Pharmacological approaches to optimize TB treatment
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Chapter 5b
Dried blood spots can help decrease the burden on patients dually infected with multidrug-resistant tuberculosis and HIV

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Dear editor,

Human immunodeficiency virus (HIV) and tuberculosis (TB) are among the leading causes of death due to an infectious disease worldwide [1]. HIV co-infection amounted to 12% of all TB cases in 2014; the African region accounted for 74% of those [1]. It has become crystal-clear that both infections must be addressed simultaneously. Additionally, multi-drug resistance (MDR) and extensively drug resistance (XDR) aggravate the problem even more [2]. The risk of having a poor MDR-TB treatment outcome is up to ten-fold higher among HIV co-infected individuals [3]. The pill-burden for patients with MDR-TB with HIV co-infection is high, and consists of a combination of at least 6 to 10 different drugs [2]. Therefore, drug-drug interactions, adverse drug reactions and/or sub-optimal plasma concentrations are common [3]. Ultimately, the goal is to tailor both TB and HIV treatment (precision treatment) to optimize outcome and reduce adverse drug events in a way that is cost-effective and feasible worldwide. Of note, in non-affluent settings where there is high disease co-endemicity, this requires a minimalistic yet effective approach while resources are limited. What is needed are tools to determine drug concentrations of all drugs and treatment response markers by means of HIV viral load and sputum smear and culture.

We postulate that therapeutic drug monitoring (TDM), the determination of plasma concentrations of drugs, could be of great value to optimize management of complex medication schemes for the treatment of MDR-TB with HIV co-infection [4]. TDM has not yet been included in routine care of HIV or TB-infected patients, but is recommended in the case of MDR-TB with HIV co-infection [5]. For TDM, plasma concentrations are measured in specialized centralized laboratories, this poses logistical and financial problems, especially in resource limited-areas. Also, TDM using venipuncture for all drugs used in the treatment of MDR-TB with HIV co-infection would be a burden for the patient and the health care system. We propose a patient-friendly method, called dried blood spot (DBS) sampling that can help resolving this problem. DBS sampling is a method that uses a drop of blood on a filter paper, collected by finger prick, for the analysis of drug concentrations [4]. DBS has several advantages over venous sampling [4]. An attractive feature in the setting of infectious diseases is the minimized biohazard risk due to the dried paper matrix. Important for TDM is the increased sample stability of DBS, eliminating cold-chain transport and thereby reducing costs and logistical problems, especially in resource-limited areas with high humidity and temperature [4].

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In the following, we summarize all aspects needed for guidance and monitoring MDR-TB/HIV patients and assess whether the different aspects in the treatment of MDR-TB with HIV co-infection could be covered by DBS.

For patients with MDR-TB, antiretroviral treatment (ART) should be initiated within 2-12 weeks after initiation of MDR-TB treatment, depending on the CD4+ count and clinical condition; in those with CD4+ count <50/mm3, early (< 2 weeks) treatment initiation was shown to reduce mortality in HIV patients by one-third [5]. At start of ART, subject to feasibility in resource-poor settings, genotyping for resistance testing ought to be performed as well as clinical monitoring of serum sodium, potassium, bicarbonate, chloride, blood urea nitrogen, ALAT, ASAT, total bilirubin, serum creatinine, hemoglobin, white cell count, CD4+ count by venous sampling [5]. Patients are re-assessed clinically one month after change of treatment and subsequently at 6 months [5]. However, serum creatinine and potassium need to be measured every 1-3 weeks for MDR-TB patients with HIV co-infection [6]. HIV viral load testing is recommended to be performed 2-8 weeks after start of ART or change of treatment and is repeated every 3-4 months until the viral load is less than 200 copies/mL, and every six months thereafter [5]. CD4+ count should be measured 3 months after initiation of ART, and subsequently every 3-6 months in the first two years of ART [5].

According to previous studies, TDM can best be performed two weeks after the start of treatment, dose change or after a new drug is added when there is a possibility of a drug-drug interaction between antiretroviral (ARV)- and MDR-TB drugs [7,8]. For treatment efficacy assessment, sputum smear and culture is performed every one to two months [6].

ART and programmatic management of MDR-TB guidelines suggest certain laboratory testing schedules. TDM could be aligned with these time points during treatment to increase feasibility and to reduce the burden for the patient [7]. Based on the available guidelines we constructed a schedule for TDM in patients with MDR-TB with HIV co-infection in an optimal and least time-consuming manner [Figure 1].

TDM could be performed using DBS by a single assay combining HIV viral load quantification and pharmacokinetic (PK) assessment [9-11]. Several assays describing the simultaneous determination of plasma concentrations of ARV drugs in DBS are available [9]. For second-line anti-TB drugs this seems also feasible using similar analytical procedures [11,12].
Serum creatinine was also shown to be quantifiable using DBS [13]; nevertheless, clinical monitoring through venipuncture is performed routinely in less specialized non-central laboratories and could therefore still be performed using venipuncture. This is in contrast to TDM, viral load assessment and CD4+ count which need to be determined in central laboratories, and which is difficult to perform through venous sampling due to above mentioned reasons. However, CD4+ count measurement by DBS has not yet been fully developed, yet initial steps have been made towards that direction [10].

To further tailor treatment to the individual patients, genotypic resistance testing needs to be performed at start of treatment. Genotypic resistance testing for several HIV-1 pseudospecies has been validated for DBS in multiple studies [10]. Also, HLA genotyping through whole genome sequencing of DBS derived samples has already been performed. The use of whole genome sequencing opens perspectives for future genetic studies from DBS, for instance studies into \textit{M. tuberculosis} mutations leading to resistance to second-line anti-TB drugs resulting in XDR-TB [14].

**Figure 1: Therapeutic drug monitoring of patients with multidrug-resistant tuberculosis and human immunodeficiency virus.**

The bar is a time-line with the number being the amount of months. Above the bar is monitoring that can be performed using dried blood spots; below the bar other monitoring is listed, including sputum smear and culture and clinical monitoring (biochemistry, liver- and kidney- function tests and blood count).

- ➤ : Sputum.
- ☐: dried blood spot.
- ☐: Venous sampling  ☐: Therapeutic drug monitoring monitoring.
- * repeated if needed for lack of response, ADE, DDI if dose is changed new DBS has to be collected for confirmation. # If <200 copies/mL, repeat every 3-4 months; if >200 copies/mL, repeat every 6 months.
- ‡ repeat every 1-3 weeks. * If two consecutive cultures are negative, do not repeat.

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$\uparrow$: start of treatment. $\uparrow$: stop treatment. DBS: dried blood spot; TDM: therapeutic drug monitoring; ARV: antiretroviral; MDR: multidrug-resistant; TB: tuberculosis; K: Potassium; Scr: Serum creatinine; ART: antiretroviral treatment; SS: sputum smear; SLD: second-line anti-tuberculosis drugs; VL: viral load; SC: sputum culture [5,6].

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Additionally, pharmacogenetic testing to identify enzyme polymorphisms can also be performed with DBS. It was shown that DBS has several advantages over current DNA isolation kits, because allows isolating DNA in fewer steps, taking up less time, and reduces costs for transport and DNA isolation. Identifying enzyme polymorphisms, such as cytochrome P450 polymorphisms, can help individualize treatment because these are involved in several drug-drug interactions and can therefore predict possible drug toxicities or inefficacy [3,15].

The next step will be to evaluate this approach to further enhance MDR-TB-HIV coinfection treatment. We showed that DBS can be used for different aspects like measuring drug concentrations and genotypic resistance testing of HIV for the use in TDM [9,11,13,14]. TDM could be a tool to decrease toxicity, increase efficacy and detect resistance early; thereby preventing further resistance development in a potentially cost-effective way, by preventing hospitalization due to toxicity or drug-drug interactions. Further implementation of DBS in TDM needs to be examined. Also, outcomes from this proposed monitoring needs to be compared with outcomes of current care to determine the added value of TDM using DBS by means of a randomized controlled trial or operational research.

References


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