Digital adherence technologies: technical guidance & budget for Global Fund funding request

Empowering patients with digital adherence technologies

While tuberculosis (TB) can be cured with appropriate treatment, long and complicated treatment regimens increase the probability of poor adherence. Research has established that TB treatments are highly unforgiving to poor adherence - missing even a few daily doses or interrupting treatment can lead to resistance to TB medicines and/or relapse.

Digital adherence technologies (DATs) were developed to be affordable approaches to support patients with the challenges of remaining adherent to treatment. In addition, DATs can facilitate the identification of high-risk patients for home visits or escalated treatment. DATs have been deployed at both small and large scale in different contexts with a growing body of evidence around them to support patient-centered care in TB and have been endorsed by the WHO.

This document provides an overview of the necessary steps for planning and budgeting a DAT deployment, ranging from countries without current DAT experience to others looking to scale up promising early-stage deployments.

An estimated 10 million people fall ill each year with TB, with an estimated 1.5 million people dying from the disease in 2018 alone.[1] This is unnecessary as TB can be cured with appropriate treatment. A number of barriers, however, prevent patients from recovering from this disease, including long and complicated treatment regimens that involve the daily intake of medicines over the course of 6-24 months. Missing even a few daily doses or interrupting treatment can lead to resistance to the TB medicines and/or return of the disease later in life. Therefore, patients normally need to be observed when taking their daily medication either by visiting the health center or by a health care worker at their home. Obviously, these supportive measures put a burden on both the patient and the health system.

By leveraging today's smart information and (mobile) communication technologies, digital adherence technologies can help to support TB patients with their treatment in a modern and more effective way. These are digital tools that utilize mobile phone, computer, web-based and/or electronic sensor technology to support the capture of detailed, timely, patient-specific adherence data. These technologies empower patients to take their daily medication at a time and place that suits them best. Additionally, they provide real-time information to the TB doctor or nurse, helping to determine the most appropriate

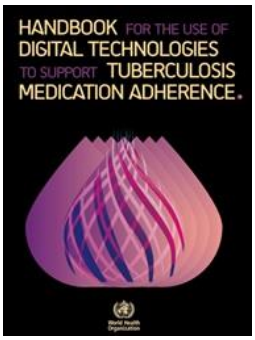
[1] World Health Organization. Global Tuberculosis Report 2018 (WHO, 2018).
[2] World Health Organization. Handbook of the use of digital technologies to support TB medication adherence.

treatment approach for each individual patient and by enabling focused efforts on those patients that require extra support.

The potential impacts of DAT-assisted therapy are significant. Effective TB treatment with DATs can avert a substantial number of clinic visits for the patient, resulting in both health system efficiencies and patient savings. From a public health perspective, DATs could avert many disease relapses. In some patient populations, such as those with a higher probability of low adherence, DAT interventions could cut relapses and deaths from drug-susceptible TB (DS-TB) by over 50%. Lastly, DAT use provides patients with more autonomy and insight into their treatment, potentially reducing stigma as a result of reduced clinic visits.

Digital adherence technologies: An overview

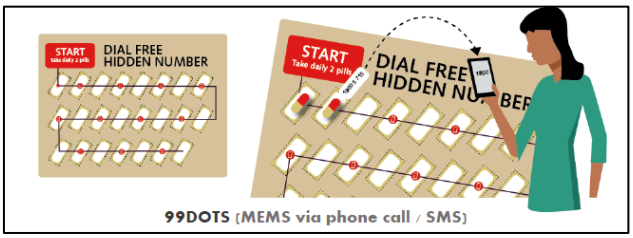
There are currently several different types of DATs available. The WHO describes various solutions in their Handbook of the use of digital technologies to support TB medication adherence[2] including the available evidence base and the three types of DATs covered in this document:



- **Medication sleeves**
  Medication sleeves combine customized packaging and utilize free or low-cost interactions such as phone calls, SMS, USSD, or other messaging technology.
- **Smart pill boxes**
  Smart pill boxes employ electronic sensors that automatically log daily doses via a mobile internet connection.
- **Video-supported treatment**
  Video-supported treatment utilizes a video connection between the patient and the health care provider to observe medication intake remotely.

While not covered in this document, it is worth noting that evidence and implementation experience is currently being generated for new types of DAT or approaches such as the use of ingestible sensors (also called Wireless Observed Treatment[2]) or two-way communication to support patient recovery by Keheala[3] in Kenya that uses basic feature phones and behavioral strategies.

Medication sleeves



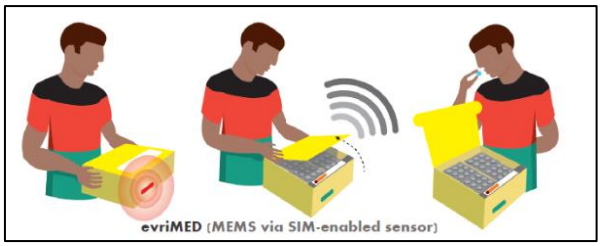
The patient receives their anti-TB medication in customized or augmented packaging. On a daily basis, patients make a toll-free call, text a code, or interact via USSD (Unstructured Supplementary Service Data) to automatically log their daily dose. This can be done using any mobile phone, even basic, shared phones without data access. The modality of patient interaction - calling versus texting - as well as the language, dimensions and design of the medication sleeve should be tailored to each individual country context. An example is 99DOTS[4], which pairs customized medication packaging with basic phone call / SMS technology to provide accurate, real-time data on patient treatment adherence. In this approach,

[2] https://www.proteus.com/
[3] https://www.keheala.com/
[4] https://www.99dots.org/

existing medication blister packs are inserted into a custom cardstock sleeve with a series of unpredictable hidden toll-free phone numbers or SMS codes that are revealed each time a patient removes their pills for the day. Patients engage with 99DOTS by placing a free call or sending a free SMS daily to the revealed number, at which point the system will automatically log their medication intake on the adherence platform. Other adaptations of 99DOTS have also used stickers on pill bottles for ARV medications which do not come in standard blisters.

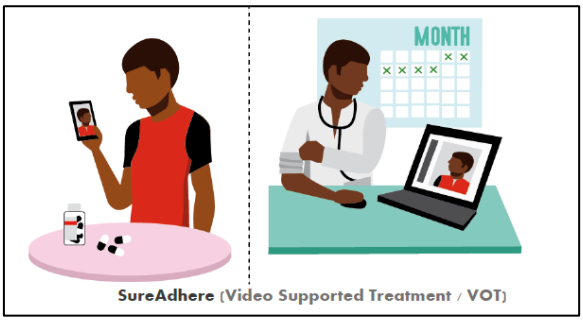
Smart pill boxes

The patient is provided with a specially designed box to store their TB medication and every time the patient opens the box, the embedded electronic device sends a signal in real-time to automatically log their daily dose via a mobile internet connection. When internet connectivity is not available, opening events are stored in the device memory and uploaded automatically when internet connectivity is available again. The box can usually be customized to divide compartments to sort by medications (including medication for other diseases) or daily dosing. It can also include treatment-specific instructions and its small light-emitting diode (LED) display and speaker enable configurable audio-visual reminders.



An example is evriMED[5], a digital medication monitor that combines the functionality of a low-cost cardboard or plastic medication box with a small-scale, battery-powered sensor and mobile data connection. Patients store and organize their TB medications in the box, and when they open the box for daily medication intake, the sensor is activated and sends dosing event information in real-time to the adherence platform using the mobile data connection.

Video-supported treatment



Synchronous video-supported treatment utilizes a video-conferencing technology to enable a connection between the patient and the health care provider to observe medication intake in real-time remotely. *Asynchronous* video-supported treatment utilizes video recording and mobile communication to remotely monitor and support TB medication intake. Both approaches allow health care providers to observe the medications actually being ingested. These videos are encrypted, sent and stored on an adherence platform, where they can be reviewed by the patient's health care provider at any time. An example of video-supported treatment is SureAdhere[6], a smartphone application for Android and iOS devices that utilizes video recording and mobile communication to remotely monitor and support TB medication intake.

Using an asynchronous video approach, patients are guided to record videos of themselves ingesting their daily medication. These videos are automatically synced via secure mobile connection with the adherence platform, where they are reviewed by the patient's health care provider and marked as complete. This

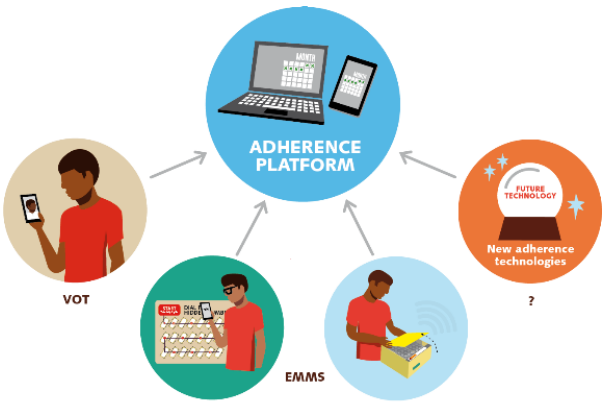
[5] https://www.wisepill.com/evrimed
[6] http://www.sureadhere.com/

approach also makes it possible for patients to make videos without a network connection and upload videos when a connection is obtained.

Digital adherence technology platform

A function that all types of DATs have in common is the ability to generate a digital record of medication intake. When multiple types of DATs are implemented in a country context, it is desirable to consolidate this data into a unified digital adherence technology platform. Such a platform enables NTPs to integrate and aggregate data generated by different types of DATs. Health care workers can monitor adherence via a single user interface to support patients' efforts to manage their treatment, independently of the type of DAT being used by the respective patient. Aggregated adherence data at the country level can further contribute to a better understanding of adherence challenges across geographies and over the course of treatment.

Further, a digital adherence platform allows countries to implement whichever DAT is most appropriate for patients in each context. Integration of multiple adherence technologies through a standardized platform creates the opportunity to use different adherence technologies for different patient populations, as well as to switch between technologies without sacrificing the functionality and data utilization of the platform. Lastly, a single, adaptable platform will allow new types of DATs to be added in the future and establish linkages with existing national patient management or disease surveillance systems.



An example of an integrated DAT platform is the Everwell Hub,[7] a comprehensive, open-source platform for adherence and patient management where health care providers can log into a single portal to register and follow up with patients who send digital adherence data from their choice of DATs.

Implementation approach for digital adherence technologies

The implementation approach for DATs is largely dependent on the level of country experience with these or other digital health products. For countries without any prior DAT experience, a phased implementation starts by determining the necessary infrastructure (e.g. data hosting) and customizing of the technology and platform to match with the country needs. This step will establish the technical groundwork for DATs to function effectively in subsequent phases of implementation.

Phase 0: Customization, configuration and testing of infrastructure, DATs, and platform.

Phase 1: Small rollout (>2000 patients/1-2 regions/districts) to contextualize interventions, customize country specific workflows, develop local DAT protocols, etc.

Phase 2: Scaled implementation in multiple districts, >2000+ patients

Phase 3: Province or country-wide scale, consider migrating from cloud hosting to in-country hosting using servers, etc.

[7] https://www.everwell.org/

For countries with DAT experience and infrastructure in place, it will be possible to scale the DAT intervention at an accelerated pace. Activities can start form Phase 2 or 3 depending on the extent of prior experience.

KNCV DAT implementation toolkit

In 2019, KNCV published a Digital Adherence Technologies Implementation Toolkit to present important considerations, learnings, and strategies from past and ongoing implementations of digital adherence technologies. The toolkit is a shared resource, leveraging experiences from a wide range of settings by NTPs, implementing partners, and DAT vendors who have supported the deployment of these technologies globally. The toolkit consists of background information, training materials, step-by-step implementation approaches and advocacy materials. All information can be used freely.

Budget

Per patient costs for implementation of a digital adherence technology

There are a number of factors that influence the per patient cost of implementing and scaling DATs in a given country. These factors include the cost of data and SMS, frequency of interactions, patient population, type of DATs used, and whether the necessary infrastructure is already (partly) in place.

Based on actual cost in a variety of countries, the estimated cost to implement a DAT for countries with **5,000 to 10,000 patients** per year will be approximately **$35.00 USD per patient** ranging between $25.00 USD and $45.00 USD. This price range reflects the variance in factors listed above and is reduced as a country scales beyond 10,000 patients. In the range of **10,000 to 50,000 patients**, we estimate the costs to be **$24.00 USD per patient** with a range between $17.00 USD and $31.00 USD.

These prices account for all potential costs associated with DAT implementation, including necessary infrastructure both hardware and software (for countries who do not already have it), the DAT products themselves, and programmatic costs such as technical support and training.

Please note: The price ranges quoted above are based on a scenario in which hosting of an adherence platform is supported through cloud-based servers. Due to the array of factors, it's difficult to establish a one-size-fits-all price for utilizing DATs within each individual health system. For more detailed costing information specific to your country, please contact either the relevant DAT vendors or the ASCENT project, whose contact information can be found at the end of this guidance document.

Infrastructure

In order to have a successful DAT deployment, a country or implementer must ensure the required technical infrastructure for DAT implementation is in place. There are two categories of infrastructure costs: one-time costs such as set up, platform customization, and technical integration with other platforms (if present) or telecom infrastructure; and recurring costs such as hosting, communications (I.e. SMS/Interactive Voice Response (IVR) or USSD), and maintenance. One-time costs depend on existing

infrastructure, ability to leverage shared resources like cloud-based infrastructure, and degree of customization. Recurring costs depend on duration and scale of the implementation (I.e. duration, patient population, number of centers, type of treatment [DS-TB, DRTB, LTBI]). For smaller deployments, the one-time costs will likely exceed the recurring costs. As deployments scale, the per patient costs decrease drastically as evidenced by India and China's large-scale deployments. In addition, once the necessary infrastructure is in place, there are often no additional costs to add a new technology to the product mix in a country.

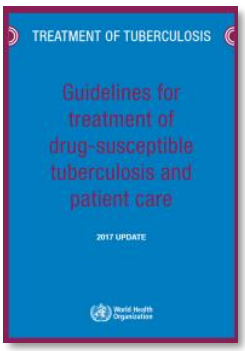
Products

The second category of costs is the per treatment costs of DATs, such as medication sleeves, smart pill boxes and video-supported treatment. Cost components can vary by DAT product. For medication sleeves, it comprises the physical sleeves as well as daily costs to support interactions between patient and provider. The cost for the smart pill box is comprised of the module itself and supporting equipment (battery, magnet, charging cable), as well as SIM card and mobile data fees. For video-supported treatment, this could be the additional cost of storing videos, data and/or mobile devices for patients that do not have data and/or mobile devices available.

Program

The third source of costs are the programmatic costs associated with scaling many types of health products, including health care provider training, distribution, and visual and written materials. In this category, costs related to patient outreach can also be included, as well the provision of technical support including adaptations and updates for technology partner(s). It is critical to note that no DAT intervention is successful simply by setting up and deploying the technology – while a necessary first step, every DAT should be part of an intervention as an enabler of human resources to facilitate self-monitoring by patients supported by targeted counseling from staff. For countries and implementers, devising context-appropriate escalation protocols and having well-trained, motivated staff and treatment supporters available to leverage the information that DATs provide is critical to success.

Global policies, guidelines and evidence



The WHO's updated Guidelines for the treatment of drug-susceptible tuberculosis and patient care (2017) recommends that providers *"offer one or more treatment adherence interventions to patients such as tracers and/or digital adherence medication monitors (conditional recommendation, very low certainty in the evidence)."*

There is a significant evidence base for the acceptability and utility of digital adherence technologies across randomized control trials and peer reviewed academic papers. The potential benefits that may accrue to patients and providers as a result of adopting DATs include: better health outcomes for patients; reduced costs for patients who no longer travel to clinics for DOT; health system savings due to providers no longer conducting DOT; reduced stigma for patients; and improved data and decision-making at national and global levels.

In India, where medication sleeves have been widely adopted, initial research has shown that the DAT is both feasible and acceptable.[8] Studies on feasibility, acceptability, and effectiveness with regard to

[8] https://dl.acm.org/doi/abs/10.1145/3287098.3287102

treatment outcomes are currently ongoing on medication sleeves in India, Tanzania, Uganda and the Philippines. A rigorous cluster-randomized trial in China of 4500 TB patients in rural and urban settings showed that the use of the smart pill box reduced poor medication adherence by 40%–50% compared to SMS messaging alone or the standard of care.[9] In addition, an ongoing cluster randomized trial in China is evaluating the health outcomes and cost-effectiveness of incorporating a smart pill box in TB treatment.[10]

Likewise, the implementation of video-supported treatment in London, UK improved TB treatment adherence and communication between patients and providers[11]. Studies of video-supported treatment in the USA,[12] Mexico,[13] and Belarus[14] show comparable treatment outcomes to traditional directly observed treatment (DOT), but with reduced health system costs.

Recent modeling conducted to understand the potential impact of DATs, suggests that for populations where more people are likely to have low adherence (likely defaulters), DAT interventions could cut relapses and deaths from DS-TB by over 50%.[15] For DR-TB the potential impact is a reduction of between one-third and one-half of relapses and deaths.[16]

The proposed large scale multi-country study that will be conducted during the ASCENT project (see below) will evaluate effectiveness outcomes relevant to stakeholders in contexts under similar investigation and will include sub studies on acceptability, feasibility and costs that will help drill down on for whom DAT interventions work and why.

Country implementations and projects

TB REACH: In 2018, Stop TB Partnership's TB REACH funding mechanism granted funding for 14 distinct demonstration projects to assess the implementation of DAT interventions to improve TB treatment outcomes. These projects are ongoing in 11 countries using a variety of DATs (such as 99DOTS, evriMED and video-supported treatment), across populations of mainly DS-TB patients and some populations of DR-TB patients (three settings).

ASCENT: The Unitaid-funded ASCENT project aims to support patient adherence to TB treatment using DATs. The project started in July 2019 and will be implemented until December 2022 aiming to reach nearly 70.000 patients in Ukraine, Ethiopia, Tanzania, South Africa and the Philippines. It focuses on facilitating country adoption and uptake of DATs; generating crucial evidence for optimal use and scale-up; and creating a global market and implementation plan for digital adherence technologies.

[9] Liu, X. ; Lewis, J.J. ; Zhang, H. ; Lu, W. ; Zhang, S. ; Zheng, G. ; Bai, L. ; Li, J. ; Li, X. ; Chen, H. ; Liu, M. ; Chen, R. ; Chi, J. ; Lu, J. ; Huan, S. ; Cheng, S. ; Wang, L. ; Jiang, S. ; Chin, D.P. ; Fielding, K.L. ; Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med (2015) 12(9):e1001876; DOI: 10.1371/journal.pmed.1001876; PMID: 26372470
[10] http://www.isrctn.com/ISRCTN35812455
[11] Story A, Garfein RS, Hayward A, et al. Monitoring therapy compliance of tuberculosis patients by using video-enabled electronic devices. Emerging Infect Dis 2016; 22: 538–540
[12] Garfein, Emerging Infectious Diseases, 2019
[13] Garfein R et al. Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study. Int J Tuberc Lung Dis 2015; 19: 1057–1064.
[14] Sinkou H, Hurevich H, Rusovich V, et al. Video-observed treatment for tuberculosis patients in Belarus: findings from the first programmatic experience. Eur Respir J 2017; 49
[15] ASCENT Project Modeling, 2019
[16] ASCENT Project Modeling, 2019

DAT scale up in China and India: Beyond TB REACH and ASCENT, China and India have both implemented a large-scale rollout of DATs in recent years. In China, the Plan on TB Control (2016–2020) included the adoption of an electronic medication monitor (EMM) for TB case management.[17] In addition, the China Center for Disease Control developed a scale-up plan for three provinces in the country. In India, over 200,000 patients have been enrolled on treatment using 99DOTS.[18] India's National Strategic Plan 2017-2025 lays out an ambitious plan and commitment to increase coverage of digital adherence technologies nationwide. An overview of digital adherence projects and country implementations can be found in **Annex 1** at the end of this document.

Place for digital adherence technologies in funding request

In the Global Fund Tuberculosis Information Note (July 2019), DATs are identified as tools that can contribute to the provision of appropriate people-centered support to TB patients to ensure successful treatment outcomes. As guided by the Global Fund Modular Framework Handbook, *"supportive activities to improve treatment including digital technologies"* should be placed as a Treatment intervention under either the TB Care and prevention or MDR-TB module.

The implementation of digital adherence technologies can contribute to the following Outcome and TB Care and prevention indicator(s):

- Outcome TB O-2a: Treatment success rate of all forms of TB -bacteriologically confirmed plus clinically diagnosed, new and relapse cases
- Outcome TB O-4(M): Treatment success rate of RR TB and/or MDR-TB: Percentage of cases with RR and/or MDR-TB successfully treated
- TCP-2(M): Treatment success rate-all forms: Percentage of TB cases, all forms, bacteriologically confirmed plus clinically diagnosed, successfully treated (cured plus treatment completed) among all TB cases registered for treatment during a specified period, new and relapse cases
- MDR TB-4: Percentage of cases with RR-TB and/or MDR-TB started on treatment for MDR-TB who were lost to follow up during the first six months of treatment
- MDR TB-9: Treatment success rate of RR-TB and/or MDR-TB: Percentage of cases with RR-TB and/or MDR-TB successfully treated

More information and contact

This document was developed by the Unitaid funded ASCENT project (KNCV Tuberculosis Foundation, PATH, the Aurum Institute and the London School of Hygiene and Tropical Medicine), Everwell Health Solutions and SureAdhere. The document also includes input from the Stop TB Partnership and the Bill and Melinda Gates Foundation.

More information can be found via www.digitaladherence.org, you can also contact the ASCENT project directly via ascent@kncvtbc.org or any of the relevant DAT vendors.

[17] https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4521-2
[18] https://www.microsoft.com/en-us/research/uploads/prod/2019/02/99DOTS-ICTD.pdf

Annex 1: Overview of DAT projects and implementations

Country	GF funding request	Project	DAT category	DAT type	Patient type and population	Number of patients on DAT	Region(s)/District(s)
Belarus		WHO/Belarus NTP	Video-supported treatment	Custom build	DS-TB patients MDR-TB patients	694	Minsk
China		NTP	Smart Pill Box	custom build	DS-TB and DR-TB patients		
India	Yes (2)	NTP	Smart Pill Box Medication sleeves	evriMED 99DOTS	DS-TB and DR-TB patients		
India	Yes (2)	NIH	Video-supported treatment	Emocha	DS-TB patients		Pune
India	Yes (2)	IDAT	Video-supported treatment OpAsha Medication sleeves	ZMQ OpAsha 99DOTS	DS-TB patients		
Myanmar	Yes (1)	PSI	Medication sleeves	99DOTS			
Ethiopia	Yes (3)	TBR wave 6 ASCENT	Smart Pill Box Medication sleeves	99DOTS evriMED	DS-TB and DR-TB patients	5000	Addis Ababa, Oromia
Kenya	Yes (3)		Other	Keheala	DS-TB patients		Nairobi
Uganda	Yes (1)	TBR wave 6 TBR Scale up	Medication sleeves	99DOTS	DS-TB patients	753	
Uganda	Yes (1)	NIH Pilot NIH R21	Video-supported treatment	SureAdhere	DS-TB Patients	200	Kampala
Uganda	Yes (1)	ZMQ Pilot	Video-supported treatment	ZMQ			
Philippines	Yes (1)	TBR wave 6	Medication sleeves	99DOTS	DS-TB patient in private sector	1000	National Capital Region
Philippines	Yes (1)	ASCENT	Medication sleeves Smart Pill Box Video-supported treatment	99DOTS	DS-TB/DR-TB Public	10000	Bulacan, Pampanga
Philippines	Yes (1)	TBR wave 6	Video-supported treatment	SureAdhere	MDR TB patients	100	National Capital Region
Paraguay	Yes (2)	University Pilot	Video-supported treatment	SureAdhere	DS-TB patients	50	Asuncion
Ukraine	Yes (2)	TBR wave 6	Smart Pill Box	evriMED	DS-TB and DR-TB patients	900 (800 DS-TB, 100 (DR-TB)	Odeska, Mykolaivska
Ukraine	Yes (2)	ASCENT	Smart Pill Box Video-supported treatment	EvriMED SureAdhere	DSTB and DR-TB patients		Odeska, Lvivska, Donetska, akarpatska, Mykolayivska oblasts
Moldova	Yes (2)		Video-supported treatment	Custom build	DS-TB and DR-TB patients	650 (516 DS-TB, 134 DR-TB)	
Mozambique	Yes (2)	USAID/HAI (Pending 2020)	Video-supported treatment	SureAdhere	MDR-TB and XDR-TB	200	Maputo City
South Africa		TBR wave 6	Smart Pill Box	evriMED	DS-TB patients	2610	Gauteng, Western Cape, Kwa-Zulu Natal
South Africa		ASCENT	Medication sleeves Smart Pill Box Video-supported treatment	99DOTS EvriMED SureAdhere	DS-TB and DR-TB patients	10000	Western Cape, Tshwane
South Africa		TBR Wave 7 (Pending 2020)	Video-supported treatment	SureAdhere	XDR-TB patients	150	Durban, Kwa-Zulu Natal
Eswatini	Yes (3)	MSF Pilot (Pending 2020)	Video-supported treatment	SureAdhere	MDR-TB patients	50	Mbabane
Kyrgyzstan	Yes (1)	TBR Wave 6	Video-supported treatment	SureAdhere	MDR-TB patients DS-TB patients	100	Bishkek
Tanzania	Yes (2)	TBR wave 6	Medication sleeves	99DOTS	DS-TB patients among mining population	1000	Geita region
Tanzania	Yes (2)	TBR wave 6	Smart Pill Box	evriMED	Smear positive TB patients and presumptive TB cases	660	Kilimanjaro
Tanzania	Yes (2)	ASCENT	Medication sleeves Smart Pill Box Video-supported treatment	99DOTS Evrimed SureAdhere	DS-TB and DR-TB patients	10000	Arusha, Geita, Manyara and Mwanza
Namibia	Yes (1)	TBR Wave 6	Medication sleeves	99DOTS	DS-TB patients	15	
Bangladesh	Yes (2)	TBR wave 6	Medication sleeves	99DOTS	DS-TB patients	1000	Dhaka, Chattogram

Haiti	Yes (1)	TBR wave 6	Video-supported treatment	SureAdhere	DS-TB patients, prisoners / recent parolees	150	Port Au Prince, remote prison sites
Vietnam	Yes (2)	Woolcock Institute	Video-supported treatment	SureAdhere	DS-TB patients	50	Hanoi
Vietnam	Yes (2)	TBR Wave 5	Video-supported treatment	SureAdhere	DS-TB patients	10	Ho Chi Minh City