Digital Technology for Tuberculosis Medication Adherence: Promise and Peril

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In this issue of *AnnalsATS*, Stagg and colleagues (pp. 438–449) present an analysis of digital adherence data from 1,104 participants in the control arm of a pragmatic cluster randomized trial of electronic reminders to improve treatment adherence among patients with pulmonary tuberculosis (TB) in China (1). These data reflect date-and-time stamps of medication container openings as a proxy for pill ingestion. The authors used this highly granular monitoring approach to explore adherence patterns for nonfixed dose combination medications taken every other day for drug-susceptible TB over a 180-day treatment course. Treatment was self-administered or supervised by family members or healthcare workers, although documentation of support was not available. They found high levels of nonadherence, with nearly 25% of doses missed and 36% of participants discontinuing treatment early. We commend the authors on this informative analysis, which we believe raises three key points for further consideration: the future of adherence monitoring for TB, the advantages and disadvantages of digital monitoring, and the importance of including sociobehavioral science in the development and implementation of digital adherence technology.

Directly observed therapy (DOT) has long served as a central strategy for monitoring and supporting medication adherence in TB programs globally. The value of traditional, in-person DOT, however, has been questioned in recent years. Some patients report a significant financial burden, undesired low levels of autonomy, and stigma because of DOT (2). Moreover, many TB control programs do not implement DOT or do not implement it well (e.g., without adequate support systems and staffing oversight) (3), and observation is often limited to routine work days. A recent systematic review suggests that outcomes are often no better with DOT than with self-administered therapy (4). In response, several digital tools have arisen as alternatives to in-person DOT, including "smart" packaging (as was used by Stagg and colleagues), cell phone–based call-in and text messaging platforms, video DOT, and ingestion sensors (5). These technologies can potentially result in economies of scale, as a small number of healthcare workers can remotely monitor a large number of patients with objective indications of adherence. They can then triage resources to those who need them most precisely when they are needed. Pilot studies have suggested the feasibility and acceptability of some of these technologies in a research context (5), and larger studies in high-income, low–TB-burden countries have demonstrated that video DOT and ingestion sensors facilitate greater observation of doses compared with in-person DOT (6, 7).

From a research perspective, these technologies create exciting opportunities to understand TB medication adherence and develop evidence-based interventions. For example, Stagg and colleagues show that missed doses early in treatment are predictive of later treatment discontinuation, arguing for the importance of early intervention. The authors cite prior studies showing associations between nonadherence and unfavorable outcomes, which were based on in-person DOT; however, their analysis demonstrates that such data could be obtained electronically, with the above-noted potential advantages. That said, support from family members or healthcare workers may have impacted monitor use and/or adherence, the extent of which should be tracked in future studies. In addition, clinical outcomes (e.g., disease-free survival and/or development of drug resistance) were not available and would have strengthened the value of their analysis. Associations of various adherence patterns (e.g., sporadically missed doses vs. sustained gaps) with poor clinical outcomes have been well-defined for human immunodeficiency virus (HIV) antiretroviral therapy (8) and should be explored further for TB. For example, our understanding of the extent to which TB regimens "forgive" nonadherence is limited (9), and it is unclear how well the World Health Organization (WHO)-recommended practice of treatment extension addresses incomplete adherence (10).

Despite this promise, digital adherence tools are potentially limited by several factors, including technical challenges and device nonuse, with resulting inaccuracy, as well as cost and health system burdens. These issues are especially relevant in low-income settings, which account for the vast majority of the global TB burden. Although cellular infrastructure and mobile phone ownership are advancing globally, poor network coverage, low-quality phones, and shared phone usage remain as limitations. Importantly, a study in Peru showed that mobile phone access is lowest among the poorest patients with

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TB, who have the worst clinical outcomes (11). In Stagg and colleagues' analysis, nearly 20% of participants had "technical issues" and another 10% were excluded because they could not be monitored for the entire treatment period. In another recent study in China, patients with TB were offered the choice of electronic medication monitoring versus in-person DOT (12); over 25% declined to use the electronic monitor. Moreover, most healthcare workers in that study believed that the device moderately increased their workload.

The extent of these challenges within a research context raises concerns about their use in routine clinical practice. Early findings from implementation of 99DOTS, a cell phone–based TB adherence monitoring system, in India have revealed important challenges. A comparison of 99DOTS data with unannounced urine isoniazid testing showed that 99DOTS had an accuracy of 69%, specificity of 61% (owing to patients reporting doses that were actually not taken), and a negative predictive value of 21% (because of poor engagement with the technology) (13). Engagement with 99DOTS was lower in the continuation phase than in the intensive phase, even though adherence measured by urine isoniazid testing was similar in both treatment phases. Although Stagg and colleagues cite prior validation of electronic monitoring with urine rifampicin levels, the pharmacokinetics of that drug limit interpretability. Poor monitor engagement could explain some of the recorded nonadherence in their analysis, thus reducing the strength of their conclusions. Additional validation studies and attention to device use will be important for future studies involving this monitoring approach.

Despite these limitations, digital technologies have great potential to inform adherence interventions when combined well with sociobehavioral science. Stagg and colleagues identified temporal associations with nonadherence, yet they were only able to comment on a few factors (i.e., age, sex, and location) that could inform intervention development. TB is a social disease, largely afflicting poor and marginalized populations. Evidence from various contexts shows strong associations between sociobehavioral risk factors—including depression and alcohol use disorder—and unfavorable treatment outcomes (14, 15). These associations may be mediated by poor adherence and should be considered for development of the targeted adherence interventions Stagg and colleagues call for. The HIV field has used digital monitoring for many years to explore individual, health system, and structural barriers associated with incomplete adherence (16) and can serve as a model for future TB research.

In sum, Stagg and colleagues' analysis highlights the importance of paying careful attention to adherence for successful TB treatment. The WHO has recommended the inclusion of digital medication monitors for adherence intervention, although with "very low certainty in the evidence base" (10). Various countries, including China, India, Tanzania, Uganda, and Ukraine, are starting to pursue these tools in their TB programs (17). Additional data on measurement accuracy and device implementation will be critical to ensure that these approaches are at least as good as (and ideally better than) the current standard of care. Given the variability in resources and preferences, options for digital and nondigital monitoring will be important for optimized clinical outcomes. Perhaps most importantly, these technologies risk failure to fulfill their promise without an adequate investment in developing sociobehavioral and structural interventions that can leverage the adherence data they generate. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Moving the Bar on Chronic Obstructive Pulmonary Disease Readmissions before and after the Hospital Readmission Reduction Program: Myth or Reality?

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More than 5 years after the Centers for Medicare and Medicaid Services (CMS) integrated chronic obstructive pulmonary disease (COPD) into the list of conditions affected by the Hospital Readmission Reduction Program (HRRP), ongoing debate continues about the appropriateness of a policy that penalizes hospitals for their COPD readmission rates. At the center of this debate is the question of whether COPD readmissions are preventable. Before the policy took effect, there were little to no data on interventions to reduce COPD readmissions, indicating that the policy was not evidenced based. Currently, the evidence is not much stronger, with most trials focusing on single-site interventions that frequently fail to demonstrate effectiveness, and some showing increased risk of harm (1–3). In 2016, the American Thoracic Society convened a workshop to evaluate the evidence regarding potential solutions to reduce COPD readmissions, which largely found that significant additional data are needed (4).

In this issue of *AnnalsATS*, Myers and colleagues (pp. 450–456) provide important data on the impact of the initial HRRP roll-out on COPD readmission rates (5). Initial HRRP penalties focused on three non-COPD conditions (heart failure, myocardial infarction, and pneumonia), and there was a 2-year delay before COPD was incorporated as a condition impacted by HRRP. The study used longitudinal data from seven State Inpatient Databases to examine trends in COPD readmissions during the period preceding HRRP penalties for COPD. Remarkably, the authors found that COPD readmissions declined after initial HRRP penalties for non-COPD conditions took effect.

There are several possible reasons why readmissions after COPD hospitalizations changed in response to the initial HRRP penalties. First, organizational changes to avoid HRRP penalties may have had systemic effects that improved multiple disease outcomes, including for COPD. Second, hospitals could have made changes in COPD care in anticipation of upcoming financial penalties for COPD readmissions. Third, improving treatment for heart failure, myocardial infarction, and pneumonia could have improved care for patients with COPD, who have frequent comorbidity with these other conditions. Fourth, practices to avoid HRRP penalties by "gaming the system" could have impacted patients who present with diverse conditions, including patients with COPD. Finally, overall readmission rates had been falling nationally even before the HRRP went into effect in 2012. It is not possible to know which of these effects was most impactful in reducing COPD readmissions, although this study provides important data that warrants further examination.

Organizational change is notoriously difficult. In one of the most widely cited management books, "Organizational Culture and Leadership," Edgar Schein contends that organizational culture only changes when there is a collective sense of "survival anxiety" (6). The study by Meyers and colleagues suggests that HRRP penalties may have been severe enough to induce extensive organizational changes that broadly affected the culture of acute care. Meyers and colleagues describe in detail the behavioral economics of loss aversion, which could have improved quality by indiscriminately reinforcing structures and processes of care, such as improving discharge planning and ensuring

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