Title: The use of digital technologies in adherence to anti-tuberculosis treatment.

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Running head: Digital adherence technology in tuberculosis

Summary: Tuberculosis kills over 1.5 million people per year, particularly in low- and middle-income countries. Despite recent advances, regimens are at least several months in length, which can be problematic for persons with tuberculosis. In the last decade, digital adherence technologies (DATs) have been used both to monitor and promote dose-taking. As interventions, DATs can be reminders for dose-taking and generate digital dosing histories to help triage patients. The evidence for DATs improving treatment outcomes as a result of improving adherence is mixed. Emerging evidence suggests that persons with tuberculosis value DAT functions that foster a feeling of being 'cared for' by the health system. DATs should be embedded within, rather than used as the sole replacement for, comprehensive care packages. As monitors of dose-taking, DATs provide rich dose-by-dose datasets for use in research and allow for greater empowerment of persons with tuberculosis than the directly observed therapy (DOT) used previously. They may, however, not be a perfect proxy for

adherence.

Take-home message: Digital adherence technologies (DATs) have been used extensively as monitors of, and to promote, treatment-taking in tuberculosis. Increasingly, DATs are considered part of overall care packages that also foster communication with healthcare providers.

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Introduction

Tuberculosis (TB) is a bacterial disease predominantly caused in humans by *Mycobacterium tuberculosis* (*M. tb*) [1]. In 2021, an estimated 10.6 million people fell ill with TB and 1.6 million died of it [2]. *M. tb* is mainly associated with pulmonary illness. Regimens to treat TB last many months, with difficulties shortening treatment likely due to the presence of persistent or heteroresistant bacterial populations [3, 4]. Currently, the World Health Organization (WHO) recommends four- or six-month regimens containing multiple drugs for drug sensitive TB [5] (unless it is of the central nervous system, bones, or joints) and six to nine months or longer for drug resistant disease [6].

It is well-known that persons with TB can struggle with taking every single dose of such lengthy treatment regimens, including due to side effects [7]. Non-adherence (defined as when doses of treatment are missed without the mutual agreement of the patient and healthcare provider (HCP)) [8] results from highly multifaceted causes, including social, health systems, and structural factors, which interrelate with the broader demands of being on treatment [9]. This means that individual capacity and motivation to take treatment dynamically fluctuates across the treatment course.

Concerns about non-adherence led to the WHO recommending directly observed therapy (DOT) for TB in the 1990s [10]. DOT requires the observation of persons with TB taking each dose of their medication by a HCP, community supporter, or family member, and often necessitates travel for observation. DOT is a one-size-fits-all strategy that is applied to all persons with TB regardless of how well they have or will adhere. It not only places a high demand on an individual's time and resources- as well as undermines their autonomy, confidentiality and trust [11-13]- but also a huge burden on health care systems that are often under-resourced. In recent years, digital adherence technologies (DATs) have emerged as an alternative to DOT [14] (Table 1). DATs include short message service (SMS)-based reminders [16, 17]; video supported treatment (VST) [18-21]; digital pillboxes [16, 22, 23]; and ingestible sensor-based systems [24]. From a healthcare perspective, DATs provide a less invasive and demanding approach than DOT, while offering opportunities to individualise adherence management strategies based on real-time adherence data. In 2017, the WHO made conditional recommendations in their drug sensitive TB treatment guidelines on the use of DATs [25], as well as producing its first handbook on the use of DATs [25].

94 **Table 1. Digital adherence technologies for tuberculosis**

METHOD	DESCRIPTION	STRENGTHS	WEAKNESSES*
Direct monitoring			
Ingestible pill sensors	Ingestible sensor embedded in TB medications. Pill interacts with gastric acid, and a signal is transmitted to adhesive monitor on person with TB, which in turn transmits information to smartphone.	No reliance on sample collection.	Cost; relies on person with TB wearing the adhesive monitor; individual acceptability.
Indirect monitoring: device-facilitated			
Digital pillbox / bottle cap	Medications placed in pill box/bottle. Opening/closing of box/bottle- a proxy for dose-taken- is documented (in real-time) via SIM card. Older studies have not used real-time monitoring but downloaded the data at regular intervals, such as at monthly pharmacy refills. Some interventions combine DAT with differentiated care when non-engagement has been observed.	Monitors adherence in real-time (if pill box/bottle cap transmits); low cost (relative to HCP DOT).	Pill box opening/bottle cap removal may not reflect an ingestion of dose; non-opening may not reflect non-ingestion of dose if medications are not stored in box/bottle or if 'pocket doses' are taken out earlier than required.
Indirect monitoring: person with TB-facilitated			
SMS messages	Person with TB sends SMS message to HCP when a dose has been ingested. Some interventions combine DAT with differentiated care when non-engagement has been observed.	Monitors adherence in real-time; low cost; reminders can also be sent via SMS.	Person with TB needs to be familiar with SMS messaging and have access to a phone and signal at the right times of day; SMS message sent may not reflect an ingestion of dose; non-receipt of SMS may not reflect non-ingestion of dose.
Other feature phone-based technologies, including medication sleeves (e.g. 99DOTS)	Verification of dose ingestion through SMS or phone calls using a variety of approaches, as well as other uses of feature-phone based technologies such as the systematised use of real-time voice calls. With medication sleeves, a paper sleeve is placed over a medication blister pack. A hidden phone number is revealed when the person with TB dispenses a dose, which the person calls to indicate a dose taken.	Monitors adherence in real-time; low cost.	SMS or phone call may not reflect an ingestion of dose; non-receipt of phone call may not reflect non-ingestion of dose.
Live VST (synchronous)	Ingestion of each medication dose is videoed by person with TB and observed by a HCP in real time. HCP observation could be replaced by artificial intelligence	Monitors adherence in real-time; convenience for person with TB; live interaction allows	Cost (HCP review of live video, smartphone); person with TB and HCP acceptability; non-

	applications.	HCPs to assess for medication side effects.	engagement with video call may not reflect dose non-ingestion; HCP and person with TB required to be online at the same time.
Recorded VST (asynchronous)	Ingestion of each medication dose is videoed by person with TB and sent to HCP to be viewed later.	Lower cost (than live VST); convenience for person with TB; convenience for HCPs.	Cost (HCP review, smartphone); person with TB and HCP acceptability; depending on when videos are viewed, may not monitor adherence in real-time; non-receipt of video may not reflect dose non-ingestion.

* An additional weakness across all the DATs is that they require HCPs to review dosing histories and act on them. DAT- digital adherence technology, HCP- healthcare provider, SMS- short message service, TB- tuberculosis, VST- video supported treatment. Adapted from Vernon *et al.* 2019 [15].

In this chapter, we will discuss the use of DATs to support persons with TB to take their treatment, including the evidence to date on how well they work. We will focus on low and middle income country examples as this is where the burden of TB morbidity and mortality is largely centred [2], but we will include examples from high income settings where pertinent.

Why is non-adherence to anti-TB treatment problematic?

Non-adherence to anti-TB treatment is broadly associated with a greater risk of 1) unfavourable treatment outcomes, 2) secondary drug resistance, 3) post-treatment relapse, and 4) an increased window for transmission of infection [26].

The association between non-adherence and unfavourable treatment outcomes has been documented across multiple studies, which usually use a binary classification of non-adherence (<80% of doses taken vs. ≥80% or <90% vs. ≥90%). In recent years, efforts have been made to move beyond these simple thresholds [27, 28], with calls for research examining non-adherence 'pattern' variability and its clinical importance [26].

The development of secondary drug resistance has been a concern from the earliest trials of antibiotics to treat TB [29]. Worries about the link between non-adherence and secondary drug resistance were a key reason that DOT was recommended as part of an overall Directly Observed Therapy, short-course (DOTS) management strategy [10] when the WHO declared TB to be a global health emergency in 1993 [30]. Since this period, studies have been undertaken suggesting a parabolic relationship between non-adherence and drug resistance, as at low levels of dose-taking bacterial exposure to drugs is insufficient for selection to occur [31]. Individual pharmacokinetics is likely to be a modifying factor; people with the least favourable pharmacokinetic profiles may be more susceptible to the detrimental impact of non-adherence [32]. As new drugs such as bedaquiline- the cornerstone of modern drug resistant TB treatment regimens- have come into use, this has renewed interest in the link between non-adherence and drug resistance.

How are DATs used?

The use of DATs as monitors

DATs can monitor adherence directly or indirectly, the latter through device- or person with TB-facilitated reporting (Table 1). DATs as monitors are used both in clinical practise to help persons with TB and HCPs, and secondly in research (including in clinical trials).

In comparison to DOT, DATs can provide a remote and more individually empowering mechanism by which both persons with TB and HCPs are able to keep track of adherence across the course of treatment without the need for direct observation and daily health care visits. This digital observation of pill-taking facilitates compilation of digital dosing histories. Such remote observation and visualisation reduce the time and resource burden on both HCPs and persons with TB versus in-person activities.

In observational epidemiology, DATs are an important tool to improve our knowledge of how exactly non-adherence is associated with the four consequences of non-adherence. Prior to their arrival, detailed data on dose-by-dose adherence patterns (including the timing of doses within a day) displayed by real-world persons with TB were not available, as DOT datasets were often paper-based, inaccessible to researchers, or thought to be unreliable. For example, in 2020 Stagg *et al.* published an analysis of adherence patterns displayed during a trial of digital pillboxes in China and found that persons with TB who miss doses early on were at higher risk of early discontinuation, highlighting the need for early intervention to support persons with TB struggling with treatment [16, 33]. Results from large pragmatic studies looking in depth at different adherence patterns are expected forthwith [34, 35].

Within drug trials, DATs provide an important tool for measuring adherence that is more granular than pill counts and more accurate than self-report. The use of DATs in trials is particularly important when it comes to defining per-protocol populations and for the associated statistical approaches required in order to recover the statistical protection derived from randomisation in per-protocol analyses [15, 36].

The use of DATs as interventions

In addition to simply being monitors, DATs may enable *intervention* in care to protect against the four consequences of non-adherence (Figure 1). This can occur in two ways, which are not mutually exclusive. DATs may provide reminders for medication-taking- including via SMS or audiovisual cues (e.g. for digital pillboxes)- and be part of interventional packages that contain other motivational content e.g. messaging and gamification. Secondly, digital dosing histories can be used to triage persons with TB. This can occur either via computer algorithms (e.g. by automatically notifying HCPs about people who have missed doses) or by HCPs viewing adherence histories using a computer or smartphone application. HCPs can then provide individualised treatment support (differentiated care) to people deemed to have problematic levels of non-adherence. For example, in randomised trials in China, data from digital pillboxes were used to identify people who might need intensified care (potentially including transition to DOT), although HCP fidelity to the escalation of patients through the differentiated care model was suboptimal [16, 37]. Determining the right ‘trigger’ point for differentiated care requires additional research to determine the most problematic adherence patterns to enable effective action.

Emerging evidence suggests that persons with TB value other DAT functions that foster a feeling of being ‘cared for’ by the health system. These include the ability to communicate with HCPs, enhanced access to TB knowledge (e.g. via educational SMS or apps), and improved ability to report and seek advice about side effects [38]. Future DATs should incorporate these

additional functions, which may better enhance person-centred care.

What is the evidence that DATs work?

In 2017, the WHO updated treatment guidelines indicated that DATs could be offered to persons with TB [39] and, five years later in 2022, the WHO consolidated treatment guidelines [5] suggested that VST or DOT be used to support adherence; both were conditional recommendations, with very low certainty of evidence. Since that time, there has been a large increase in studies on DATs seeking to fill this evidence gap.

The use of DATs as monitors

Evidence about whether DATs are providing accurate data as monitors (Table 1) is largely derived from comparing their performance to urine testing for rifampicin or isoniazid metabolites. For example, in India, a comparison between 99DOTS person with TB-reported doses and urine testing found that the sensitivity of 99DOTS was 61% (95% confidence interval 57-65%) and the specificity was 70% (58-81%) [40]. Sensitivity increased (89% (86-91%)) and specificity decreased (33% (22-45%)) when HCP-reported doses were also accounted for. Equivalent studies have been done for the digital pillboxes [41], and other DATs, with varying results. Urine testing is not a perfect gold standard, particularly as dose-by-dose information cannot be obtained using this measure. Despite the concern that DAT data are a mixture of adherence information and information on engagement with the technology, DATs remain our best current source of dose-by-dose non-adherence data, particularly for non-adherence patterns in normal care.

The use of DATs as interventions

In drug sensitive TB, studies of whether DATs work as an intervention to improve disease outcomes have commonly used medication adherence (often based on a proxy of DAT engagement), and end of treatment outcomes as their endpoints of interest, although some are also assessing the impact of DATs on subsequent treatment recurrence [35, 37, 42]. Recent systematic reviews summarising the evidence on whether digital approaches improve adherence have reported variable intervention effects [38, 43, 44].

The strongest evidence of DATs improving end of treatment outcomes (and having positive cost implications [19, 45]) is for VST, and mainly limited to high income countries [38, 43, 46]. Replacing HCP observation of videos by artificial intelligence applications is being piloted [47] and could potentially reduce HCP's time and health systems costs.

Studies assessing SMS-style interventions show variable results. Most SMS-style interventions have not demonstrated improved end of treatment outcomes, although exceptions include a complex intervention in Kenya [48] and a 99DOTS intervention in Uganda (further details of which are presented in the next section) [49]. In the complex intervention in Kenya, unsuccessful treatment outcomes were reduced by nine percentage points, mainly through reducing on-treatment loss to follow-up. In Uganda a per-protocol analysis of a pragmatic stepped-wedge trial, defined as receiving the SMS-style intervention in the intervention phase, showed improved cure/treatment completion of 16 percentage points, although this could have resulted from uncontrolled confounding as this was not observed in the intention to treat analysis [49].

Studies assessing pillbox reminders- often combined with compiling digital dosing histories and differentiated care for those persons with TB for whom non-engagement with the DAT is documented- have shown variable effects for end of treatment outcomes, despite improving adherence. A small study in Peru of pillbox digital confirmation, SMS reminders, and support

from a relative or treatment monitor demonstrated improved treatment success of 13 percentage points, although only in the per-protocol population [50]. Similar results have been reported from South Africa, where DAT and differentiated care improved adherence but failed to show impact on treatment outcomes [51, 52]. A combined intervention of pillbox reminders and real-time digital observation linked with enhanced care coupled with a treatment supporter conducted in Tibet demonstrated reduced levels of poor treatment outcomes (died, lost to follow-up, treatment failure) by 22 percentage points [53]. The first trial assessing the effects of a DAT on a combined endpoint of poor treatment outcome and recurrence, conducted in China, showed no impact on the composite unfavourable outcome, although medication adherence was improved [37]. Across studies, apparent improvements in adherence without a consistent corresponding improvement in treatment outcomes may result from a) adherence being measured on DAT-engagement without external confirmation of drug intake, such as urine isoniazid testing or b) limitations in measuring treatment outcomes in pragmatic trials due to lack of specificity of the end of treatment outcome and/or small numbers of repeated sputum cultures to measure recurrence.

How, and where, have DATs been used in routine practice?

DATs have been implemented in routine practice in a few low- and middle-income countries. In India from 2017 to 2020, 99DOTS was scaled up to more than 200,000 people as an intervention aimed at improving outcomes in the country's public sector program [54]. People with TB who missed calling in multiple sequential doses were flagged through automated SMS texts to HCPs or when HCPs accessed a smartphone or computer application. As such, 99DOTS prompted HCPs to intervene through phone calls or home visits. This initiative facilitated a shift from sometimes restrictive facility-based DOT models [13] and enabled integration of digital adherence reporting into Nikshay, India's electronic TB medical record [54].

At the same time, 99DOTS was not associated with improved treatment outcomes [55, 56], and implementation challenges led to a decline in use in India. At the level of people with TB, multiple barriers contributed to suboptimal cellphone accessibility, including shared use within families, low cellphone literacy, and lack of cellular signal [55, 57]. These challenges and perceptions of increased stigma (due to greater visibility of pill-taking) led to suboptimal 99DOTS engagement by people with TB, which contributed to its limited accuracy for detecting non-adherence [40, 58]. At the health system level, the emergence of different TB drug manufacturers made it difficult to procure 99DOTS sleeves that could match variations in medication blister packs. Additionally, the cost of paper for sleeves rose up to 60% during the Covid-19 pandemic [59]. Given these challenges, India's TB program is pivoting the 99DOTS initiative in new directions. In South Africa, roll-out of medication sleeves with cellphone reporting, similar to 99DOTS, faced many challenges including difficulty with SMS, the requirement for a cellphone, and technical glitches with network providers [60]. This led to the reduced use of this technology compared to digital pillboxes, and eventually a discontinuation of implementation.

In Uganda, 99DOTS was adapted using human centred design methods in collaboration with local stakeholders and end users [61]. Medication sleeves were altered by adding a flap- adorned with a calendar or map of Uganda- to conceal pills and reduce stigma. The inside cover contained a personalised message and contact information from a local HCP, pictorial pill-taking instructions, and a choice of stickers for tailored TB education. Pill-taking order was indicated with colours, arrows, and cellphone icons. When persons with TB 'called in' doses, they heard rotating audio messages centred on the themes of prevention and reassurance that TB is curable.

Following the results of the stepped-wedge trial described in the previous section, the 99DOTS-based intervention was expanded to 12 health facilities in the Greater Kampala Metropolitan Area, with provision of low-cost phones (US $8) to people who lacked access in order to expand 99DOTS' reach and enhance equity. Responsibility for adherence monitoring was shifted from HCPs to community HCPs, with provision of automated task lists to facilitate follow-up. An interrupted time series analysis of this expansion is in process, with early findings suggesting that cellphone provision facilitated enrolment of 87% of adults with pulmonary TB in 99DOTS and that 99DOTS-based supervision achieved similar outcomes to routine care. These findings suggest that 99DOTS can improve the treatment experience without compromising treatment outcomes [62].

In Eastern European and Central Asian (EECA) countries- home to 24% of people with multidrug resistant or rifampicin resistant TB and 47% of people with pre-extensively drug resistant TB globally [2]- VST is the most commonly implemented DAT. VST is being programmatically implemented as an alternative to DOT that still allows for visual observation of dosing, in a region where preventing further development and transmission of drug resistant TB is a priority. Several countries initially used available telecommunication platforms to manage persons with TB. More recently, shifts have been made to dedicated commercial or locally developed DAT platforms (in Belarus, Georgia, and the Republic of Moldova, for example) to ensure data privacy and allow for asynchronous video uploads. VST platforms developed in Georgia and Moldova have been adapted for use by Armenia, Azerbaijan, Tajikistan, Turkmenistan and Uzbekistan [63]. Ukraine has implemented VST but is also rolling out digital pillboxes, which have allowed HCPs to maintain contact with people taking treatment during the COVID-19 pandemic and the ongoing war [64, 65]. Early data from EECA countries suggest that VST saves patient time and costs in comparison to travel to and from a facility for DOT; however, challenges with internet connections- particularly in rural areas- have been noted and people with TB have also expressed privacy- and stigma-related concerns as well as frustration with having to upload videos daily [66, 67].

What generalisable learning can be taken from the experience of using DATs in TB?

DATs cannot be used as the sole replacement for more comprehensive care packages

The lack of improvement in treatment outcomes in most randomised trials of DATs may speak to the limitations of these technologies as a sole replacement for more comprehensive TB care packages.

DATs may have limited effectiveness because non-adherence has multiple root causes, many of which may not be directly addressed by DATs. Despite early work laying out multiple dimensions of adherence barriers (e.g. economic, structural, person with TB-related, regimen complexity, person with TB-HCP relationships, mode of healthcare delivery) [9], studies of non-adherence in TB have largely focused on demographic and clinical factors [68]. Additionally, not only do the root causes of non-adherence vary among people with TB, but a single person taking TB treatment may encounter different adherence barriers at different points across the treatment course. A comprehensive understanding of context-specific adherence barriers is critical to inform the development of effective interventions. This understanding must extend beyond demographic factors to include the health system, structural, and psychosocial forces at play within a given setting [68-71].

DAT-based interventions may also fall short because non-adherence may not be the sole mechanism through which unfavourable outcomes occur. Disease severity, individual pharmacokinetics, and comorbidities (including HIV, diabetes, hepatitis C, mental illness, and

malnutrition) may negatively impact TB treatment outcomes through direct biological mechanisms (e.g. immune suppression, hepatotoxicity) that are, in part, independent of treatment adherence [72-75]. Effectively addressing these root causes by providing early access to care and treatment, ideally integrated within TB services, will pay dividends by improving TB treatment outcomes via multiple pathways while enhancing health outcomes more broadly.

Viewed in the context of these multi-faceted challenges faced by people with TB, the impact of many DAT-based interventions may be limited to individuals with specific adherence barriers. For example, a DAT may be a useful tool for someone who forgets to take pills or struggles to manage a complicated regimen as a mechanism to facilitate early outreach with HCPs, but may be insufficient to counteract the food, water, and housing insecurities that challenge adherence for many people with TB globally [76, 77].

Future digital adherence technology interventions should be multifaceted and integrate strategies for addressing root causes of non-adherence

Although DATs cannot replace more comprehensive care packages, they may facilitate more efficient delivery of comprehensive care to people with TB experiencing adherence barriers. However, most DAT-based strategies to date have not integrated evidence-based interventions that may address root causes of non-adherence, such as counselling to enhance treatment literacy [78], therapy for alcohol use disorder [79], or treatment of depression.

Notably, the only two randomised trials showing that DAT-based interventions could improve TB treatment outcomes in low- and middle-income country settings both used digital adherence data as the starting point for intensifying care using person-centred strategies. In the previously mentioned complex intervention in Kenya, TB survivors promptly engaged in phone outreach to people with TB who did not provide a daily SMS response indicating dose ingestion [48]. The intervention also included weekly motivational SMS messages, a gamification component, daily SMS reminders, and a data platform for people with TB to confirm daily adherence. In the previously mentioned complex DAT-based intervention in Tibet, a digital pillbox was also only one component of a much broader intervention [53]. The intervention also included a linked smartphone app that allowed audio, video, and SMS-based communication between people with TB and HCPs (with provision of a free smartphone data plan); training of a family member to support the person with TB in their TB care and technology use; and transition to monitoring by VST for people who did not report more than three consecutive doses using the digital pillbox. Building upon the learnings from these successful interventions, future DAT-based strategies should move beyond a focus digital observation alone towards integration of stronger people-centred support.

What does this mean for subclinical TB?

As well as causing TB disease, *M. tb* can also infect people subclinically [80]. To prevent subclinical infections progressing to disease, treatment lasting one to six months is generally recommended [81]. Adherence to treatment for subclinical TB suffers from many of the same complexities as that for TB disease, with the addition that individual motivation to take treatment is often lower as people do not feel unwell. DATs may be useful in this context [82-84].

What does this mean for other respiratory conditions?

The complexity of adherence behaviour is not unique to TB. There has been substantial interest in non-adherence to treatment for other respiratory conditions, including chronic obstructive pulmonary disorder (COPD) and asthma.

For many chronic respiratory conditions, inhalers are an important component of disease management. Thus, there has been work to develop smart inhalers [85] that can transmit data about when the inhaler has been activated, similar to smart pillbox technologies. Smart inhalers have generally been shown to improve adherence with similar efficacy to SMS message reminders [86], however most of these studies have been conducted in high-resource settings. It is also important to bear in mind that asthma and COPD treatments are largely better tolerated than TB medication, where side effects can further compound individuals' non-adherence.

There is shared interest across TB and other respiratory conditions about digitally-collected biomarkers that can track treatment response and potentially provide early warning systems about suboptimal adherence. In TB, cough monitoring provides a potential non-invasive treatment response biomarker [87]. In people with cystic fibrosis, at-home spirometry has been used to detect early signs of exacerbations [88]. Similarly, in people with COPD, a digital symptom screen and home pulse oximetry reading was also able to predict oncoming exacerbations [89].

Many respiratory conditions share the same complexities as TB in our approach to non-adherence. For example, both biological and social factors affect individual adherence to treatment [86]. In addition to socioeconomic factors [90], individual beliefs about potential harm of medication and over-prescription are associated with lower adherence in people with asthma and COPD [91]. Non-adherence patterns can likewise be complex, resulting in similar methodological advancements in how we analyse adherence data, including trajectory-based analyses and clustering approaches to more fully capture the complexities of adherence behaviour. These approaches have been applied to TB cohorts [92], as well as people with COPD [93] and asthma [94]. They can help explore the diversity of adherence behaviours in cohorts and may help establish phenotypes of individuals that could require different adherence support.

Finally, we note that DATs- including the use of artificial intelligence on mobile devices- are also being applied in non-respiratory conditions, such as schizophrenia [95].

Conclusion

Several decades on from the WHO DOTS strategy, discussion about how best to support persons with TB taking their treatment is now inclusive of digital tools. Just as DOT was always intended to be part of an overall care package supporting persons with TB, DATs should be similarly visualised. Evidence of DATs improving outcomes is limited, however studies from multiple settings suggest they are acceptable to persons with TB [96]. It is highly unlikely that there is a one-size-fits-all model that can be globally recommended to promote adherence to anti-TB treatment. Different interventions will suit different settings, with varying degrees of effectiveness, cost-effectiveness, and acceptability linked to the healthcare system in which an intervention is implemented and the existing interventions in place. As DOT is frequently already being used in settings when DATs are trialled, it is often taken as the comparator of interest. As a costly and high-effort intervention (when implemented fully) that reduces patient autonomy, the use of DOT in this way has inevitably influenced data on DAT acceptability and the relative burden of its cost. In line with their two-fold nature as both monitors and interventions, DAT data are being used to further our understanding of how precisely non-adherence occurs, and what patterns of non-adherence are particularly problematic.

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Conflicts of interest/disclosures

RS declares grants/contracts from Bill and Melinda Gates Foundation, Doris Duke Charitable Foundation and National Science Foundation in the past 36 months. AK declares support from The Stop TB Partnership since the initial planning of the work and that The Stop TB Partnership, TB REACH received funding from the Bill and Melinda Gates Foundation to support implementation and evaluation of digital adherence technology projects in the past 36 months. SC declares support from the Aurum Institute since the initial planning of the work and UNITAID ASCENT grant funding in the past 36 months. SH declares grants/contracts from US National Institute of Health and University of California San Francisco Research Allocation Program, as well as support for attending meetings/travel from the Canadian Institutes of Health Research in the past 36 months. SL declares grants/contracts from Canadian Institutes for Health Research Fellowship (Patient-Oriented Research Award TS1 170663) in the past 36 months. HRS declares support from the UK Medical Research Council (MRC) since the initial planning of the work as well as funding from the National Institute for Health Research (NIHR) UK, membership of the WHO Ethics Review Committee for the ASCENT project, co-chairpersonship of UK Academics and Professionals To End Tuberculosis, core group membership of the WHO European Tuberculosis Research Initiative, membership of the WHO Scientific Guidance on Evidence Generation on new regimens for tuberculosis treatment Development Group, and membership of the UK MRC Applied Global Health Faculty of Experts in the past 36 months. The other authors have no conflicts to disclose.

Funding

SH is supported by a Canadian Institute of Health Research Postdoctoral Fellowship. HRS is supported by the UK MRC [MR/R008345/1].

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Acknowledgements

We thank Marisa Muckian (London School of Hygiene & Tropical Medicine) for her help compiling this chapter.

Figure legends

Figure 1. Functions of digital adherence technologies for potentially enhancing medication adherence for people with tuberculosis while also enabling monitoring, triage, and delivery of differentiated care by health systems.

'Differentiated care' refers to providing different intensities and types of care based on an individual's level of medication adherence as measured by the DAT. Reproduced from Subbaraman *et al.* BMJ Global Health 2018 [14].