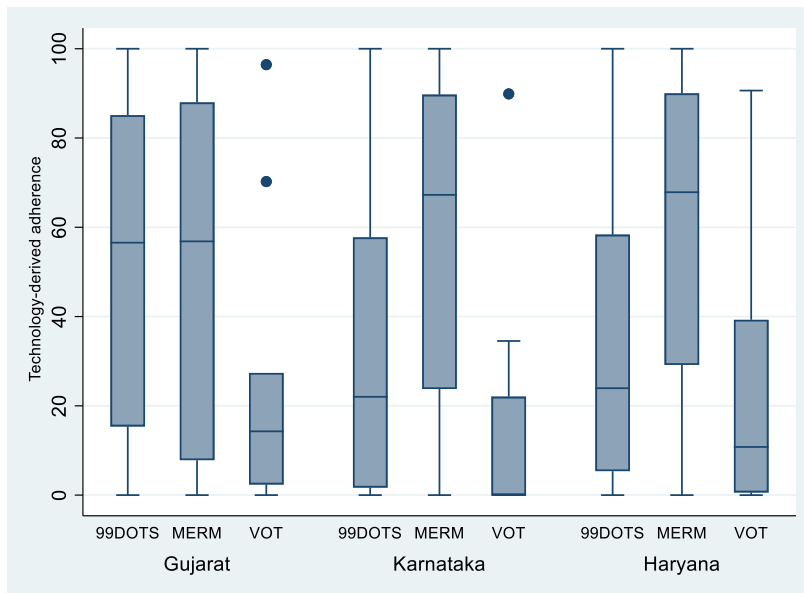


Figure 2: Technology-derived adherence over time, by technology and state (n=12,100)

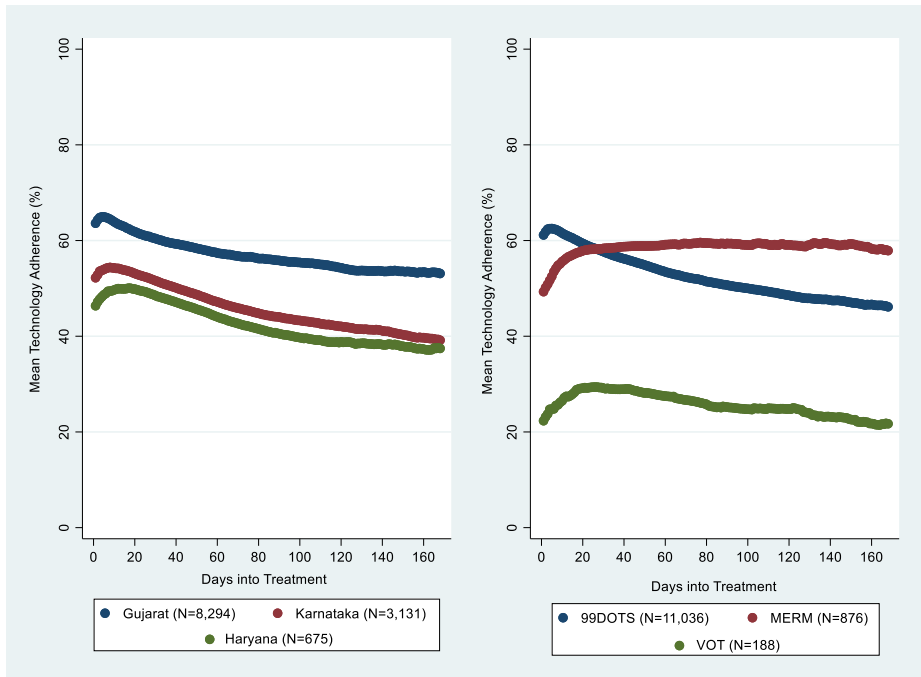


Table 2 indicates the key factors associated with the outcome of technology-derived adherence. Implementation geographies with weaker health systems, patients treated in the private sector, an HIV positive status, and MDR status had significant negative associations with the outcome measure. Relative to the DAT option of 99DOTS, enrollment in MERM improved technology-derived adherence by 18 percentage points while enrollment in VOT decreased technology-derived adherence by 13.6 percentage points. A month into treatment harmed the outcome with latter months of 3-6 decreasing technology-derived adherence ranging from 8.5 to 14.1 percentage points.

Table 2: Multivariate associations of various patient, technology, and system characteristics with technology adherence (n=11,052)

	Coefficient	95% CI	p-value
State			
Gujarat	(ref)		
Karnataka	-16.3	(-17.8, -14.7)	<.0001
Haryana	-19.4	(-22.3, -16.4)	<.0001
Sector			
Public	(ref)		
Private	-8.2	(-10.1, -6.4)	<.0001

Technology			
99DOTS	(ref)		
MERM	18.0	(15.1, 20.9)	<.0001
VOT	-13.6	(-18.5, -8.7)	<.0001
Month into Treatment			
1	(ref)		
2	-5.7	(-9.1, -2.3)	.001
3	-10.7	(-14.3, -7.2)	<.0001
4	-12.8	(-16.2, -9.4)	<.0001
5	-14.1	(-17.5, -10.7)	<.0001
6	-8.5	(-11.2, -5.7)	<.0001
Gender			
Male	(ref)		
Female	0.88	(-.45, 2.2)	0.194
Age			
1-25	(ref)		
26-45	-1.2	(-2.7, 0.28)	.112
46-60	-5.0	(-7.0, -3.1)	<.0001
>60	-9.7	(-12.2, -7.2)	<.0001
HIV	-17.6	(-20.7, -14.5)	<.0001
Diabetes	6.9	(4.4, 9.4)	<.0001
Site			
Pulmonary	(ref)		
Extrapulmonary	4.5	(3.0, 5.9)	<.0001
Type			
New	(ref)		
Retreatment	-2.5	(-4.1, -0.8)	.003
MDR	-16.4	(-24.3, -8.5)	<.0001

Qualitative Results: Conceptual Categories

Surveillance = Being Cared for by the Government

Patients understood DATs to be surveillance tools used to verify their daily intake of doses.

Although surveillance was described in paternalistic terms that treated patients as subordinates and empowered government oversight for the patient's benefit, patients ultimately perceived

DAT surveillance as symbolic of government care. “Care” was not attributed to any specific feature or functionality of the technologies themselves but rather to the creation and visibility of detailed records and the perception that higher government authority was overseeing this information as it pertained to their treatment. DAT-enabled surveillance translated to care through the interpretation that government was taking responsibility, serving its intended function, and bridging a gap in otherwise apathetic systems.

“It’s like giving your attendance. After taking medicine when I call, they say thank you- it means today’s attendance is marked. I just know that if I call my attendance is marked that I took medicine today, and the government will come to know whether I am taking my medicines or not...They made it mandatory so that they can verify that I am taking my medicines on a regular basis. No one can skip medicines even if they want because it is recorded.”

“I would do it [engage with DAT] because it is more secure, and I feel that I am treated to the 100 percent. Suppose if I don’t take the medicine one day, there is loss in that...They can make a note of this at the [government] headquarters. There will be a record of everything...it’s good that a complete record is maintained. It feels like somebody is making a note of everything. It feels like someone is caring.”

“It [provision of DATs] means the government is active. In today’s world, no one cares about each other. Even then, if someone takes care of you and your medicines ,it means the government is doing its job by taking responsibility”

“Yes, it helps us remember. We are mentally prepared that if we don’t take our medicines and if we don’t call them, they will know about it. No matter what system is there in their phone, they will come to know that we haven’t taken our medicine on time. But in the end, this is for our safety, for our own good, right?”

Patient Engagement with DATs is Passive

Patient motivation to engage with DATs was passive in ways that did not render DATs central to the long-term management of their treatment. Although patients acknowledged the benefits of technology features and expressed a broad acceptance of DATS, the primary motivation for DAT engagement was often ascribed to the authority of healthcare providers. Providers also employed strategies of limited engagement whereby DAT participation was linked to valued services such as access to future TB drugs and the direct beneficiary transfer (a monthly cash transfer provided by the government to TB patients). Patients were motivated to engage with DAT in order to ensure continued access to these services.

“Since the doctor asked me to call, I am calling. The doctor said that as soon as you take your medicine, you should call. And they say thank you. Since the doctor says, we must abide by it.”

“How can it {DAT engagement} be problematic to me? No, not at all. They are government workers and we don’t have any idea about their responsibilities. We just follow whatever is asked from us. Once a lady came and said that we would have to give a missed call to a phone number when you take your medicine in the morning, so that is what we did”

“When I go to the clinic, they say that if they get a call or information that that I haven’t used the box and forgotten to take my medicine, then they will not give me any more medicines. He said that I should take medicines and not be negligent.”

“Good means we have to do it, so we do it [engage with DATs]. They told us that our money will not be deposited if we don’t do it. So we do it. It is important because if we don’t, then we won’t get the 500 rupees every month in our account...That is what the doctor told us.”

Motivation for Medication Adherence is Aspirational

Patients who were persistent with TB medication, including those who suffered from adverse drug reactions and clinical deterioration, were motivated by various, specific aspirations that included ensuring the safety and security of their family, preventing disease recurrence, pursuing future endeavors, taking pride in resilience, and a state of mind that was forward-looking. The motivation for medication adherence, therefore, relied on mental health and placing sufficient value on one’s own life and contributions in order to project an aspirational goal.

“No, not even one day. I never forget to take my medicines because I have this eagerness and an urge to get cured quickly. I want to go back to school. I have already lost so much time.”

“It was very difficult. First, when I started to take medicine, I always had fever, and cough increased as well. I couldn’t sleep. Then as I was taking medicine, I had pain in my limbs...I wanted to quit...But, the reason I didn’t quit was that I got to know if I quit, then this might happen again. Then I made up my mind, no matter how difficult this would get, I will not stop taking medicine. I didn’t want to get it again, and I didn’t

want somebody else to be affected because of this. I want to be able to help my kids. That was the reason I never quit.”

“I felt terrible. Of course, I was scared a lot, my heart used to beat faster. And because I had to get well as there is no one else to earn a living for us apart from me. I wanted to get back to providing for my family. How can I leave my family alone?”

DATs Distort Healthcare Worker-Patient Interactions

IDAT implementation influenced the behaviors and decision-making of healthcare workers who sought to optimize technology-centric metrics instead of patient-centric metrics of care, primarily because only the former was visible to them and used to hold them accountable. The focus on technology metrics was amplified by interpreting patient adherence through only a lens of green and red colors (green indicating dose is taken and red indicating a missed dose). The drive to optimize the “technology green,” also led the exclusion of vulnerable patients from IDAT enrollment since they were thought to engage poorly with DATS. Counseling on technology engagement also began to displace counseling on TB adherence where the primary interactions between the healthcare worker and the patient became defined by DAT reporting and data collection, effectively altering the role of healthcare workers from counselors to surveyors, making patient disclosure of non-adherence less likely.

“Excessive calling to follow up on technology flaws negatively affects the relationship with the patient. Calling the patient all the time irritates them. It is also time consuming. If DATs are not working, we go and count the medicine to see how many doses were given and how many were consumed. Because we are always coming to count, patients get frustrated—they stop taking our

calls or even throw away the medicines sometimes, and in this case, the family members have to notify to us, or it's never known at all.”(Healthcare worker)

“We don't provide technologies to patients who are migrants, illiterate patients, elderly patients, or patients with alcohol or addiction problems.... They are less likely to engage with technologies and more difficult to track. We would see too much red in the calendars, and all their adherence scores would be 0. Then we get calls from supervisors asking why this is all red.” (Healthcare worker)

Discussion

The integration of multiple digital adherence technologies into health systems is complex, requiring technology infrastructure, supply chain management, a coordinated healthcare workforce, and intensive monitoring. We found that geographies with relatively weaker health systems (i.e., Haryana) were negatively associated with technology-derived adherence. Similarly, the negative effect of the private sector on technology-derived adherence reflects the implementation strength of health systems. The private sector is highly fragmented with heterogeneity in treatment practices, poor penetration of FDC regimens, high patient volumes, and higher rates of patient migration—requiring new systems and resource support to retain patients in care.

Implementation strength also affects the accuracy of DAT signals. Differentiated care begins with accurately identifying nonadherent patients for healthcare workers to triage. An accuracy study of 99DOTS using urine isoniazid testing showed a positive predictive value (PPV) of 93% and a negative predictive value (NPV) of 21%. This means that about 8 out of 10

missed doses, as indicated by 99DOTS, were in fact doses taken. The main factor contributing to this low NPV was limited patient access to mobile phones. Achieving optimal signal accuracy through IDAT—by ensuring access to multiple DAT options that match patient needs, technology literacy, functionality, and monitoring—is a direct function of health system capacity. Without the parallel strengthening of health systems, IDAT models risk the same failures of the DOT models they intend to replace, whereby adherence protocols exist in principle but poorly implemented.

Ensuring the accuracy of signals also requires patients to engage effectively with DATs over a longer treatment duration period. We found that patients did not perceive cognitive barriers such as forgetfulness to be a central barrier to adherence. However, forgetfulness and habit formation are the only problems that DATs are designed to address through various text, visual, and audio reminders. Patients, therefore, engaged with DATs passively, contributing to technology fatigue over time. Temporal factors such as month into treatment, especially post IP phase, had a significant negative effect on technology-derived adherence. Healthcare workers subsequently spent time and effort in ‘chasing’ down, devising strategies, and compelling otherwise adherent patients to participate in DATs. IDAT design and implementation were, therefore, flawed in that it required the changing of patient behavior to fit technologies instead of technologies fitting the behavior of patients. Behavioral design research focused on improving features or messaging of DATs to more closely reflect patient values and needs—such as speaking to patient aspirations, reflecting positivity and encouragement, and appreciating resilience—can improve patient engagement.

Differentiated care requires addressing the underlying causes of non-adherence once identified. Several studies highlight the necessity of granular, DAT dosing histories in order to

tailor interventions, including targeting psychosocial and structural causes of non-adherence such as depression, alcohol & substance abuse, and migration. However, we found that healthcare providers excluded these same categories of patients from DAT enrollment due to their likely poor engagement with DATs. Furthermore, healthcare workers' attempts and willingness to assess psychosocial and structural barriers at the point of treatment initiation suggests that the prevalence and severity of these barriers can be identified upfront with the introduction of validated screening tools, adapted to TB workflows. Patients meeting relevant criteria may subsequently be enrolled in specialized interventions early in the treatment cycle.

A common challenge identified by healthcare workers through DAT patient escalations was therapy-related toxicities and complexity of regimens related to co-morbidities. Patients with HIV and MDR patients had a significant negative effect on technology-derived adherence, reflecting the more complex clinical management of cases and severe, longer duration of side effects. Despite the identified cause of nonadherence, no interventions or individualized care protocols exist to address adverse drug reactions or clinical deterioration. These patients, similar to all other patients, receive the same messaging emphasizing the importance of daily adherence, thus failing to deliver 'differentiated' care. The integration of adverse drug reaction workflows into the Nikshay platform to manage a history of adverse events, recommend actions, monitor patient responsiveness to various changes or adjustments in regimens and coordinate referrals for specialized care can substantially address this gap.

The study had several limitations. It does not measure the accuracy of various DAT signals and therefore cannot comment on the extent to which technology-derived adherence deviates from "true" adherence. Factors indicating significant effects on this outcome can be a combination of changes in DAT engagement and changes in actual patient adherence behavior.

The study also relies on operational data made available through the national Nikshay platform and is therefore incomplete in the inclusion of variables that influence the outcome measure of technology-derived adherence.

REFERENCES

1. Global tuberculosis report 2019. Geneva: World Health Organization.
2. Leung ECC, Yew WW, Leung CC, Leung WM, Tam CM. Shorter treatment duration for selected patients with multidrug-resistant tuberculosis. *European Respiratory Journal*. 2011;38(1):227-30.
3. John TJ. Tuberculosis control in India: why are we failing? *Indian pediatrics*. 2014;51(7):523-7.
4. Neelakantan V. Tuberculosis control in postcolonial South India and beyond: Fractured sovereignties in international health, 1948-1960. *Wellcome Open Res*. 2017;2:4-.
5. Choudhary B. Colonial Policies and Spread of Tuberculosis (1890-1940). *Journal of Health and Development*. 2008;3.
6. Brimnes N. Vikings against Tuberculosis: The International Tuberculosis Campaign in India, 1948-1951. *Bulletin of the History of Medicine*. 2007;81(2):407-30.
7. Soper FL. Problems to be solved if the eradication of tuberculosis is to be realized. *American journal of public health and the nation's health*. 1962;52(5):734-48.
8. The Making of a Tropical Disease: A Short History of Malaria. *Emerg Infect Dis*. 2008;14(10):1679-.
9. Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. *Lancet (London, England)*. 1995;345(8964):1545-8.
10. Amrith S. In Search of a 'Magic Bullet' for Tuberculosis: South India and Beyond, 1955–1965. *Social History of Medicine*. 2004;17(1):113-30.
11. Tuberculosis Chemotherapy C. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. *Bull World Health Organ*. 1959;21(1):51-144.
12. Ramakrishnan CV, Rajendran K, Mohan K, Fox W, Radhakrishna S. The diet, physical activity and accommodation of patients with quiescent pulmonary tuberculosis in a poor South Indian community. A four-year follow-up study. *Bull World Health Organ*. 1966;34(4):553-71.
13. Fox W. Self-administration of medicaments. A review of published work and a study of the problems. *Bulletin of the International Union against Tuberculosis*. 1962;32:307-31.
14. Ormerod LP. Directly observed therapy (DOT) for tuberculosis: why, when, how and if? *Thorax*. 1999;54 Suppl 2(Suppl 2):S42-S5.
15. Annas GJ. Control of Tuberculosis -- The Law and the Public's Health. *New England Journal of Medicine*. 1993;328(8):585-8.
16. Gostin LO. Controlling the resurgent tuberculosis epidemic. A 50-state survey of TB statutes and proposals for reform. *Jama*. 1993;269(2):255-61.
17. Gopalan N, Santhanakrishnan RK, Palaniappan AN, Menon PA, Lakshman S, Chandrasekaran P, et al. Daily vs Intermittent Antituberculosis Therapy for Pulmonary Tuberculosis in Patients With HIV: A Randomized Clinical Trial. *JAMA internal medicine*. 2018;178(4):485-93.
18. Wright CM, Westerkamp L, Korver S, Dobler CC. Community-based directly observed therapy (DOT) versus clinic DOT for tuberculosis: a systematic review and meta-analysis of comparative effectiveness. *BMC infectious diseases*. 2015;15:210-.
19. Muniyandi M, Ramachandran R, Balasubramanian R. Costs to patients with tuberculosis treated under DOTS programme 2005.
20. Sagbakken M, Frich JC, Bjune GA, Porter JDH. Ethical aspects of directly observed treatment for tuberculosis: a cross-cultural comparison. *BMC Medical Ethics*. 2013;14(1):25.
21. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews*. 2015(5).
22. Tian JH, Lu ZX, Bachmann MO, Song FJ. Effectiveness of directly observed treatment of tuberculosis: a systematic review of controlled studies. *The international journal of tuberculosis and*

lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2014;18(9):1092-8.

23. Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2005;9(5):556-61.

24. Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG. Risk factors associated with default among new smear positive TB patients treated under DOTS in India. PloS one. 2010;5(4):e10043.

25. Assawasuwannakit P, Braund R, Duffull SB. Quantification of the Forgiveness of Drugs to Imperfect Adherence. CPT Pharmacometrics Syst Pharmacol. 2015;4(3):e00004-e.

26. Subbaraman R, de Mondesert L, Musiimenta A, Pai M, Mayer KH, Thomas BE, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. BMJ global health. 2018;3(5):e001018.

27. Engel GL. The need for a new medical model: a challenge for biomedicine. Science (New York, NY). 1977;196(4286):129-36.

28. Morgan S, Yoder LH. A concept analysis of person-centered care. Journal of holistic nursing : official journal of the American Holistic Nurses' Association. 2012;30(1):6-15.

29. McMillan SS, Kendall E, Sav A, King MA, Whitty JA, Kelly F, et al. Patient-centered approaches to health care: a systematic review of randomized controlled trials. Medical care research and review : MCRR. 2013;70(6):567-96.

30. Odone A, Roberts B, Dara M, van den Boom M, Kluge H, McKee M. People- and patient-centred care for tuberculosis: models of care for tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(2):133-8.