An Inca trail to the Holy Grail

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Published in:
International Journal of Tuberculosis and Lung Disease

DOI:
10.5588/ijtld.21.0613

INT J TUBERC LUNG DIS 26(1):1–3

http://dx.doi.org/10.5588/ijtld.21.0613

EDITORIAL

An Inca trail to the Holy Grail: digital medication adherence support for TB care

In 2007, the ancient Inca city Machu Picchu in Peru was voted one of the new seven wonders of the modern world.[1] The path that leads to this mysterious city, known as the Inca Trail, is arguably as famous as the wonder itself. It is a winding trek with stunning high passes, but also cloudy valleys and dark tunnels with the potential for altitude sickness. But when a visitor finally passes the Sun Gate at the end of the Trail, they are rewarded with magnificent views and the entrance to Machu Picchu. It is on such a winding road that we currently find ourselves in our quest for the Holy Grail of TB medication adherence management (Figure). We live in an era of effective drugs to treat TB, but these only work if taken consistently. The failure to take medication as prescribed, also referred to as "treatment non-adherence", is associated with significantly increased treatment failure, development of multidrug-resistant TB (MDR-TB), increased mortality and greater economic burden for TB patients and society.[2,3] Fortunately, in this issue of the Journal, a research group from Peru has helped to guide our way forwards with publication of a TB adherence intervention study in Latin America.[4] We will come to this study shortly, but first some background information to better understand the field.

To ensure proper adherence, the WHO has traditionally promoted the use of directly observed treatment (DOT).[5] During DOT, a healthcare professional or family member of a person with TB observes and confirms intake of TB medication. However, while considered theoretically effective, systematic reviews indicate that DOT has not been shown to be universally effective, partly because of variations in implementation models, but also because of the high cost and burden on patients and healthcare professionals.[6–8] In addition, given the increasing emphasis on patient empowerment and self-management, this strategy is viewed by many as paternalistic and outdated. Fortunately, we live in a digital age and digital technologies offer potential alternatives to the DOT strategy. Modelling studies and economic projections estimate that digital strategies (such as video-observed therapy [VOT], medication monitors and SMS reminders) could decrease TB incidence by reducing the number of missed doses and treatment default,[9] and provide cost savings of up to 58%.[10] However, as noted by the authors of these projections, proper evaluation of their models requires high-quality clinical evidence on the effectiveness of these digital interventions, and that is still relatively scarce. In fact, until 2019, there was only one large high-quality randomised controlled trial (RCT) that had formally assessed digital health technologies used for TB medication adherence.[11] Conducted in over 4,000 TB patients in China, this cluster RCT was the first to highlight the effectiveness of electronic medication monitors and reminders, fuelling our growing expectations of digital solutions. However, it took another 4 years for the next RCTs in support of digital TB adherence to be published. Two of these were small to medium-sized ($n = 61$ and 226 participants), carried out in high-income countries, and focused on smartphone-based VOT in the United Kingdom,[12] or wireless observed therapy (using an ingestible sensor and patch) in the United States,[13] respectively. These studies concluded that digital interventions were more effective, more acceptable and cheaper than DOT. However, these studies required owning a smartphone as an inclusion criterion or using a mobile device, which may not be affordable or available in many low-resource, high-burden TB settings. But that same year, the first large ($n = 1{,}104$) RCT in Africa reported on an SMS health service that was compatible with affordable "feature" phones.[13] It included reminders, motivational messages and a competitive element, and met its primary outcome, reduced treatment failure (intervention group: 4.2%; control group: 13.1%, $P < 0.001$). Unfortunately, shortly after these positive studies, the global COVID-19 pandemic began, dampening our expectations and threatening TB adherence management.[15] Around the same time, the second RCT in Africa (conducted in Uganda) to assess the 99DOTS approach yielded a somewhat disappointing result, indicating the same effectiveness for 99DOTS versus standard care.[16] In short, 99DOTS is a low-cost technology that requires TB patients to call toll-free numbers that are provided with no predictable pattern on opening a pill blister pack. However, it should be noted that the 99DOTS strategy has been criticised as being unreliable, because it relies on additional patient actions beyond their normal pill-taking behaviour.[17]

Given the mixed results from previous studies, we

Article submitted 7 October 2021. Final version accepted 8 October 2021.

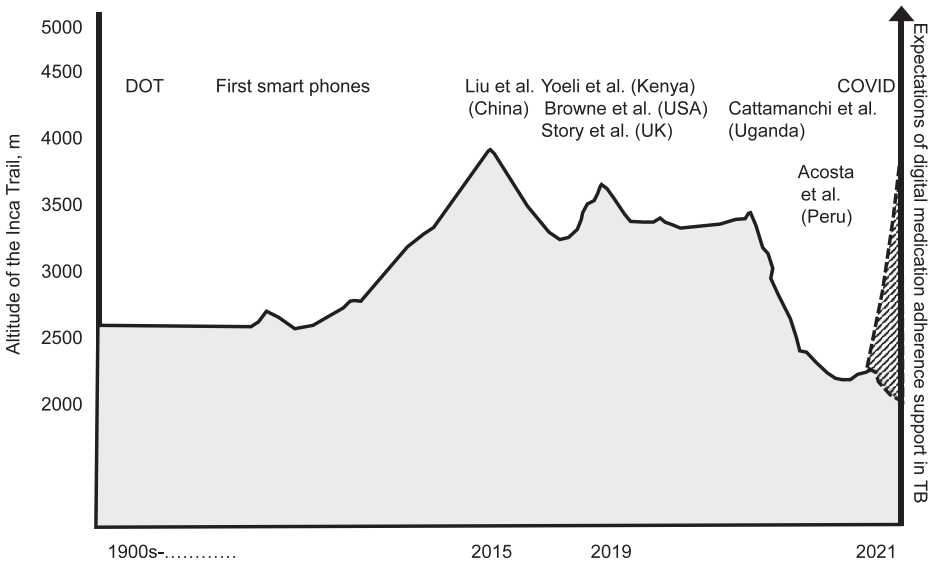

Figure The Inca Trail towards the Holy Grail in digital medication adherence support of people with TB.

were eagerly awaiting more evidence on digital strategies for managing TB adherence. Who better to continue our journey towards this Holy Grail than a research group from Peru. In this issue, Acosta et al. report the first RCT in Latin America to use a digital TB adherence intervention.[4] This RCT included 102 patients with drug-susceptible TB who had completed the first phase of treatment (daily isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months) using the DOT strategy across 19 primary health care centres in Peru. After Phase 1, patients were randomised to either continue DOT (control group) or to have DOT replaced with a Medication Event Reminder Monitoring (MERM) system, consisting of an electronic dispenser pill box, a web server and SMS health service. Patients were followed up for the next 54 doses and the primary outcome was treatment success, defined as no additional treatment required after Phase 2. The study met this endpoint with a success rate of 98% in the intervention group vs. 85% in the control group (Relative risk 1.15; $P = 0.03$). Also, the proportion of patients who missed at least one dose and those who missed more than 10% of the total doses were higher in the control group. To note, an earlier evaluation of MERM in a government programme for people with MDR-TB in India showed a generally high level of acceptance, but indicated that efficacy studies were required, further underscoring the relevance and timing of this study.[18] Although the authors are to be commended for delivering this important study, there is still room for improvement. Compared to most previous RCTs assessing digital interventions,[11,14,16] this study has a relatively small sample size resulting in low power for sub-group analyses. Indeed, the primary outcome lost significance when four patients who withdrew from the intervention were counted as treatment failures. In terms of adherence outcomes, these were slightly disappointing compared to previous applications of MERM.[11] The authors relate this to the selection criteria for this study, which focused on patients with a low probability of non-adherence, and therefore less room for improvement. Also, many technical issues arose (e.g., around three quarters received SMS reminders when the bottle had already been opened), which prevented proper implementation of the devices. Another obvious limitation is that opening a pill bottle is not a guarantee of medication intake. Here, additional monitoring tools (such as hair analysis) can provide supporting evidence for actual intake and drug exposure.[19] As such, this study provides us with another piece of the jigsaw, but the puzzle is far from complete and larger studies, preferably across different global settings are necessary before large-scale implementation can be considered.

Looking forward, there are still challenges to be mastered, including device design, technological compatibility and usability, as well as optimal and cost-effective implementation of digital TB adherence technologies in daily care.[11,18] In many low-resource countries, this includes requirements such as higher mobile phone ownership and appropriate networks. Also, the adherence data generated by digital monitoring require correct interpretation and the provision of tailored interventions to address local issues of patient non-adherence. These issues can include unintentional forms of non-adherence such as forgetfulness, but also deliberate non-adherence (e.g., due to stigma, side effects or financial reasons). Different reasons for non-adherence require different interventions, and current one-size-fits-all approach-

es may need further refinement. As an example, sending reminders does not solve the problem for patients who are experiencing side effects. While these challenges remain, the current global pandemic may also present opportunities. Although COVID-19 initially slowed our research progress, it could now offer opportunities to accelerate the uptake of digital health through a sharp increase in the use of telemedicine, as reported in a recent multi-country survey.[20] The Inca trail has many ups and downs, but it seems we are getting closer to the Sun Gate!

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