

Digital adherence technology and TB care delivery: What gaps in information still exist? What is on the horizon?

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Objectives

1. Describe the “problem” of adherence in TB care
2. Describe the functions of digital adherence technologies (DATs) and the landscape of these technologies
3. High-level, selective summary of evidence on DATs being used in TB care
4. Highlight critical knowledge gaps and future directions for research and implementation

1. THE PROBLEM

Non-adherence to TB medications is associated with poor treatment outcomes and high disease relapse in trials

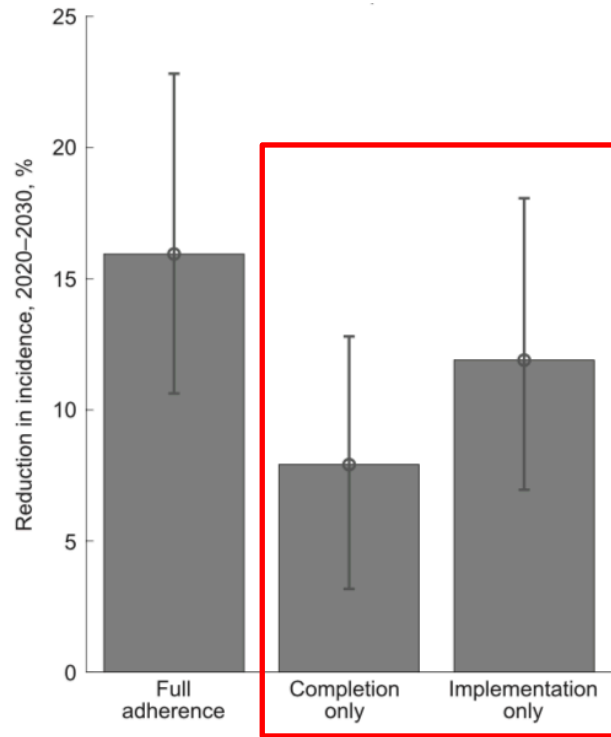
Quality of dosing implementation	Unfavorable treatment outcomes N (%)	Total N
100% of doses	85 (9%)	913
90%—99% of doses	37 (16%)	230
<90% of doses	16 (37%)	43

Imperial et al. Nat Med 2018;24(11):1708-1715.
Vernon et al. PLOS Med 2019;16(12):e1002884.

Meta-analysis of the control arms (standard RIPE regimen) in the OFLOTUB, REMox, and Rifaquin treatment shortening trials showed:

- Increasing risk of poor treatment outcomes and post-treatment disease recurrence with increasing non-adherence
- In multivariate analysis, patients with <90% adherence had 5.6 times increased adjusted hazard ratio for poor outcomes
- Similar association between non-adherence and post-treatment disease relapse seen in India's national TB program (Thomas A, et al. Int J TB Lung Dis 2005; 9(5): 556-561)

Potential epidemiological benefits of closing the adherence gap



Arinaminpathy et al. Int J TB Lung Dis 2020; 24(5): 526-533.

Mathematical modeling study of transmission dynamics in India found:

- Eliminating TB medication non-adherence in India's public and private sectors could reduce TB incidence in 2030 by ~12%
- By comparison, increasing treatment completion would reduce incidence by ~8%
- Reducing missed doses may be as important as improving treatment completion
- Study assumes that DATs may be able to close this adherence gap; however, evidence base is still in progress on this question
- Multiple interventions likely needed to close the adherence gap

The Context: Rethinking Directly Observed Therapy (DOT)

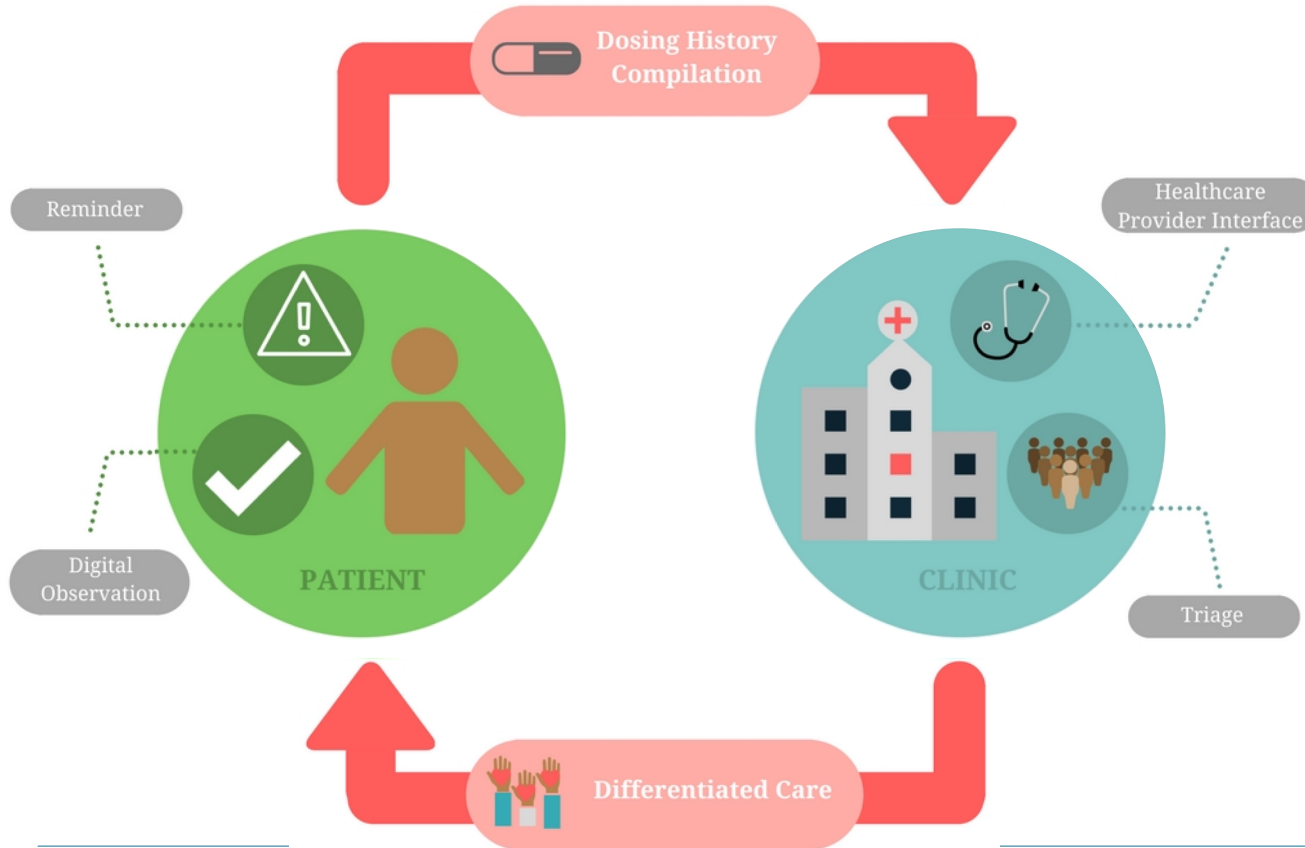


Source: Wikimedia commons, CC BY-SA 3.0 license

- DOT emerged from the ashes of the post-sanatorium era as the central approach for supporting adherence to TB medications
- Marked a unique obsession with “observation” as part of TB care
- However, recent studies highlight challenges to the DOT model:
 - Systematic reviews show no or variable advantage of DOT over self-administered therapy for improving treatment outcomes
 - DOT—particularly facility-based models—may result in loss of patient time, money, employment, autonomy, and privacy
 - Studies from China, Uganda, and India suggest a large proportion of patients on “DOT” are not actually being observed by healthcare workers

2. FUNCTIONS AND LANDSCAPE OF DATs

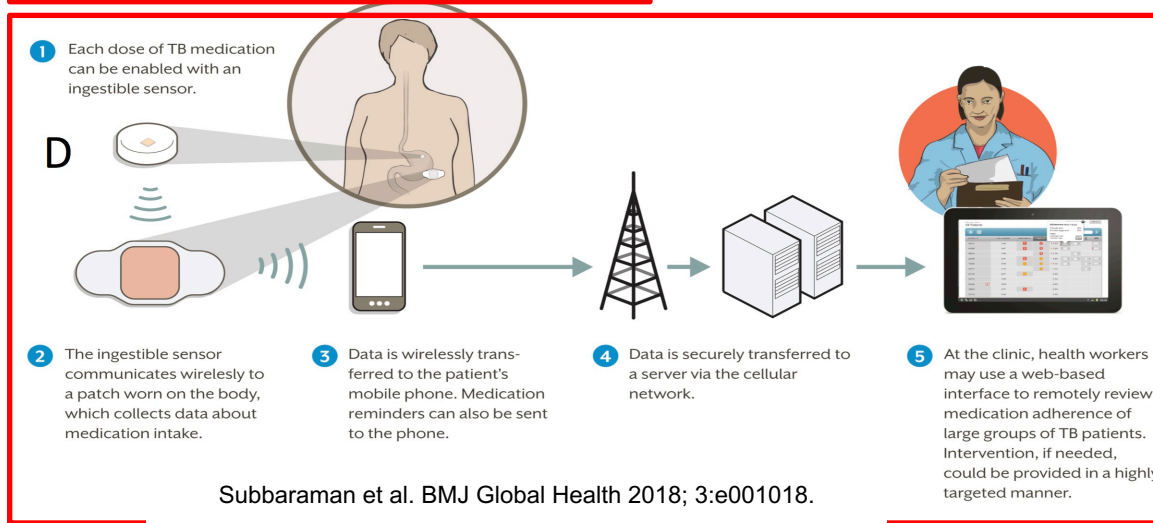
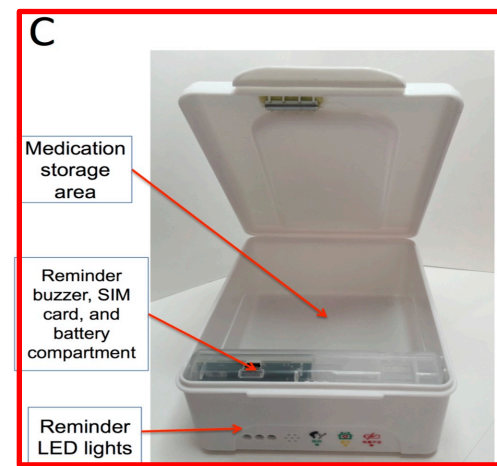
The Functions of Digital Adherence Technologies (DATs)¹



- **Graphical cues to help with dosing confusion**
- **Reminders**
- **Digital “observation”**
- **Dosing history compilation**
- **Healthcare provider interface**
- **Triage**
- **Differentiated care**

Landscape of DATs for TB

- A. Feature (non-smart) phone-based technologies – two-way SMS, 99DOTS
- B. Video DOT
- C. Digital pillboxes
- D. Ingestion sensors



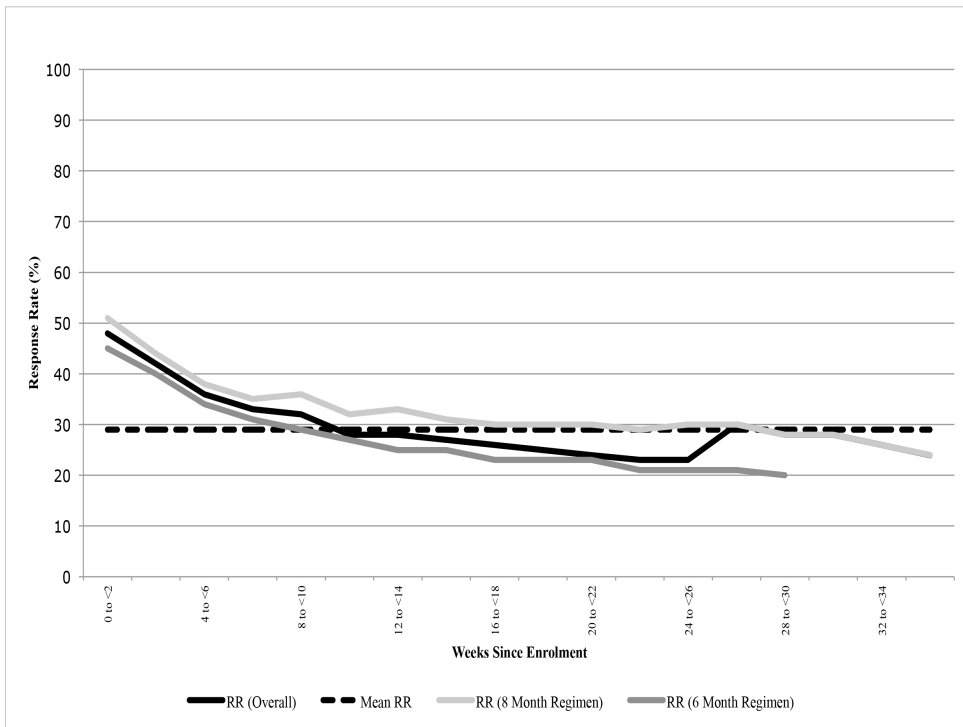
3. EVIDENCE AND FUTURE DIRECTIONS

Selected research dimensions I will touch upon

Research dimension	Description
Acceptability and feasibility	<ul style="list-style-type: none">• Is a technology ethically, culturally, and practically acceptable to patients and healthcare providers? (e.g., privacy concerns with VDOT, surveillance concerns, duration of engagement with technologies)• Can a technology function in a given health system or setting? (e.g., network coverage, feature / smartphone availability, device failure, supply chain capacity)
Accuracy	<ul style="list-style-type: none">• How well do signals in the dosing history correlate with actual medication ingestion? (e.g., specificity, sensitivity, PPV, and NPV of dosing record for measuring true adherence)
Effectiveness / Clinical Outcomes	<ul style="list-style-type: none">• How does use of the adherence technology impact clinical outcomes?<ul style="list-style-type: none">➢ Medication adherence (i.e., dosing implementation) or treatment interruptions➢ Treatment success, treatment failure, or death➢ Post-treatment TB recurrence-free survival at 12 months
Cost Effectiveness	<ul style="list-style-type: none">• How much does it cost to implement a technology, and is it cost-effective?• (e.g., material costs, communication costs, personnel costs for current and prior care models)
Reach, or uptake, in real world implementation	<ul style="list-style-type: none">• What proportion of patients in actually use these technologies in real world implementation?

ACCEPTABILITY

Discordance between high “acceptability” in a qualitative study and low actual patient use with a two-way SMS strategy in Pakistan



Mohammed S, et al. J Telemed Telecare 2012;18:404-8.
Mohammed S, et al. PLoS One 2016;11(11):e0162944.

In the pilot qualitative study:

- Patients received up to 3 daily SMS reminders a day to take TB medications
- Patients sent SMS responses indicating doses taken
- Qualitative interviews with 24 patients found that patients found technology “helpful and encouraging”
- SMS response rate was 57% in the first month in the pilot study
- Two-way SMS was “acceptable” and “appreciated”

In the randomized trial:

- SMS response rate dropped from 48% to 20% from the start to end of therapy
- No difference between two-way SMS and control groups for the outcomes of self-reported adherence or treatment success

Acceptability may vary by study approach or country context: Medication Event Reminder Monitor (MERM) in China and Vietnam



Study in China:

- Interviews and focus group discussions with 10 providers and 30 TB patients after 3 weeks of using the MERM
- Likert scale scores averaged >4 for MERM features
- Study found “high degree of user performance, acceptability, satisfaction”

Liu X, et al. *Int J of Env Res Public Health* 2017;14:1115.

Study in Vietnam:

- Interviews with 20 patients using the MERM in a RCT
- Half of patients did not use the device as intended
- Challenges with MERM use: separation of time of ingestion from time of box opening, device not portable, reminder not received when patients at work
- MERM data did not reflect actual medication ingestion patterns

Drabarek D, et al. 2019;14(7):e0219891.

Getting more out of acceptability studies

- Limitations of acceptability studies:
 - Pilot studies often miss patients with challenges engaging with technology
 - High social desirability bias
 - Few studies look at DAT acceptability later in therapy, when technology fatigue sets in
 - Perceptions of acceptability influenced by the alternative model of care (usually in-person DOT)
 - Few studies compared DATs to self-administered therapy with other forms of support

- Studies should focus on who uses (or doesn't use) the DAT and why—rather than whether the technology is “acceptable” or not:
 - How does stigma within the family or community shape acceptability – and who is excluded?
 - How does shared cellphone use within a family impact cellphone-based adherence monitoring strategies?
 - How does patient travel impact DAT engagement and the accuracy of adherence data?
 - Use of technology acceptance frameworks to understand reasons for low and high use (Thomas BE, et al. *JMIR mHealth uHealth* 2020;8(7):e16634.)
 - Use of qualitative data to iteratively improve technologies (Patel R, et al. *JMIR Formative Research* 2020;4(12):e19270.)

ACCURACY

Does the digital adherence record represent true ingestion?

Urine isoniazid testing can facilitate rigorous evaluation

		True adherence per urine isoniazid test	
		Positive INH (true adherence)	Negative INH (not adherent)
99DOTS reported adherence	Adherent per 99DOTS	True positive	False positive (calling but not taking pills)
	Non-adherent per 99DOTS	False negative (taking pills but not calling)	True negative

- 99DOTS has been rolled out to >300,000 TB patients in India
- Researchers conducted unannounced home visits for 597 TB patients in Mumbai, Chennai, and Vellore
- Urine sample collected at home visit and tested for isoniazid content
- Comparison of the 99DOTS record to the urine isoniazid test result allowed estimation of 99DOTS' accuracy for measuring adherence:
 - Sensitivity
 - Specificity
 - Positive predictive value
 - Negative predictive value

99DOTS accuracy study findings

N=597
patients

		True adherence per urine isoniazid test	
		Positive INH (true adherence)	Negative INH (not adherent)
99DOTS reported adherence	Adherent per 99DOTS	367	28
	Non-adherent per 99DOTS	159	43

- True adherence (positive urine test) = 88%
- 99DOTS engagement (any call in last 3 days) = 66%

- Accuracy (proportion correctly classified) = 69%
- Sensitivity = 70%
- Specificity = 61%
- Positive predictive value (PPV) = 93%
- Negative predictive value (NPV) = 21%

What does this mean?

- NPV: For every 10 patients reported as not taking their medications by 99DOTS, 8 were actually taking their TB medications → increases inefficiency for health providers
- Specificity: 99DOTS “missed” detecting 4 out of every 10 TB patients who were not taking their medications → patient were calling 99DOTS but not ingesting doses
- ***If the goal of 99DOT is to efficiently detect non-adherent TB patients, this strategy has significant limitations***
- *Cautionary note for other DATs: we must be careful not to assume that digital signals indicate true adherence*

EFFECTIVENESS / CLINICAL OUTCOMES

Medication Event Reminder Monitor (MERM): Cluster Randomized Trial in China

Study arm	Proportion of patient months with >20% of doses missed	Adjusted mean ratio	Total N
Control	30%	Ref	1,104
SMS text only	27%	0.95	1,008
MERM only	17%	0.58	997
MERM + SMS texts	14%	0.42	1,064

- Cluster randomized trial of drug-susceptible TB patients in 36 districts/counties in China
- 4 arms: (1) SMS reminders, (2) MERM, (3) Both, or (4) no intervention (standard of care)
- Outcome: proportion of patient-months with >20% of doses missed
- MERM improved adherence, while SMS texts alone did not
- SMS texts alone reduce patient loss to follow-up, while MERM did not (study not powered for this outcome)
- Limitation: adherence measured by “silent” versus “active” MERM – patients may have been more likely to open active MERMs due to the alarm, even if dose wasn’t taken

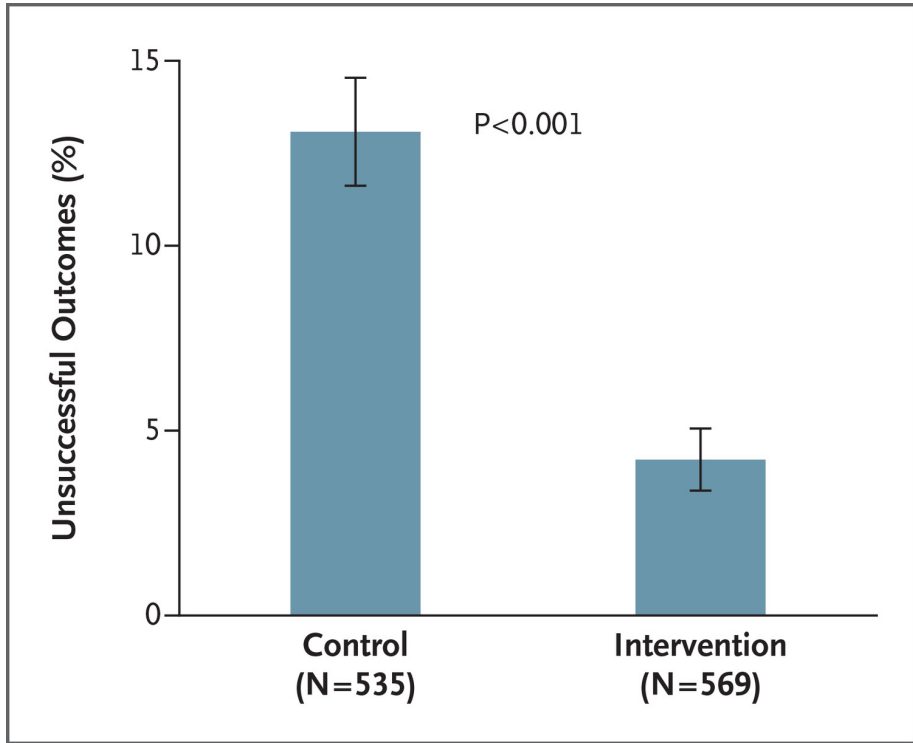
Video DOT: Randomized trial in England

Study arm	Proportion of patients completing $\geq 80\%$ of scheduled treatment observations	Adjusted odds ratio	Costs per patient (British pounds)
In-person DOT	31%	Ref	5700 per patient
Video DOT	70%	5.48	1645 per patient

Story A, et al. *Lancet* 2019;393:1216-24.

- Randomized, analyst-blind trial of TB patients (non-MDR) recruited at 22 clinics
- 58% of patients had history of homelessness, imprisonment, drug or alcohol use, or mental health problems
- 2 arms: (1) asynchronous video DOT; or (2) in-person DOT (standard of care)
- Smartphones and data given free of charge
- Primary outcome: proportion of scheduled treatment observations completed in 2 months
- Higher proportion of doses observed, lower time spent, and lower costs with video DOT
- No differences in sputum culture conversion or treatment outcomes (70—80% success)
- Similar findings in other randomized trials of video DOT in Moldova (Ravenscroft L, et al., *Eur Res J* 2020) and ingestion sensors in the U.S. (Browne S, et al. *PLOS Med* 2019;16(10):e1002891.) as compared to different DOT approaches

Randomized trial of a two-way SMS-based intervention in Kenya



Yoeli E, et al. NEJM 2019;381:986-987.

- Individual level randomized trial at 17 clinics in Nairobi
- Two-way SMS intervention included:
 - Up to 3 SMS reminders per day to take medications
 - Outreach by within <24-48 hours from TB survivors if no SMS response sent from patient
 - “Adherence contest” – comparison with other patients
- 2 arms: (1) two-way SMS texts; or (2) self-administered therapy with weekly / biweekly refills (standard of care)
- Outcome: unsuccessful treatment outcomes
- Results: significantly lower unsuccessful outcomes in two-way SMS arm (4.2%) vs. standard of care (13.1%)
- Similar to other non-smartphone-based interventions (two-way SMS, 99DOTS), SMS response rates from patients dropped off over time
- Highlights benefits of focusing on patient support and motivational aspects, rather than “observation”

COSTS AND COST-EFFECTIVENESS

Potential cost savings from DATs (compared to DOT)

Digital support strategy	Cost per person (US \$) <small>(Patient costs + health system costs)</small>	Incremental savings versus DOT (US \$)
DOT	1249	Comparator
VOT	718	531
Wisepill (electronic pillbox)	574	675
99DOTS	545	704

Nsengiyumva et al. Eur Resp J 2018; 52: 1801363.

Decision analysis models estimated the potential cost savings from using DATs for monitoring treatment adherence (versus DOT):

- All interventions led to health system cost savings ranging from 39% to 58% for patients with drug-susceptible TB
- Combining patient and health system costs for treatment of drug-susceptible TB resulted in cost savings ranging from 43% to 56%
- These analyses had two assumptions: (a) in-person DOT is the comparison (not self-administered therapy); and (b) equivalent treatment success rates with DOT and DATs
- Self-administered therapy (SAT) could have greater cost-savings--question remaining is whether DATs achieve better outcomes than SAT

REACH, OR UPTAKE, IN REAL WORLD IMPLEMENTATION

Reach of an electronic pillbox in large-scale implementation in China

Subgroups	Total N
Notified TB patients	2,294 (100%)
Eligible for device	1,810 (79%)
Started on device during treatment	1,314 (57%)
Continued use of device without shift back to DOT	1,180 (51%)
Sustained use of device through the end of treatment	897 (39%)

Wang N, et al. PLOS One 2020;15(4):e0232337.

- Study of implementation of an electronic pillbox in 30 counties in China
- Cascade of decline in use of device from:
 - Non-eligibility
 - Not being given device
 - Shift of patients back to DOT
 - Patients stopping use for other reasons
- Among those using the device, 25% of patient-months had missing electronic adherence data
- Reason for missing data was unclear
- Prior study similarly showed 49% uptake in a single province in China
- Similar decline in engagement seen with 99DOTS rollout to >20,000 TB patients in Mumbai, India (Cross A, et al. ICTD '19; Ahmedabad, India)

4. FINAL THOUGHTS

Monitoring alone does not address most causes of non-adherence: Two examples

Alcohol use disorder in Chennai, India²⁹

- 31% of TB patients had alcohol use disorder based on the AUDIT screening tool
- Strong desire for alcohol interventions voiced by TB patients and families in qualitative studies
- In a quasi-experimental trial of a 4-session alcohol use intervention:

	Control arm	Alcohol treatment arm
Treatment success	62%	87%
Treatment default	35%	6%
“Regular” adherence	18%	39%

Depression in Ethiopia³⁰

- In a cohort study of 648 TB patients:
- 54% had probable depression at baseline
- Outcomes for TB patients with baseline depression were considerably worse than for patients without depression:

Outcomes for depressed TB patients	Adjusted risk ratio (aRR)
Treatment default	9.1 times increased risk
Death	3.0 times increased risk
Disability at end of treatment	Linear increase in disability with higher depression scores

What levels of adherence are possible without DATs or DOT?

Country	% of patients on ART with viral suppression
Zimbabwe	87%
Zambia	89%
Uganda	84%
Tanzania	88%
Namibia	91%
Malawi	91%

- Columbia University's PHIA initiative conducts population-based surveys of HIV treatment in 14 high-burden countries
- PHIA shows that a high % of patients on HIV treatment are virally suppressed in many countries
- This is despite the fact that:
 - HIV treatment is life-long
 - Resistance develops quickly to efavirenz-based regimens with missed doses
 - Efavirenz-based regimens associated with some early neuropsychiatric adverse affects

Take Home Messages

1. *Medication adherence is a central challenge* for ensuring optimal treatment and post-treatment outcomes for TB patients
2. *Patients prefer DATs over DOT* in acceptability studies and randomized trials – but few comparisons to self-administered therapy with patient support
3. *Accuracy of digital data for measuring adherence may be limited* with some DATs – caution when using as a proxy for true adherence
4. *Randomized trials highlight possible benefits of DATs* for improving “observed” adherence – but few studies on treatment outcomes
5. *Implementation gap*: DATs may have lower uptake in clinical implementation than in trial conditions – major barrier in low-income countries
6. **Technology ≠ Care**. Future work should ideally focus on address causes of non-adherence and supporting patients—rather than just “observing” them.
7. *DATs may not achieve their promise* if they simply extend the TB community’s obsession with observation into the digital era.

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