

# Point-of-care test to monitor adherence to anti-tuberculous treatment

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## Abstract

**Background** In the fight against the global tuberculosis epidemic, it is essential to ensure that patients adhere to the treatment prescribed. As the treatment is given for a minimum of 6 months it is common for patients not to take their drugs regularly. Strategies are therefore needed to assess adherence to treatment. One established method is to examine the patient's urine for the presence of drug metabolites. A rapid point-of-care test would overcome some of the drawbacks associated with currently available methods.

**Method** A rapid, safe point-of-care test for isoniazid metabolites (IsoScreen, Surescreen Diagnostics Limited, Derby, UK) has been developed and used to help assess adherence to treatment in a busy clinic for tuberculosis patients in South London.

**Results** Urine samples were examined from 191 patients receiving isoniazid, usually in combination with rifampicin and other anti-tuberculous drugs. IsoScreen was positive in 93.2% of patients, suggesting that 6.8% might be poorly adhering to treatment. By contrast, examining the same urine samples for evidence of rifampicin ingestion gave positive results in only 43.5%, due to the fact that this test is only positive for a few hours after drug ingestion.

**Conclusion** IsoScreen has been shown to provide a rapid and safe point-of-care test, which contributes to the detection of non-adherence in patients with tuberculosis.

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## Introduction

Tuberculosis (TB) remains the commonest preventable cause of death in adults in less developed countries. The incidence of the disease in the UK, and particularly in London, is increasing due to the global pandemic, changing immigration patterns and co-infection with HIV.<sup>1</sup>

Anti-tuberculous therapy is highly effective, but the patient must adhere correctly to a regimen of isoniazid (INH), rifampicin (RIF) and other anti-tuberculous drugs. Failure to comply with this routine is the major cause of the development of multi-drug resistant TB, which is harder and much more expensive to treat. One approach which is used to increase adherence is directly observed therapy, advocated by the World Health Organization, where an observer makes sure that each dose is swallowed. Other methods, such as

pill counts and urine testing for the presence of anti-tuberculous drug metabolites, provide much less rigorous ways of assessing adherence, but nonetheless are universally used in TB clinics. RIF can be easily detected visually, as it turns the urine orange. However this effect is short-lived and so not always seen. A laboratory test is available for INH metabolites, called the Arkansas method,<sup>2</sup> but this is relatively expensive, time consuming, and not readily available in areas with high incidence of the disease.

We have developed a simple-to-use, 5-minute, colorimetric point-of-care test for INH metabolites in urine, which is a modification of a previous test for smoking.<sup>3</sup> The aim of the current study was to use the new test, referred to as IsoScreen, to audit adherence to anti-tuberculous drug therapy and compare this with the established method of visual detection of RIF in orange-stained urine.

## Method

A plastic testing device consisted of an upper 2 mL syringe and a lower reaction chamber. This contained dried chemicals for the Arkansas method: barbituric acid (20 mg), potassium cyanide (10 mg) and chloramine-T (10 mg); all provided by Sigma Aldrich Co. Ltd, Poole, UK. In use, unprocessed urine was aspirated using the syringe part of the device, injected onto the dried chemicals and shaken. A colour change was apparent in a few seconds, but 5 min was allowed for stable colour development. Presence of dark blue/purple denoted the presence of INH metabolites and indicated adherence to treatment, green indicated presence of the metabolites, but probably not taken in the last 36 h and no colour change indicated non-adherence.<sup>4</sup>

Urine samples ( $n = 191$ ) were collected from patients from the local multi-ethnic population who attended an outpatient TB clinic in outer London [mean age 29 yrs (range 5–82 years), 53.9% male]. All were receiving daily anti-tuberculous drugs, some as chemoprophylaxis for latent TB. Patients were asked when they had last taken their drugs, note was taken of the time of urine sampling and the difference calculated. Other drug treatment was also noted. The presence or absence of orange staining was observed. The IsoScreen test was performed and at 5 min the resultant colour noted.

The vast majority of samples ( $n = 186$ ) were taken from patients on INH/RIF combination therapy, sometimes with other anti-tuberculous drugs such as pyrazinamide and/or ethambutol.

## Results

Samples from those taking RIF as part of their treatment ( $n = 186$ ) showed that only 81 (43.5%) had orange-stained urine. In contrast, from those taking INH as part of their treatment ( $n = 191$ ), the results of the IsoScreen were positive in 178 samples (93.2%) and negative in three samples (1.6%), representing three patients who were probably not taking their drugs regularly. Equivocal results were obtained in 10 samples (5.2%). Figure 1 shows the percentage with positive results for both INH and RIF against time. The RIF staining was seen to peak after 3 h and decline rapidly, while the INH test was positive in 94.5% of samples up to 24 h and 16/20 (80%) between 24 and 30 h.

## Discussion

The Arkansas method for isoniazid metabolites in urine has been successfully transferred to a point-of-care testing device. In a busy outpatient clinic it was deemed easy-to-use and convenient. The sealing of the reagents before use and reactants after use safely

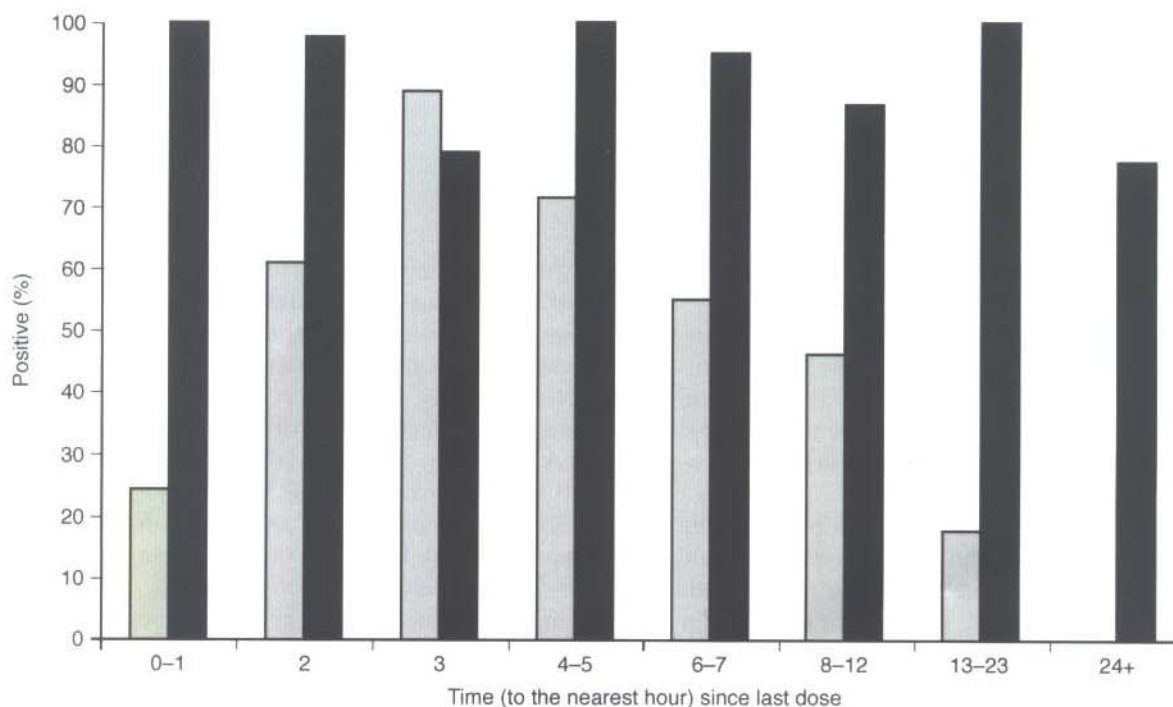


Figure 1. The time to the nearest hour since last dosage of anti-tuberculous treatment, against the percentage of positive urine tests for isoniazid (black bars) and rifampicin (grey bars). Isoniazid was detected by IsoScreen and rifampicin by visual inspection of the urine for orange staining.

protected the user from hazardous chemicals and potentially infected urine samples.

Urine staining from RIF was present in less than half of the samples taken from patients taking the drug, whereas IsoScreen was positive in over 90% of those taking INH. The IsoScreen results showed that only three (1.6%) were deemed non-adherent, with another 10 (5.2%) requiring further support and follow-up. The metabolism of INH is variable and determined by acetylator status. This may affect the time course for positive urine tests, and we plan to investigate this phenomenon further, together with the effect of dosages taken more than 24 h previously.

## Conclusion

In the fight against TB, as non-adherence leads to drug resistance, new measures to improve patient adherence are required.<sup>4</sup> This new test contributes to the detection of those patients who require extra monitoring, further education as to the importance of taking their drugs every day, or to be transferred to directly observed treatment.

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