



## Early View

Research letter

### **Combining digital adherence technology and therapeutic drug monitoring for personalised TB care**

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# Combining digital adherence technology and therapeutic drug monitoring for personalized TB care

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***To the editor:***

Tuberculosis (TB) is the world-leading cause of infectious disease related mortality, apart from COVID-19 presently (1). Standard TB treatment for drug-susceptible (DS) TB takes 6-9 months and requires daily intake of multiple medications (1). Notably, proper treatment adherence is essential for successful treatment outcome (1,2). To improve adherence, counseling and education are important. For specific patient groups, such as those with drug-resistant TB, HIV co-infection and those on intermittent treatment regimens, the World Health Organization (WHO) advises to use the Directly Observed Treatment (DOT) strategy. However, even with DOT, treatment completion is still challenging and cure rates and outcomes remain suboptimal (3). Therefore, exploring novel options to monitor treatment adherence and optimize TB drug dosing are required (2,3). Digital adherence technology (DAT) and therapeutic drug monitoring (TDM) have been applied as stand-alone options (4–8), yet combining both could further personalize TB care while supporting patients self-management and autonomy and improve outcomes (2,9). Therefore, this study aimed to investigate if DAT is feasible as a novel tool to monitor medication adherence and guide TDM in TB patients.

Adult patients with DS-TB admitted at the Tuberculosis Center Beatrixoord (Haren, part of the University Medical Center Groningen, the Netherlands) receiving rifampicin 600 mg/isoniazid 300 mg (RIFINAH) as a part of their treatment regimen were eligible for inclusion. Patients who signed informed consent forms also needed to own an Android or iPhone mobile phone with operating system versions Android  $\geq 6.0$  or IOS  $\geq 11.4$ . There were no exclusion criteria except when a patient informed that he/she could or would not participate. The study was exempted from the Medical Research Involving Human Subjects Act by the Medical Ethical Review Board of the University Medical Center Groningen (2020/483) and registered at the Netherlands Trial Registry (NL9006).

At visit 1, the day before the start of the study, participants received information on the trial and a training on how to use the DAT (Smart Pill Bottle, Elucid Pill Connect System, eLucid mHealth Ltd, Manchester, United Kingdom). Of note, the DAT provides patients with automated smart phone reminders based on Bluetooth in case doses were missed (Figure 1) and allows real-time clinician assessment of patient's dispensing. Subsequently, participants received the smart pill bottle containing 28 tablets of RIFINAH, to be taken from the next day until day 15. The technical specifications of the DAT are described in our earlier published study among healthy volunteers (10). At visit 2 (end of the second week), patients returned the bottles and completed validated questionnaires. The System Usability Scale (SUS) was used to evaluate patient acceptance of the new system whereas the Medication Adherence Report Scale (MARS) was used to capture patient's self-reported adherence (11,12). Finally, the Self-Efficacy for Appropriate Medication use Scale (SEAMS)

measured patients' self-confidence in carrying out the medication-related tasks (13). Other satisfaction questions specific to the DAT were self-designed. Furthermore, a saliva sample was collected from each patient by the healthcare personnel at a random day within 10-14 days of treatment, without patients being aware upfront of the exact day. Rifampicin levels were quantified by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the laboratory of Clinical Pharmacy and Pharmacology of University Medical Center Groningen (14). Of note, saliva has previously been shown as a feasible tool for saliva-based TDM of rifampicin (14).

The primary outcome was the percentage of tablets successfully taken according to the intended dosing schedule. To confirm actual intake, DAT data were validated with the saliva samples. Secondary outcomes were user acceptance (SUS), satisfaction, self-reported adherence (MARS) and self-efficacy (SEAMS) (11–13). Descriptive statistics were used where applicable to report the outcomes.

The study included ten hospitalized TB patients who used DAT to self-administer rifampin/isoniazid for 14 days of their TB treatment. Of ten patients, one withdrew from the study on day 5 of the treatment because the patient chose to be treated at the center near his residence area. Patients originated from different WHO regions (n=9), with five being from the European region. All patients completed Visit 1. All nine patients completed both study visits. The median age of included patients was 41 years (IQR: 24-44). Eight out of nine patients were male and had pulmonary TB. Only one patient had an extra-pulmonary TB; two had diabetes-mellitus and none of the included patients tested positive for HIV. During the study (October 2020 - April 2022), 252 RIFINAH tablets were pre-dispensed from the pharmacy and put inside the DAT for all nine patients. Of total 252 tablets, 250 were successfully taken by the patients, resulting in an overall dispense adherence of 99% to the intended dosing schedule (between 7:00 am - 6:00 pm every day). One patient missed a dose on day 8 of the treatment (two tablets) because of human error. Another patient received a double RIFINAH dose due to miscommunication. In the MARS questionnaire, seven participants had high self-reported adherence with only two patients reporting difficulty with adherence. Furthermore, on a 13-item self-efficacy scale (SEAMS), of nine, five patients reported high self-confidence in their ability to carry out medication related tasks while the rest scored lower. The majority of the patients evaluated the DAT usability as acceptable, with a mean SUS score of 75.6 (range: 57.5 to 97.5). However, on the technical front, six out of nine participants reported that they encountered difficulties during dispensing and had to try multiple times before successfully dispensing the medication. In one case, the tablets broke inside the bottles while shaking. Patients were still positive about the DAT with suggestions to improve on the technical front. Salivary rifampicin levels on day 14 are shown in Figure 1. For two patients, rifampicin salivary levels were below the lower limit of

quantification (LLOQ). Of note, DAT data confirmed that in these patients, RIFINAH was not taken in the hours before sampling, highlighting the value of DAT data for more tailored TDM and vice versa. On a side note, the recruitment took place in the middle of the COVID-19 pandemic which resulted in a very slow inclusion. Still, all patients who were screened and deemed eligible, participated in the study. We had only one case of screening failure and one patient who with-drew from the study on day five of the treatment.

This was a first clinical proof-of-concept study that evaluated the combined use of DAT and saliva sampling for TDM among TB patients in a hospital setting. Our study showed that TB patients can use DAT with acceptable reliability. Adding DAT data to TDM could help distinguishing low drug concentrations because of nonadherence from other reasons and guide targeted interventions. Acceptable scores on SEAMS and MARS highlight that patients are confident in their ability to self-manage their medications and ready to take this next step. This was also the first study that validated digital adherence data with rifampicin levels in saliva to confirm actual intake. For the two patients with undetectable rifampicin levels, it could be directly confirmed in the online database that indeed they had not taken their drugs at the time of sample collection. Therefore, DAT in combination with monitoring salivary drug levels could be truly game changing in supporting adherence and personalizing dosing while at the same time supporting patients to carry out medication related tasks independently. When priced reasonably, DAT could be an attractive alternative to DOT in TB treatment. Additionally, in the future, hair analysis could be an important addition to the current diagnostics for evaluating long-term drug exposure and adherence compared to a particular day with matrices like saliva, plasma and urine (15). Notably, telehealth options such as DAT are of particular value during global pandemics such as COVID-19 (16).

This study was limited by the small sample size, but the promising results might warrant future extensive studies, including follow-up in high-burden settings. The results must be interpreted with caution as they were achieved under hospitalized conditions and may differ for patients at home in real-life settings.

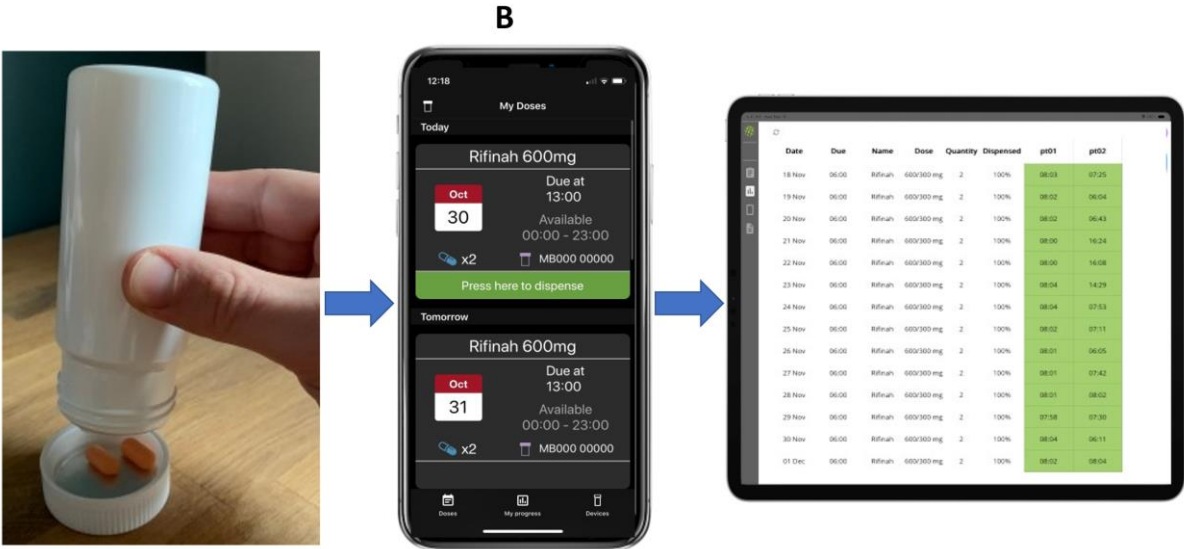
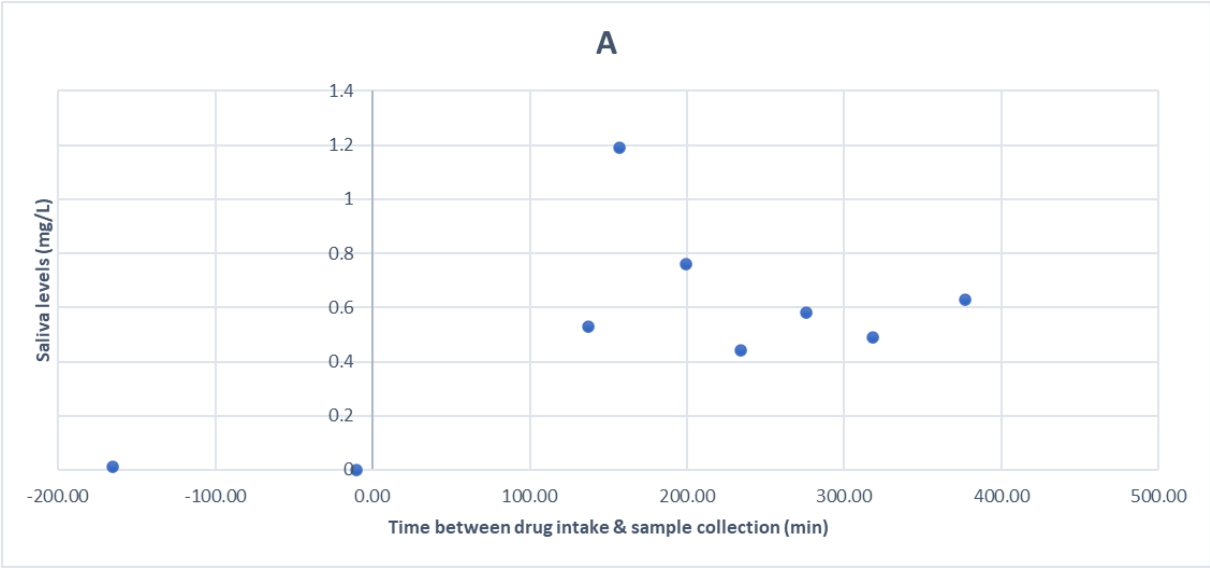
In conclusion, the use of DAT along with TDM to support patients self-management is feasible in clinical settings. The optimal application of DAT needs to be further assessed in larger studies in out-patient settings and the system needs technical improvements before a more large-scale roll out of its use.

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Figure 1



Caption : A: Rifampicin salivary levels (mg/L) measured in 10 patients on different moments in time before and after drug intake (min) B: Data flow of Digital adherence technology, showing the Smart Pill bottle, Smart Phone, and Digital Platform (left to right)