

# Implementation science: point-of-care diagnostics in HIV and tuberculosis

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## ABSTRACT

**Implementation science uses methods to promote the scaling up and use of evidence-based practices by health systems to improve quality and outcomes. Its use is vital to maximise the efficiency of limited resources for health care in tropical settings. HIV and tuberculosis (TB) are two of the major causes of morbidity and mortality in sub-Saharan Africa, and globally. Although effective treatments are widely available, lack of diagnosis remains a large barrier to accessing treatment, particularly in resource-limited settings. We explore HIV and TB diagnostics that can be used at point-of-care in any settings, and outline some important principles and applications of implementation science to aid their application and use. Despite robust evidence of diagnostic accuracy and efficacy in improving patient-centred outcomes, such interventions cannot be fully utilised without addressing operational barriers and knowledge gaps.**

## Introduction

The research-to-practice gap remains extensive, with the average time taken for evidence-based interventions to reach routine practice being years to decades.<sup>1</sup> This gap is a particular problem in tropical settings where research findings can often contribute to effective health care, impact public health and deliver more efficient use of limited resources, but many factors inhibit uptake and implementation. This article outlines the importance of implementation science, using examples of point of care diagnostics in HIV and tuberculosis (TB).

## What is implementation science?

Implementation science is the study of methods which promote the uptake of evidence-based practices and findings of research into routine practice, with the aim of improving the quality and effectiveness of health care.<sup>2</sup> Its focus is often at organisation or policy level, thus requiring a multi-disciplinary approach.<sup>3</sup> It differs

from clinical research in that it focusses on rates and quality of use of an intervention rather than the impact of the intervention itself on health outcomes, although implementation studies often also measure 'real-world' effectiveness of interventions.

## Challenge of diagnostics in resource-limited settings

Diagnostics have improved substantially over recent decades, and are a fundamental part of medicine and health care in high-income countries. Due to expensive equipment which requires skilled technicians, reliable electricity and reagent supplies, and stable operating environments, most laboratory tests are inaccessible to patients and clinicians in resource-limited settings.<sup>4</sup>

## Key points

Implementation science is the study of methods promoting the uptake of evidence-based practices and findings of research into routine practice, with the aim of improving the quality and effectiveness of health care

The ASSURED criteria have been developed to help point-of-care diagnostics be used in any setting (eg with poor access to electricity), and reduce barriers to implementation.

Rapid HIV sequential testing algorithms allowed for HIV mass testing and subsequent roll-out of life-saving antiretroviral therapy. Self-testing for HIV can be done using oral fluid, and has potential to access hard to reach populations and reduce testing and linkage to care gaps

Urine lipoarabinomannan lateral flow assays significantly improve tuberculosis (TB) diagnosis and can reduce mortality in HIV-positive patients admitted to hospital both with and without classic symptoms of TB (despite imperfect accuracy).

Improving uptake and scaling up of both of these assays will require addressing knowledge gaps and barriers through implementation research

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### Box 1. The ASSURED criteria for point-of-care diagnostics (World Health Organisation)

**Affordable** (<5 US\$ per test)

**Sensitive** (ideally 99%)

**Specific** (ideally 98%)

**User-friendly** (requiring minimal training)

**Robust** (no cold chain) and **rapid** (<1 hour: same-day results and same-day care) and require little or no operator calibration, and minimal routine maintenance (eg wiping spills, dusting)

**Equipment-free** (battery-operated, few moving parts, handheld/compact)

**Deliverable** (commercially available and approved).

Often, algorithmic care predominates with little diagnostic certainty. This public health approach results in both over- as well as under-treatment. Thus the need for diagnostic methods that can function without access to centralised laboratories (point-of-care, POC) remain high on research and policy agendas.<sup>5</sup> POC tests also have the advantage of providing results rapidly, not relying on patients returning to collect results, and have the potential to improve health care services and outcomes in a patient-centred manner. The development of POC tests has focused on infectious diseases in resource-limited settings, for example HIV and, more recently, TB. The ASSURED criteria have been proposed to promote POC diagnostics that are accessible in all settings (Box 1).

### Burden of HIV and TB

HIV and TB are still major causes of morbidity and mortality in tropical settings. By 2017, there were estimated to be 36.7 million people living with HIV (PLHIV) worldwide, including 1.8 million new infections that year.<sup>6</sup> Although HIV is a global epidemic, the burden of prevalence, incidence and mortality lies in sub-Saharan Africa, where 70% of PLHIV and 65% of HIV deaths occur.<sup>6</sup>

TB is still the leading single infectious cause of death and one of the top ten leading overall causes of death worldwide.<sup>7</sup> An estimated 10.4 million people had TB disease in 2016, of whom 25% lived in the African region. Furthermore, sub-Saharan Africa is where the HIV-associated TB epidemic resides, with an estimated 1 million cases and 0.4 million TB deaths among PLHIV.<sup>7</sup> Both HIV and TB epidemics are fuelled by underdiagnosis, late presentation and ongoing transmission which cannot be addressed without POC diagnostics.

### Point-of-care diagnostics: oral self-testing for HIV

Antiretroviral therapy (ART) is a potent tool for both individual and public health control of HIV - there were an estimated 21.7 million people receiving ART as of 2017.<sup>6,8</sup> However, ART requires knowledge of HIV status, and this would not be possible without rapid POC tests for HIV diagnosis, given the lack of access to quality assured centralised laboratories in high HIV-prevalence countries. POC assays for HIV, involving antigen and antibody detection, are referred to as the first generation of POC assays and are widely implemented in sequential algorithms.<sup>9,10</sup>

Whilst POC HIV diagnostics are a success story, under-diagnosis is still responsible for gaps in the HIV care cascade, particularly

in young adults and men.<sup>11</sup> One approach to reaching these populations is community-based testing or self-testing for HIV using oral fluid (eg using the OraQuick assay), which has been shown to have high sensitivity and specificity in field testing, even in the hands of 'less-trained' individuals.<sup>12</sup> Their use has also shown good subsequent linkage to care and ART initiation.<sup>13</sup>

While the diagnostic accuracy of oral self-testing has been well established (94–100% sensitivity and 99.5–100% specificity), there are several implementation questions that need addressing in order to use HIV self-testing to contribute to the 90-90-90 Joint United Nations Programme on HIV and AIDS strategy.<sup>14</sup> These include global availability of the assays; quality and quality assurance (especially when used for self-testing); acceptability to patients; adaptability to high HIV prevalence settings (the assays were initially designed for high-resource settings); strategies to deliver test kits so as to reach those underserved by facility-based HIV testing; and linking patients to HIV treatment and/or prevention services. Scaling up of self-testing is only possible based on multicountry implementational evidence confirming feasibility, acceptability and deliverability across many populations and delivery systems.

### Point-of-care diagnostics for HIV-associated TB

Diagnostic tools are also the weakest link in the TB care cascade, and a contributor to poor outcomes. HIV-associated TB is particularly challenging to diagnose owing to atypical clinical presentations, and inadequate sensitivity of traditional diagnostics such as sputum smear microscopy and chest radiography in PLHIV.<sup>15,16</sup> Missed TB cases result in increased morbidity, mortality and on-going transmission within communities.<sup>17,18</sup> Almost half of TB found at post-mortem from HIV-positive adults in sub-Saharan Africa was undiagnosed at the time of death.<sup>19</sup> The global 'gold standard' TB diagnostic, liquid culture, is expensive, requires considerable infrastructure, is slow, not available in peripheral health care facilities close to patients, and still far from 100% sensitive. If global targets to reduce TB deaths by 95% and new cases by 90% by 2035 are to be met, major improvements in diagnostic strategies are amongst the most pressing needs.<sup>20</sup>

Following many decades of neglect, the TB diagnostic pipeline looks more promising in recent years, including progress with POC assays. The Xpert MTB/RIF assay (Cepheid, USA, 'Xpert'), is the first fully automated, real-time nucleic acid amplification technology for rapid detection of TB and rifampicin resistance, and was approved for TB diagnosis for PLHIV in 2010.<sup>21</sup> Reviews of the impact of Xpert suggested it improves many diagnostic and therapeutic metrics for TB (eg decreased time to diagnosis and treatment, and pre-treatment loss to follow-up).<sup>22</sup> Although the first generation platform required a consistent electricity supply and personal computer for operation, a single cartridge unit with battery operation capability was recently introduced, making the Xpert closer aligned to POC testing.

Lipoarabinomannan (LAM), a mycobacterial cell wall lipopolysaccharide, has emerged as a TB diagnostic target, and can be detected in the urine of TB patients using a low cost, POC lateral flow assay (Determine TB-LAM Ag assay, Alere, USA). This truly POC bedside test can be performed with limited training and uses only 60 µL of unprocessed urine, which is applied to the test strip, and the result read after 25 minutes. Although the sensitivity of this assay in general populations is suboptimal, diagnostic accuracy is improved in PLHIV, and observational data shows good

specificity and significant incremental yield in patients with low CD4 cell counts (sensitivity 40–70%).<sup>23,24</sup> Urine LAM detection is thought to be a marker for haematogenously disseminated renal TB, which also explains its association with poor outcomes.<sup>25</sup>

Despite randomised evidence from two randomised clinical trials<sup>26,27</sup> of significant improvements in patient-centred outcomes among hospitalised PLHIV—increased TB diagnosis and treatment, and mortality reductions in patients with advanced immunosuppression—urine LAM testing has been poorly implemented in African hospitals.<sup>28</sup>

### Barriers to implementation of urine LAM testing

There are several barriers to implementation of urine LAM testing that need to be addressed. The assay does not show impact in all populations, and current conditional World Health Organisation guidance on urine LAM use is difficult to interpret.<sup>29</sup> The test is recommended for patients with low CD4 cell counts, but CD4 testing is often not available. Although the assay itself is relatively inexpensive (approximately US\$3 per test), the affordability of implementation by governments with very low per capita health expenditure is unclear, especially when the assay has not (thus far) been supported by international donors.<sup>30</sup> Supply chains, and optimal methods of testing have not been established for LAM assays (eg bedside testing by clinicians compared to testing in hospital laboratories). It is not clear how LAM should fit into algorithms with other TB diagnostics. Implementation research, ideally performed alongside scale-up and collecting data on implementation strategies and health impacts, are urgently needed to maximise the best TB diagnostic tools we have, such as urine LAM. The knowledge generated will also expedite implementation of better, more sensitive urine LAM assays in the diagnostic pipeline.<sup>31</sup>

### Conclusions

Implementation science is crucial to the successful scaling up and implementation of evidence-based interventions to effect populations and health care en masse. POC diagnostics, for example oral self-tests for HIV and urine LAM assays for HIV-associated TB, are crucial to the control of HIV and TB which remain two of the major public health issues in sub-Saharan Africa. Despite robust evidence of diagnostic accuracy and efficacy in improving patient-centred outcomes, such interventions cannot be fully utilised without addressing operational barriers and knowledge gaps. Diagnostics are only as good as how they are used (innovation without access is not innovation), and ‘imperfect’ diagnostics used in the right populations can still make a contribution. ■

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