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Therapeutic drug monitoring: how to improve drug dosage and patient safety in tuberculosis treatment

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SUMMARY

In this article we describe the key role of tuberculosis (TB) treatment, the challenges (mainly the emergence of drug resistance), and the opportunities represented by the correct approach to drug dosage, based on the existing control and elimination strategies. In this context, the role and contribution of therapeutic drug monitoring (TDM) is discussed in detail. Treatment success in multidrug-resistant (MDR) TB cases is low (62%, with 7% failing or relapsing and 9% dying) and in extensively drug-resistant (XDR) TB cases is even lower (40%, with 22% failing or relapsing and 15% dying). The treatment of drug-resistant TB is also more expensive (exceeding €50 000 for MDR-TB and €160 000 for XDR-TB) and more toxic if compared to that prescribed for drug-susceptible TB. Appropriate dosing of first- and second-line anti-TB drugs can improve the patient's prognosis and lower treatment costs. TDM is based on the measurement of drug concentrations in blood samples collected at appropriate times and subsequent dose adjustment according to the target concentration. The 'dried blood spot' technique offers additional advantages, providing the rationale for discussions regarding a possible future network of selected, quality-controlled reference laboratories for the processing of dried blood spots of difficult-to-treat patients from reference TB clinics around the world.

1. Introduction

In this article we describe the key role of tuberculosis (TB) treatment, the challenges (mainly the emergence of drug resistance), and the opportunities represented by the correct approach to drug dosage based on the existing strategies of the World Health Organization (WHO). In this context, the role and contribution of therapeutic drug monitoring (TDM) is discussed in detail.

The European Respiratory Society (ERS) and the WHO developed the Framework for Tuberculosis Elimination in Low-incidence Countries[1] in Rome, Italy in July 2014; this is focused on the concept of pre-elimination (defined as <10 TB cases per million population) and TB elimination (defined as <1 TB case per million population).[2–5] The vision of a TB-free world (zero death, disease, and suffering due to TB) is consistent with the new post-2015 WHO global TB strategy, which has been named the 'End TB Strategy'.[6] The overall goal of the strategy is to end the global TB epidemic, with corresponding 2035 targets of a 95% reduction in TB deaths and a 90% reduction in TB incidence (both compared with 2015). The strategy also includes a target of zero catastrophic costs for TB-affected families by 2020.

To reach this goal, a set of coherent additional actions needs to be implemented in order to improve access to high-quality TB services (prevention, diagnostic, and treatment), especially for vulnerable groups. Also, efforts should be made to address the underlying determinants that put people at risk of TB.

A recent ERS/WHO survey demonstrated that several actions or 'areas' relevant to TB elimination, particularly in the clinical field, are not fully covered in Europe;[5] thus, any information that sheds light on the best clinical and public health practices contributing to improved clinical management will favour TB elimination.

TDM is a tool that may be of help in optimizing TB treatment and is thereby likely to support TB elimination strategies. The aim

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of this study was to pinpoint the role of TDM for the most urgent cases and to present a TDM strategy that could be implemented in a programmatic setting with the scope of controlling and eliminating TB.

2. Methods

By exploring the recent literature we sought to detect TB subpopulations with the highest burden of disease or consuming the greatest health care budget. We subsequently evaluated whether TDM could be of help to solve the problems in this TB population and how it could be implemented in a programmatic treatment setting.

3. Results

A challenge to the attainment of TB elimination is represented by multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. In 2013, the WHO estimated that there were 9 million TB incident cases globally, equivalent to 126 cases per 100 000 population; out of these, an estimated 480 000 cases were affected by MDR *Mycobacterium tuberculosis* strains.[6] Among newly diagnosed patients, approximately 3.5% were infected with MDR-TB strains. Of particular worry, however, is that the prevalence of MDR-TB among new cases in some of the Former Soviet Union countries exceeds 30%.[6–9] XDR-TB has been identified in 100 countries, and the average proportion of MDR-TB cases with an XDR-TB pattern is 9.0%.[6] Furthermore, an additional problem is the emergence and spread of mycobacterial strains with 'total drug resistance',[10–12] a term currently not recognized by the WHO and replaced with 'drug resistance beyond XDR'.[13]

In the largest MDR-TB cohort ever analyzed,[14] the proportion of cases treated successfully was 62%, with 7% failing or relapsing, 9% dying, and 17% defaulting. In the XDR-TB subgroup, treatment outcomes were even worse: 40% achieved treatment success and 22% failed treatment or relapsed, 15% died, and 16% defaulted.[15]

The treatment of drug-resistant TB is more expensive and more toxic compared to that prescribed for drug-susceptible TB, and currently takes up to 2 years of therapy.[16] The cost per patient to treat MDR-TB cases is incredibly high,[17,18] and in spite of international public health efforts, the treatment outcome is not very promising.[13–15] Diel et al. showed that direct treatment-related costs for MDR-TB patients can amount to €52 259 in Germany.[19] The same group demonstrated that the average cost to treat an XDR-TB case in Europe largely exceeds €160 000.

One of the most important causes of the emergence of drug resistance is the pharmacokinetic variability of anti-TB drugs resulting in the exposure of *M. tuberculosis* strains to subtherapeutic drug concentrations.[20,21] This also applies for patients on treatment for MDR-TB. A recent study showed that patients without baseline resistance acquired fluoroquinolone resistance and second-line injectable drug resistance, with 8.9% acquiring extensively drug-resistant TB.[22] Appropriate dosing of the few and less effective antibacterial options remaining could dramatically influence the prognosis. TDM is based on the measurement of drug concentrations in blood samples collected at appropriate times and subsequent dose adjustment according to the target concentration.[23–25] Based on pharmacokinetic and pharmacodynamic principles it can indirectly assess the effect of the drugs on the bacterial target.[26] Details of the pharmacokinetic and pharmacodynamic targets for second-line drugs have been published elsewhere.[27]

In addition to the pharmacokinetic variability of the anti-TB drugs, an inadequate dose or dosing frequency and non-adherence to the prescribed regimen are also deemed to be responsible for the development of drug-resistant TB.[28–30] Although the recent introduction of new diagnostics has allowed the rapid detection of drug resistance,[31] TDM has not been implemented properly for the management of TB therapy,[32] thereby providing opportunities to adjust the dosing in the case of a low serum concentration.[32–34]

Furthermore, TDM can indirectly change the prognosis when less than five effective drugs are available. It can help prevent the development of further resistance as a result of low serum exposure; moreover, the detection of high blood levels can allow adjustment of the dosage and thus reduce the occurrence of adverse events that could decrease patient adherence.

Additional information on the implementation of TDM is reported in Table 1.

Conventional TDM is characterized by the determination of drug concentrations in plasma or serum. Many assays describing the optimal analytical procedure can be found in the current literature. However, an assay enabling the measurement of multiple drugs in a single sample is preferrable.[35] Nevertheless, many laboratories have single drug assays that require a trained

Table 1
Implementation of TDM (therapeutic drug monitoring)

	Procedure	Comments
Analytical procedure	Assay that combines first-line or second-line drugs in a single run	Combination assays reduce the sample volume required TDM saves costs
	Select local or referral laboratory to analyze patient samples	Selection of a certified laboratory is necessary to assure accurate analytical TDM results
	In the case of DBS, verify appropriate blood collection protocol and materials to be used with the laboratory	Deviations produce erratic results
Case selection	Priority to: • Patients failing to convert within 2 months of standardized treatment • Patients showing adverse drug reactions • Patients with multiple risk factors for low drug exposure at diagnosis: HIV-positive, diabetes type 2, gastrointestinal tract problems, severely ill patients	A targeted approach reduces the number of patients for whom TDM has to be performed
Sample collection	Venipuncture used to collect plasma; finger prick used to collect DBS	DBS may be preferred in the outpatient setting or in the case where samples are sent to a referral laboratory to save transportation costs
	Time points should be properly selected to enable accurate optimization of the dose	Optimized sampling may be preferred over 'trough and peak'
Dose adjustment	Dose adjustment should be based on both drug exposure and the MIC of the *Mycobacterium tuberculosis* strain in order to attain the optimal PK/PD target	This strategy avoids unnecessary dose adjustment in patients with low drug exposure and a very susceptible *M. tuberculosis* strain
	Perform follow-up at 1–2 weeks after dose adjustment to ensure that the target drug concentrations are reached	Not every dose increase results in increased drug exposure; switch route of administration of the drug to IV when available

TDM, therapeutic drug monitoring; DBS, dried blood spot; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; IV, intravenous.

nurse to obtain a blood sample of 4–6 ml per time point, making this procedure not too invasive for the patient.

An easier and less expensive approach is the use of the 'dried blood spot' (DBS; Figure 1).[36] The DBS, used successfully in other infectious disease fields (e.g., human cytomegalovirus), is an innovative methodological approach, allowing smaller blood volume collection and easier sampling, storage, and transportation. The latter features can be particularly helpful in low-income countries. The DBS has already been developed and evaluated clinically for important second-line drugs including moxifloxacin[37] and linezolid,[38] and also for clarithromycin.[39]

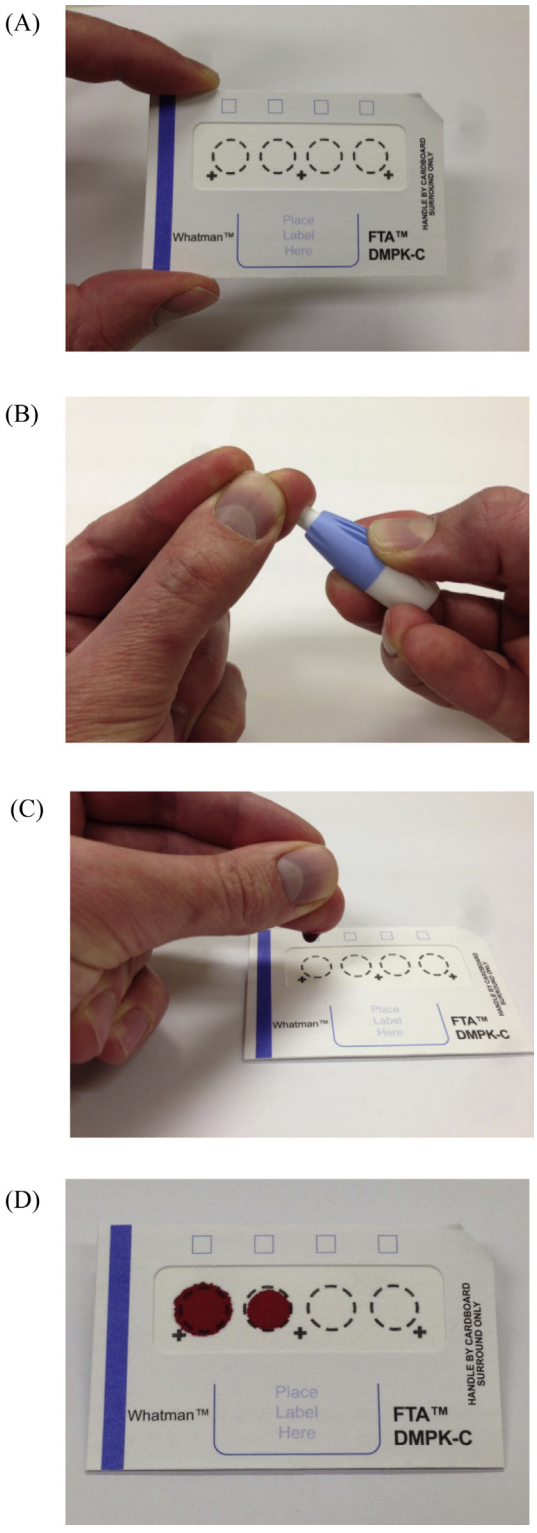

Figure 1. Procedure to obtain a dried blood spot (DBS). Images courtesy of Remco Koster. (a) Use a commercially available DBS card; ensure that the card type selected is one that your laboratory is able to analyze. (b) Pre-clean and warm the finger, prick the finger, and discard the first drop of blood. (c) Let the drop of blood 'fall' onto the DBS card; do not touch or smear the blood onto the DBS card. (d) Let the DBS card dry in air for the specified time period, store it in a zip lock bag with desiccant, and send to the laboratory.

4. Discussion

Although TDM for second-line drugs seems reasonable to optimize the treatment of MDR-TB, a lack of data from prospective studies, logistical issues, and costs are still hindering its implementation and scale-up, even in high-income countries. Only a few laboratories perform the technique and interpret TDM results.[23,40] However, in Europe a group of scientists from Nijmegen and Groningen, the Netherlands, have set up a proficiency testing programme aimed at improving the overall quality of TDM.

The cost of TDM, within country and laboratory variability, is estimated to be US$560 to test four drugs at two time points, but will likely fall with the implementation of analytical methods that can measure all drugs using a single procedure.[35] Further costs are related to the collection and shipment of the samples to the referral laboratory.[23,41] Despite this financial imbalance, a comprehensive analysis cannot take into account the costs following the occurrence of adverse events, unsuccessful outcomes, and the transmission of drug-resistant mycobacteria in the population.[17–19]

A network of national reference laboratories similar to that adopted for the surveillance of drug-resistance[42] could also be considered for TDM. DBS are easier and cheaper to send than infectious materials (*M. tuberculosis* strains), so the ordinary mail system could be used at really low cost. Selected, quality-controlled reference laboratories could receive the DBS of difficult-to-treat patients from reference MDR-TB clinics.

The reasons for its implementation, as previously discussed (including the savings related to the preservation of the safety and efficacy of current anti-TB regimens for drug-resistant cases), appear to open the door to the future involvement of low-income countries, even if further scientific evidence is needed.[16,43,44]

A health technology assessment may represent the most rapid way to obtain a clear response in an era in which the sustainability of healthcare systems (including those in high-income countries) needs to be demonstrated.

On this basis, we support the rationale of gaining further evidence not only on the clinical use of TDM, but also on the possible development of a well-organized public health vision, allowing more and more patients to benefit from this test.

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References

1. World Health Organization. Framework for tuberculosis elimination in low-incidence countries. WHO/HTM/TB/2014.13. Geneva: World Health Organization; 2014.
2. Sotgiu G, Mauch V, Migliori GB, Benedetti A. Evidence-based, agreed-upon health priorities to remedy the tuberculosis patient's economic disaster. *Eur Respir J* 2014;**43**:1563–6.
3. Voniatis C, Migliori GB, Voniatis M, Georgiou A, D'Ambrosio L, Centis R, et al. Tuberculosis elimination: dream or reality? The case of Cyprus. *Eur Respir J* 2014;**44**:543–6.

4. Diel R, Loddenkemper R, Zellweger JP, Sotgiu G, D'Ambrosio L, Centis R, et al. Old ideas to innovate tuberculosis control: preventive treatment to achieve elimination. *Eur Respir J* 2013;**42**:785–801.
5. D'Ambrosio L, Dara M, Tadolini M, Centis R, Sotgiu G, van der Werf MJ, et al. Tuberculosis elimination: theory and practice in Europe. *Eur Respir J* 2014;**43**: 1410–20.
6. World Health Organization. Global tuberculosis report 2014. WHO/HTM/TB/ 2014.08. Geneva: World Health Organization; 2014.
7. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Van Gemert W, et al. Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. *Eur Respir J* 2012;**39**:1425–31.
8. Migliori GB, Dara M, De Colombani P, Kluge H, Raviglione MC. Multidrug-resistant tuberculosis in Eastern Europe: still on the increase? *Eur Respir J* 2012;**39**:1290–1.
9. Abubakar I, Zignol M, Falzon D, Raviglione M, Ditiu L, Masham S, et al. Drug-resistant tuberculosis: time for visionary political leadership. *Lancet Infect Dis* 2013;**13**:529–39.
10. Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM. First tuberculosis cases in Italy resistant to all tested drugs. *Euro Surveill* 2007;**12**. E070517.1.
11. Udwadia Z, Vendoti D. Totally drug-resistant tuberculosis (TDR-TB) in India: every dark cloud has a silver lining. *J Epidemiol Community Health* 2013;**67**: 471–2.
12. Migliori GB, Centis R, D'Ambrosio L, Spanevello A, Borroni E, Cirillo DM, et al. Totally drug-resistant and extremely drug-resistant tuberculosis: the same disease? *Clin Infect Dis* 2012;**54**:1379–80.
13. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, Deriemer K, Centis R, et al. The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Drug resistance beyond extensively drug resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013;**42**:169–79.
14. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012;**9**:e1001300.
15. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. *Eur Respir J* 2013;**42**:156–68.
16. Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011;**38**:516–28.
17. Floyd K, Hutubessy R, Kliiman K, Centis R, Khurieva N, Jakobowiak W, et al. Cost and cost-effectiveness of multidrug-resistant tuberculosis treatment in Estonia and Russia. *Eur Respir J* 2012;**40**:133–42.
18. Loddenkemper R, Sotgiu G, Mitnick CD. Cost of tuberculosis in the era of multidrug resistance: will it become unaffordable? *Eur Respir J* 2012;**40**:9–11.
19. Diel R, Rutz S, Castell S, Schaberg T. Tuberculosis: cost of illness in Germany. *Eur Respir J* 2012;**40**:143–51.
20. Srivastava S, Pasipanodya JG, Meek C, Leff R, Gumbo T. Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. *J Infect Dis* 2011;**204**:1951–9.
21. Pasipanodya JG, Srivastava S, Gumbo T. Meta-analysis of clinical studies supports the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy. *Clin Infect Dis* 2012;**55**:169–77.
22. Cegielski JP, Dalton T, Yagui M, Wattanaamornkiet W, Volchenkov GV, Via LE, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2014;**59**:1049–63.
23. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. *Emerg Infect Dis* 2010;**16**:1546–53.
24. Peloquin CA. Pharmacological issues in the treatment of tuberculosis. *Ann N Y Acad Sci* 2001;**953**:157–64.
25. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs* 2014;**74**:839–54.
26. Pasipanodya J, Gumbo T. An oracle: antituberculosis pharmacokinetics–pharmacodynamics, clinical correlation, and clinical trial simulations to predict the future. *Antimicrob Agents Chemother* 2011;**55**:24–34.
27. Lange C, Abubakar I, Alffenaar JW, Bothamley G, Caminero JA, Carvalho AC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. *Eur Respir J* 2014;**44**: 23–63.
28. Migliori GB, Sotgiu G, D'Ambrosio L, Centis R, Lange C, Bothamley G, et al. TB and MDR/XDR-TB in European Union and European Economic Area countries: managed or mismanaged? *Eur Respir J* 2012;**39**:619–25.
29. Raviglione MC, Lange C, Migliori GB. Preventing and managing antimicrobial resistance: imperative for chest physicians. *Eur Respir J* 2011;**37**:978–81.
30. Van der Werf MJ, Langendam MW, Huitric E, Manissero D. Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis. *Eur Respir J* 2012;**39**:1511–9.
31. Tortoli E, Russo C, Piersimoni C, Mazzola E, Dal Monte P, Pascarella M, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. *Eur Respir J* 2012;**40**:442–7.
32. Srivastava S, Peloquin CA, Sotgiu G, Migliori GB. Therapeutic drug management: is it the future of multidrug-resistant tuberculosis treatment? *Eur Respir J* 2013;**42**:1449–53.
33. Bolhuis MS, van Altena R, van Soolingen D, de Lange WC, Uges DR, van der Werf TS, et al. Clarithromycin increases linezolid exposure in multidrug-resistant tuberculosis patients. *Eur Respir J* 2013;**42**:1614–21.
34. Akkerman AO, Van Altena R, Klinkenberg T, Brouwers A, Bongaerts A, Van der Werf TS, et al. Drug concentration in lung tissue in multidrug resistant tuberculosis. *Eur Respir J* 2013;**42**:1750–2.
35. Kim HJ, Seo KA, Kim HM, Jeong ES, Ghim JL, Lee SH, et al. Simple and accurate quantitative analysis of 20 anti-tuberculosis drugs in human plasma using liquid chromatography-electrospray ionization-tandem mass spectrometry. *J Pharm Biomed Anal* 2014;**102C**:9–16.
36. Vu DH, Alffenaar JW, Edelbroek PM, Brouwers JR, Uges DR. Dried blood spots: a new tool for tuberculosis treatment optimization. *Curr Pharm Des* 2011;**17**: 2931–9.
37. Vu DH, Koster RA, Alffenaar JW, Brouwers JR, Uges DR. Determination of moxifloxacin in dried blood spots using LC-MS/MS and the impact of the hematocrit and blood volume. *J Chromatogr B Analyt Technol Biomed Life Sci* 2011;**879**:1063–70.
38. Vu DH, Bolhuis MS, Koster RA, Greijdanus B, de Lange WC, van Altena R, et al. Dried blood spot analysis for therapeutic drug monitoring of linezolid in patients with multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2012;**56**:5758–63.
39. Vu DH, Koster RA, Bolhuis MS, Greijdanus B, Altena RV, Nguyen DH, et al. Simultaneous determination of rifampicin, clarithromycin and their metabolites in dried blood spots using LC-MS/MS. *Talanta* 2014;**121**:9–17.
40. Li J, Burzynski JN, Lee YA, Berg D, Driver CR, Ridzon R, Munsiff SS. Use of therapeutic drug monitoring for multidrug-resistant tuberculosis patients. *Chest* 2004;**126**:1770–6.
41. Peloquin CA. Therapeutic drug monitoring: assays and cost 2013. Personal communication; 2013.
42. Esposito S, Codecasa L, Centis R. TB elimination, individualised drug dosage and minimisation of adverse effects: the role of therapeutic drug monitoring (TDM). *Eur Respir J* 2014. in press.
43. TB CARE I. International Standards for Tuberculosis Care (ISTC), diagnosis, treatment, public health, Edition 3, The Hague, Netherlands: TB CARE I; 2014.
44. Migliori GB, Zellweger JP, Abubakar I, Ibraim E, Caminero JA, De Vries G, et al. European Union standards for tuberculosis care. *Eur Respir J* 2012;**39**:807–19.