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

Ghimire, Samiksha; Iskandar, Deni; van der Borg-Boekhout, Roelina; Zenina, Marina; Bolhuis, Mathieu S; Kerstjens, Huib A M; van Rossum, Marieke; Touw, Daan J; Zijp, Tanja R; van Boven, Job F M

Published in:
European Respiratory Journal

DOI:
10.1183/13993003.01690-2022

Combining digital adherence technology and therapeutic drug monitoring for personalised tuberculosis care

Received: 29 Aug 2022
Accepted: 14 Oct 2022

To the Editor:

Tuberculosis (TB) is the world's 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, counselling 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 optimise 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 personalise 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 6.0 or later, or iOS 11.4 or later. 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, UK). 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-based TDM has previously been shown to be feasible for rifampicin [14].

Shareable abstract (@ERSpublications)
Digital adherence technology in combination with therapeutic drug monitoring could aid in supporting adherence and personalising dosing while at the same time supporting patients to carry out TB medication related tasks independently https://bit.ly/3gh1A1c

Cite this article as: Ghimire S, Iskandar D, van der Borg-Boekhout R, *et al*. Combining digital adherence technology and therapeutic drug monitoring for personalised tuberculosis care. *Eur Respir J* 2022; 60: 2201690 [DOI: 10.1183/13993003.01690-2022].

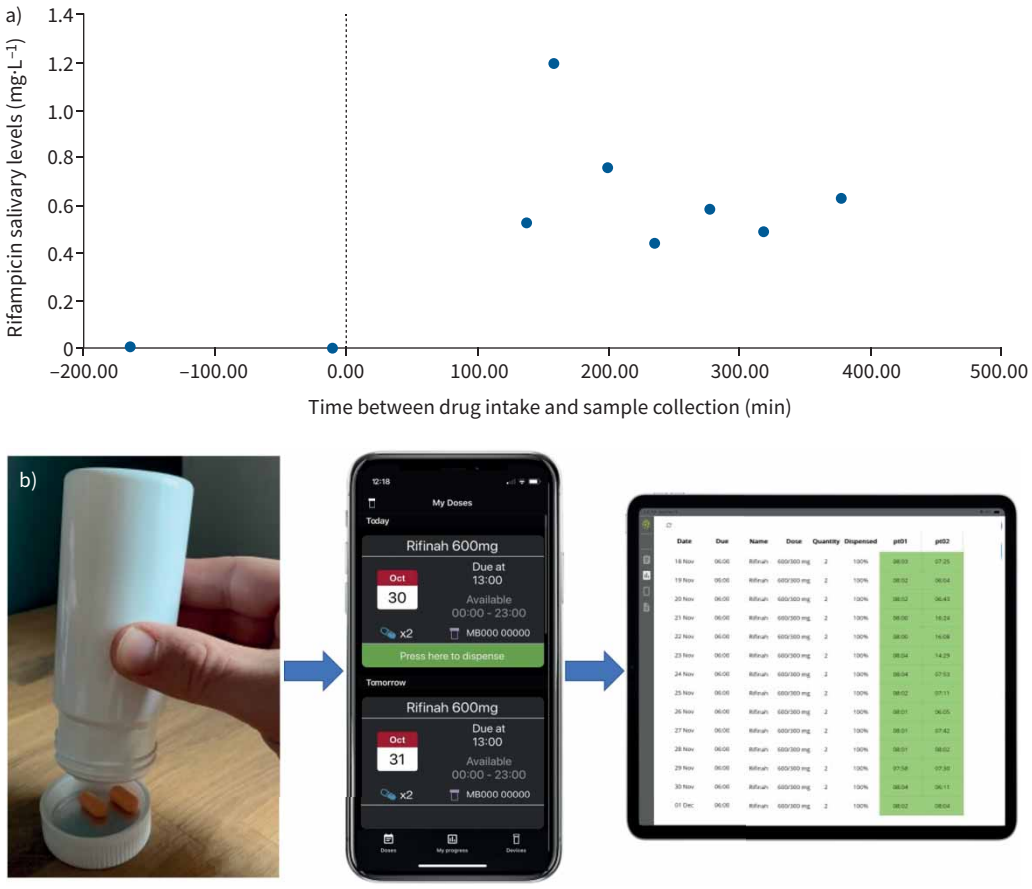

FIGURE 1 a) Rifampicin salivary levels measured in nine patients at different time-points before and after drug intake. b) Data flow of digital adherence technology, showing the smart pill bottle, smart phone and digital platform (left to right).

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 10 hospitalised TB patients who used DAT to self-administer rifampin/isoniazid for 14 days of their TB treatment. Of 10 patients, one withdrew from the study on day 5 of the treatment because the patient chose to be treated at the centre 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 (interquartile range 24–44 years). Eight out of nine patients were male and had pulmonary TB. Only one patient had extrapulmonary TB; two had diabetes mellitus and none of the included patients tested positive for HIV. During the study (October 2020 to 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 07:00 and 18:00 h 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 57.5–97.5). However, from a technical perspective, 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 tablet broke inside the bottles while shaking. Patients were still

positive about the DAT with suggestions to improve on the technical aspects. Salivary rifampicin levels on day 14 are shown in figure 1. For two patients, rifampicin salivary levels were below the lower limit of quantification. 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 withdrew 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 DAT data 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 personalising 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 hospitalised 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 rollout of its use.

Samiksha Ghimire[1], Deni Iskandar[2], Roelina van der Borg-Boekhout[3], Marina Zenina[3], Mathieu S. Bolhuis[1], Huib A.M. Kerstjens[4], Marieke van Rossum[3], Daan J. Touw[1,5,6], Tanja R. Zijp[1], Job F.M. van Boven[1,5] and Onno W. Akkerman[3,4]

[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [2]Unit of Global Health, Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [3]TB center Beatrixoord, Haren, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [4]Department of Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [5]Medication Adherence Expertise Center Of the northern Netherlands (MAECON), Groningen, The Netherlands. [6]Institute of Pharmacy, Department of Pharmaceutical Analysis, University of Groningen, Groningen, The Netherlands.

Corresponding author: Job F.M. van Boven (j.f.m.van.boven@umcg.nl)

Conflict of interest: All authors report that smart pill bottles were provided free of charge by Pill Connect/eLucid mHealth, along with grant payments (made to institution) supporting the present work. D.J. Touw reports grants from Chiesi Pharmaceuticals; consulting fees from PureIMS; lecture honoraria from PAO Farmacie; participation on a data safety monitoring board for the FORMAT trial; and participation on an advisory board for Sanquin, outside the submitted work. M.S. Bolhuis reports consulting fees from Pfizer and Kinderformularium, Pediatric formulary Netherlands; lecture honoraria from PAO Farmacie; outside the submitted work. All other authors have nothing else to disclose.

Support statement: This work was supported by Pill Connect/eLucid mHealth. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Visca D, Tiberi S, Pontali E, *et al.* Tuberculosis in the time of COVID-19: quality of life and digital innovation. *Eur Respir J* 2020; 56: 2001998.

2 Akkerman OW, Duarte R, Tiberi S, *et al.* Clinical standards for drug-susceptible pulmonary TB. *Int J Tuberc Lung Dis* 2022; 26: 592–604.

3 Chimeh RA, Gafar F, Pradipta IS, *et al.* Clinical and economic impact of medication non-adherence in drug-susceptible tuberculosis: a systematic review. *Int J Tuberc Lung Dis* 2020; 24: 811–819.

4 Margineanu I, Akkerman O, Cattaneo D, *et al.* Practices of therapeutic drug monitoring in tuberculosis: an international survey. *Eur Respir J* 2022; 59: 2102787.

5 Kim HY, Ulbricht E, Ahn YK, *et al.* Therapeutic drug monitoring practice in patients with active tuberculosis: assessment of opportunities. *Eur Respir J* 2021; 57: 2002349.

6 Pradipta IS, Houtsma D, van Boven JFM, *et al.* Interventions to improve medication adherence in tuberculosis patients: a systematic review of randomized controlled studies. *NPJ Prim Care Respir Med* 2020; 30: 21.

7 Cattamanchi A, Crowder R, Kitamuwesi A, *et al.* Digital adherence technology for tuberculosis treatment supervision: a stepped-wedge cluster randomized trial in Uganda. *PLoS Med* 2021; 18: e10036.

8 Ravenscroft L, Kettle S, Persian R, *et al.* Video-observed therapy and medication adherence for tuberculosis patients: randomised controlled trial in Moldova. *Eur Respir J* 2020; 56: 2000493.

9 van Boven JFM, Alffenaar JWC. An Inca trail to the Holy Grail: digital medication adherence support for TB care. *Int J Tuberc Lung Dis* 2022; 26: 1–3.

10 Zijp TR, Touw DJ, van Boven JFM. User acceptability and technical robustness evaluation of a novel smart pill bottle prototype designed to support medication adherence. *Patient Prefer Adherence* 2020; 14: 625–634.

11 Chan AHY, Horne R, Hankins M, *et al.* The medication adherence report scale: a measurement tool for eliciting patients' reports of nonadherence. *Br J Clin Pharmacol* 2020; 86: 1281–1288.

12 Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *Intl J Hum Comput Interaction* 2008; 24: 574–594.

13 Risser J, Jacobson TA, Kripalani S. Development and psychometric evaluation of the Self-efficacy for Appropriate Medication Use Scale (SEAMS) in low-literacy patients with chronic disease. *J Nurs Meas* 2007; 15: 203–219.

14 van den Elsen SHJ, Akkerman OW, Wessels M, *et al.* Dose optimisation of first-line tuberculosis drugs using therapeutic drug monitoring in saliva: feasible for rifampicin, not for isoniazid. *Eur Respir J* 2020; 56: 2000803.

15 Mave V, Kadam D, Gaikwad S, *et al.* Measuring TB drug levels in the hair in adults and children to monitor drug exposure and outcomes. *Int J Tuberc Lung Dis* 2021; 25: 52–60.

16 Migliori GB, Thong PM, Alffenaar JW, *et al.* Gauging the impact of the COVID-19 pandemic on tuberculosis services: a global study. *Eur Respir J* 2021; 58: 2101786.