SUPPLEMENT ARTICLE

Opportunities and Challenges for Cost-Efficient Implementation of New Point-of-Care Diagnostics for HIV and Tuberculosis

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Stakeholders agree that supporting high-quality diagnostics is essential if we are to continue to make strides in the fight against human immunodeficiency virus (HIV) and tuberculosis. Despite the need to strengthen existing laboratory infrastructure, which includes expanding and developing new laboratories, there are clear diagnostic needs where conventional laboratory support is insufficient. Regarding HIV, rapid point-of-care (POC) testing for initial HIV diagnosis has been successful, but several needs remain. For tuberculosis, several new diagnostic tests have recently been endorsed by the World Health Organization, but a POC test remains elusive. Human immunodeficiency virus and tuberculosis are coendemic in many high prevalence locations, making parallel diagnosis of these conditions an important consideration. Despite its clear advantages, POC testing has important limitations, and laboratory-based testing will continue to be an important component of future diagnostic networks. Ideally, a strategic deployment plan should be used to define where and how POC technologies can be most efficiently and cost effectively integrated into diagnostic algorithms and existing test networks prior to widespread scale-up. In this fashion, the global community can best harness the tremendous capacity of novel diagnostics in fighting these 2 scourges.

On 28 June 2011, the National Institute of Allergy and Infectious Diseases, together with the Office of the Global AIDS Coordinator, the Centers for Disease Control and Prevention, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, sponsored a workshop on "TB and HIV Diagnostics in Adult and Pediatric Populations" in Silver Spring, Maryland. One of the 3 concurrent tracks within the workshop concentrated on the "Strategies for Implementing Molecular Point-of-Care Diagnostics for HIV and TB." It brought diagnostic developers together with in-country representatives, nongovernmental organizations (NGOs), and other partner organizations that may purchase and/or use molecular point-of-care (POC) diagnostic devices. Over the next few years, several groups plan to develop easy-to-use, cost-effective diagnostic assays for human immunodeficiency virus (HIV) and tuberculosis that can detect these pathogens at or near to the POC. Appropriate and accelerated adoption of these technologies requires concerted assay evaluation and discussion of challenges beyond the technical and

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reagent cost restrictions to identify potential barriers of adoption.

The meeting provided developers and stakeholders an opportunity to discuss key issues with purchasers (representatives from country health ministries, NGOs, and US government agencies) regarding the barriers for implementing diagnostics, regulatory concerns, how purchasers are leveraging resources, the current push for global laboratory strengthening, and linkages with existing treatment programs. Other logistical issues, such as supply chain management, communication, workflow, quality assurance, and integration into the existing infrastructure, were also discussed. This paper, as well as others in this supplement (see Palamountain et al, this issue), outlines and discusses different perspectives, controversies, and challenges and provides lessons learned in implementing HIV and tuberculosis diagnostics.

Because the audience included a broad background and spectrum of expertise, a consensus definition of POC was needed for consistency and to avoid confusion. Borrowing from ISO 15189 and other regulatory documents, a working definition of POC for our purpose was "a diagnostic test that is performed near the patient or treatment facility, has a fast turnaround time, and may lead to a change in patient management." Moreover, it was felt that the test should not require trained laboratory personnel or clinical laboratory (centrifuge, pipettes, etc) or other infrastructural (power, air conditioning, refrigeration, running water, etc) support. It was accepted, however, that there will need to be some level of training, operator interpretation, maintenance, quality control, and assurance to ensure that the test is accurate and reproducible [1].

An additional point of debate is the definition of "impact" regarding the diagnostic device. Most diagnostic developers equate impact with test accuracy. However, many health officials and purchasers look beyond accuracy to determine if the inclusion of a diagnostic in a particular setting has a positive effect on epidemiological (eg, incidence) or patient-centered (eg, morbidity, mortality) outcomes (see Cobelens et al, this issue). This requires follow-up to identify infections as well as appropriate treatment options that would benefit the population where the test is performed. Although less of a concern for HIV, this is more difficult for tuberculosis diagnostics owing to the need for culture-based, phenotypic drug ssusceptibility testing resulting from the lack of defined molecular markers for certain drugs (see McNerney et al, this issue).

Point-of-care diagnostics are inherently attractive in many resource-limited settings where the healthcare, transportation, and distribution infrastructure is underdeveloped and underfunded (Table 1). The main advantage of a POC diagnostic is the ability to diagnose disease without the support of a laboratory infrastructure; this increases access, removes the need for sample transport, and shortens turnaround times from weeks (or months) to hours. As a result, more patients are effectively diagnosed, enabling faster and more complete treatment. Despite these advantages, there are barriers for implementation of POC tests. We outline these challenges here in hopes of initiating a dialogue between stakeholders that will lead to a clearer path forward through compromise, innovation, and shared experience.

CURRENT DIAGNOSTIC CHALLENGES FOR HIV

With the adoption and implementation of rapid, cost-effective, POC HIV diagnostic screening assays worldwide, many middle- and low-income countries have developed algorithms for diagnosing HIV infection using strategic orthogonal testing assays without the need for additional confirmatory testing [2]. In addition, the use of alternative samples, such as saliva, have broadened the reach of testing programs [3] despite the recent reports that saliva samples have been associated with higher false-positive rates [4] in some testing sites.

Despite the advances and successes of HIV serological rapid assays, unmet gaps for qualitative POC applications remain (Table 2). First, we need to identify acute HIV infection because recently infected individuals are seronegative but have extremely high viral loads, making them far more infectious compared with chronically infected individuals [5–7]. Early detection can result in early treatment initiation, which limits disease progression [8] and reduces transmission [9–11]. Second, we need to diagnose infants born to HIV-infected mothers, particularly in sub-Saharan Africa [12]. Due to the placental transfer of antibodies during pregnancy, infants may test positive on serological assays yet may not be infected with HIV [13]. Currently, infant diagnosis is primarily performed by collecting dried blood spots and transporting the samples to central testing laboratories for DNA testing [14]. However, many infants go undiagnosed because of long turnaround times or insufficient infrastructure (eg, unreliable sample transportation) [13]. Third, we need appropriate tests for individuals vaccinated with experimental HIV antigens in clinical trials [15]. Vaccine volunteers mount specific immune responses to the vaccine constructs, which react with many serological diagnostic tests, making future HIV diagnosis difficult, potentially unblinding trial staff, and negatively impacting society [16, 17]. Similar assays may also be beneficial in resource-limited settings to monitor antiretroviral therapy (ART) effectiveness and the potential need to switch therapy [18]. In each of these cases, new rapid molecular POC HIV screening tests will fill an important diagnostic gap.

CURRENT DIAGNOSTIC CHALLENGES FOR TUBERCULOSIS

Tuberculosis diagnostics usually rely upon microscopy, clinical screening, and chest radiography to determine the need for

therapy. However, from a program perspective, each of these tests has performance issues that limit their ability to either reliably diagnose or rule out tuberculosis disease. Clinical screening may be useful for ruling out tuberculosis but is not specific enough to make a firm diagnosis [19, 20]. Laboratory testing for tuberculosis includes sputum smear microscopy, sputum culture, and, more recently, nucleic acid amplification (see Nahid et al, this issue). These tests also have stark limitations that a POC test should attempt to address (Table 2).

The first need is for a test with improved sensitivity. Studies have demonstrated a wide-ranging sensitivity of sputum microscopy as a diagnostic test for tuberculosis, as low as 9% when compared with culture [21]. Even culture is known to miss a substantial number of cases—up to 20% among HIV-coinfected patients [22, 23]. On one hand, a POC test with improved sensitivity could dramatically impact the tuberculosis epidemic by complementing or replacing sputum smear; on the other hand, it is difficult to assess specificity in the absence of a true gold standard.

The second need is for a test with minimal requirements for infrastructure or human resources. For example, microscopy is often of low quality, and sample transport to a local microscopy center might not exist. Culture-based tests require training, biosafety disposal systems, and expensive technology, thus limiting their availability in most high-burden settings. More recently, less expensive microscopic-observation drug-susceptibility (MODS) culture assays have been introduced, but these are not well standardized. Similarly, traditional nucleic acid amplification tests require laboratory infrastructure and are either expensive (commercial platforms) or provide inconsistent results (in-house assays); as such, they are not widely used.

Third, we need a tuberculosis POC test capable of providing rapid information on viability (for following treatment progress) and drug resistance. Sputum smear offers no information in these regards, and culture results can take 6–8 weeks to finalize, with contamination of specimens often causing further delays.

The most recent World Health Organization (WHO)–endorsed platform from Cepheid (Xpert MTB/RIF) transcends some of those limitations, bringing a sensitive and specific test very close to the POC [24]. It is almost fully automated, with a 2-hour turnaround time, and it provides data on resistance to rifampicin (RIF), the most important tuberculosis drug available. Although not a classic POC diagnostic (eg, lateral flow or dipstick assay), Xpert MTB/RIF meets many of the desired criteria [25]. However, implementation in rural, underserved areas is likely to be hindered by the need for stable electrical supply, temperature control (2°C –28°C kit storage, ≤30°C operating temperature), and off-site maintenance, and it is probably too expensive (currently >$17 per test in most developing countries) to be used on the millions of tuberculosis suspects evaluated worldwide. Furthermore, the positive predictive value of a single test indicating RIF resistance may be fairly low [26], and RIF resistance is not a universally reliable proxy marker for multidrug-resistant tuberculosis [27], making it difficult to definitively diagnose multidrug-resistant tuberculosis on the basis of a positive test.

DEFINING DIAGNOSTIC GOALS AND TESTING ENVIRONMENTS

There are a variety of clinical environments in resource-limited settings, ranging from sophisticated urban hospitals to outdoor rural outreach centers. Introduction of novel technologies must be contextualized within health systems where other technologies are already operating. Therefore, selection of sites for the deployment of novel technologies should be carefully considered and should take into account data available from national programs so that the public health impact is maximized. Importantly, existing training and quality assurance programs should be upgraded to include new technologies before deployment takes place.

Infrastructure needs and operational requirements are likely to be major obstacles to scaling up POC systems for HIV and tuberculosis. Recent developments in tuberculosis diagnostics and WHO endorsement of the Xpert MTB/RIF system [28], in particular, have highlighted some of the critical elements needed for successful implementation of any POC or near-POC assay in developing country settings. Ideally, POC systems would be usable by general healthcare workers with <1 day of training and require limited preparation, material, and equipment. For a more complete list, the reader is referred to the previously published minimum technical specifications for POC HIV [29] and tuberculosis [30] diagnostics.

When deciding where to implement new POC diagnostic equipment, those in charge of a laboratory network must decide into which clinical environments to place equipment and how it would fit into the diagnostic algorithm. Similarly, when designing new diagnostic equipment, product developers must decide the clinical environments for which they are designing the equipment. When data on these clinical environments are not readily available or differ from one place to another, product developers and laboratory network managers must make assumptions (eg, using mathematical models) about the clinical environment's laboratory infrastructure, human resources, and patient flow [31].

Laboratory infrastructure is a critical consideration for POC equipment design and placement. If a POC device requires stable electricity, then it will not be deployable to a majority of clinical locations in high-burden areas [32]. The frequency and duration of electricity outages and power surges are not typically tracked, making it difficult for laboratory network managers to weigh the investment in an uninterrupted power supply and/or generator to accompany a POC device. In addition to

Table 1. Current Issues and Deficiencies of HIV and Tuberculosis Diagnostics/Laboratory Services in Resource-Poor Countries

Disease	Endorsement	Assay	Examples	Advantages	Disadvantages
Tuberculosis	WHO recommended	Microscopy	Light, fluorescent LED, sputum filtration, bleach microscopy	Ease of use, low cost, infrastructure present in many countries, most widely used test worldwide	Low sensitivity especially for children and HIV-infected patients, no information on drug resistance or viability, technician dependent
		Culture	MGIT, MODS, standard solid media, colorimetric, nitrite reductase, TLA	Highly sensitive commercial and noncommercial assays are the gold-standard tests	Noncommercial assays not standardized, require training and biosafety disposal systems, culture contamination issues, suited to larger laboratories, long time to acquire results
		Chest x-ray	Conventional vs portable devices	Able to confirm radiologic findings consistent with tuberculosis infection, portable devices help reach some hard-to-reach populations	X-ray film quality affects results, low sensitivity/specificity, lack of availability, operator dependence, cost
		Nucleic acid	LPA, Xpert MTB/RIF	High analytical sensitivity, rapid turnaround time, standardized, appears to be substantially better than smear microscopy	Expensive, require electricity, continued need for DST beyond INH/RIF
	Not recommended by WHO	Antibody	Several are commercially available	Ease of use, low cost	Low sensitivity/specificity, high FP rate, high variability and heterogeneity between individuals, low sensitivity for HIV-positive patients
	Recommended for LTBI	In vivo	IGRA, TST	Relatively low cost, TST is easy to perform, IGRA requires laboratory support	High FP/FN rate in high-burden settings, unable to differentiate LTBI from active tuberculosis
	Research use only	Antigen	Urine LAM	May be useful if targeted to high-tuberculosis-burden HIV-infected patients with low CD4 counts, rapid nonsputum-based assay	Low sensitivity in most patients with active tuberculosis and in patients with high CD4 counts, limited use, unproven performance requiring further evaluation
		POC	None currently available	Diagnose active tuberculosis in all populations, all tuberculosis-infected (including LTBI), treatment monitoring assays, predict LTBI progression to disease	Likely will need to compromise in other parameters (cost, speed, accuracy), new biomarkers needed to address clinical questions
		Other	LAMP, VOC, phenotypic tests	Potential to develop a low-cost assay is of interest	Unproven technology still needs validation
HIV	May have regulatory approval	Antibody	EIA, WB, IFA, POC	Cheap, easy to use and widely adopted for both screening and confirmatory testing, cost effective and POC permitting community-based testing	Misses window phase infections ($RNA^{+}Ab^{-}$), not useful for EID, WB indeterminant issues, high FP rates in HIV-vaccinated volunteers

Table 1 continued.

Disease	Endorsement	Assay	Examples	Advantages	Disadvantages
		Antibody/Antigen (4th generation)	EIA, POC	Reduces window period by capturing individuals who are seronegative but anigenemic, cost effective	Misses window phase infections (RNA^+Ag^-), not useful for EID, high FP rates in HIV-vaccinated volunteers
		Nucleic acid	Commercial kits, in-house assays	High sensitivity/specificity, able to monitor treatment	High cost, requirement for laboratory facilities and skilled staff
	Not currently available	Nucleic acid	POC	Useful for acute infection, EID, drug resistance monitoring, and vaccine testing	Likely need to compromise in other parameters (cost, speed, accuracy)
		Ultra-sensitive p24	EIA, POC	Best used for EID, potential for identifying most acute infections	Likely need to compromise in other parameters (cost, speed, accuracy)

Abbreviations: DST, drug susceptibility testing; EIA, enzyme-linked immunoassay; EID, early infant diagnosis; FN, false negative; FP, false positive; HIV, human immunodeficiency virus; IFA, immunofluorescence assay; IGRA, interferon-γ release assay; INH/RIF, isoniazid/rifampicin; LAM, lipoarabinomannan; LAMP, loop-mediated amplification; LED, light emitting diode; LPA, line probe assay; LTBI, latent tuberculosis infection; MGIT, mycobacteria growth indicator tube; MODS, microscopic observation drug susceptibility test; MTB/RIF, *Mycobacterium tuberculosis*/rifampicin; POC, point-of-care; TLA, thin-layer agar test; TST, tuberculin skin test; VOC, volatile organic compound; WB, Western blot; WHO, World Health Organization.

electricity, a POC device may require water or a cold chain, which may similarly exclude most health facilities from the placement decision [33].

As a result of extensive discussions in the public health communities [17, 34], developers have started to consider specific user requirements from resource-limited settings in their product designs. Consequently, new generations of products have been designed with a clear focus on these end-user requirements. This development has been greatly facilitated by technological advances like high-capacity lithium-ion batteries, light emitting diode light sources for imaging, molded optical setups, and rugged fluidics and mechanics. Most importantly, freeze-dried, high-quality reagents, stable without refrigeration, have enabled development of products capable of delivering laboratory-quality test results at the POC.

QUALITY ASSURANCE FOR POC TESTING

Ensuring quality of testing is the cornerstone of assuring the reliability of POC diagnostic testing. The lack in quality assurance has been criticized by clinicians and laboratorians and results in low acceptance of data from these types of devices. The Pima instrument (Alere), the first fully field-deployable CD4 product, has been extensively evaluated and shown to have excellent analytical performance [35, 36]. However, for successful implementation, certain parts of existing systems of quality assurance, such as sample collection, have to be reconsidered. Currently, valid external quality assurance (EQA) standards have been developed and agreed on based on the feasibility on the ground. However EQA practices rely on distributing stabilized samples to each individual test site. New EQA methods may need to be developed for whole blood to verify proper sample collection and processing.

Despite significant efforts, no sample used in EQA schemes so far has been proven to be sufficiently stable to fulfill the requirements of CD4 POC testing at the ground level. A distribution network for incorporating proficiency testing must be considered as part of any rollout plan. An additional concern may be the development of quality control procedures for sample collection. One solution to this is the development of internal controls in conjunction with integrated connectivity, thus allowing the transmission of quality data to a central site for independent review. Obstacles include developing the necessary communications infrastructure and establishing standardized connectivity protocols to create a truly decentralized yet fully quality-assured network of test sites in any part of the world.

Monitoring quality across a large number of testing sites will require new models of quality assurance that provide meaningful, real-time feedback on test performance. Despite user-friendly design, monitoring of the routine prospective

Table 2. Key Unmet[a] Needs for Rapid HIV and Tuberculosis Diagnostics

Disease	Gap	Current Issues or Rationale
HIV	Acute infection	• Often symptomatic and may represent an important opportunity for early HIV diagnosis.
		• May account for a disproportionate amount of HIV transmission, which could be averted by early diagnosis and treatment [5]
	Early infant diagnosis	• HIV-exposed infants (in utero, postdelivery, breast milk) may have HIV antibodies but are not HIV infected, reducing the utility of rapid antibody-based tests; long turnaround times associated with laboratory-based testing may result in high patient loss to follow-up
	Vaccine-induced seroreactivity	• As HIV vaccines are tested and brought to market, they may elicit serological cross-reactivity, rendering existing rapid HIV tests unable to distinguish between vaccination and disease. Alternative POC HIV tests are needed to overcome this limitation.
Tuberculosis	Analytical sensitivity	• Because mycobacterial burden is often low, the sensitivity of tests based on bacterial or antigen detection is limited. POC tests are unlikely to surpass the sensitivity of culture, which itself misses an important subset of cases.
		• Because the humoral immune response to *Mycobacterium tuberculosis* is variable, existing serological tests have poor sensitivity and specificity.
	Infrastructure requirements and cost	• Existing high-sensitivity tests (eg, culture) require biosafety precautions, substantial processing time, and technical expertise. Newer rapid tests (eg, Xpert MTB/RIF) are simpler but still require electrical supply.
		• The cost of many tuberculosis tests is high and volume dependent, necessitating specimen transport networks for economy of scale.
	Assessment of viability and drug resistance	• Rapid tests are needed that can monitor treatment (ie, discriminate between live and dead bacilli) and provide full drug resistance profiles.

Abbreviations: HIV, human immunodeficiency virus; MTB, *Mycobacterium tuberculosis*; POC, point-of-care, RIF, rifampicin.

[a] This table lists representative, high-priority unmet needs. Other important needs exist, as described in the text and cited articles.

performance of POC and similar systems will be paramount to ensure the integrity and validity of the test result. Turnaround time and performance characteristics associated with a particular POC diagnostic assay, 2 pieces of a much larger programmatic puzzle, must be evaluated. Several additional parameters, including suspect identification, specimen collection and transport, result reporting, result interpretation, treatment initiation, and monitoring, should also be considered. Therefore, performance indicators, potentially in the form of operational research, should be designed to measure the various preanalytic, analytic, and postanalytic phases of diagnostic testing. In doing so, areas for strengthening the laboratory–program interface can be identified, and quality improvement projects can be easily monitored systematically.

OBSTACLES TO UPTAKE OF POC TECHNOLOGIES

A number of elements present barriers to both the uptake and the effective utilization of laboratory testing for service delivery. Here we describe 3 key challenges: legal constraints, clarity of normative and regulatory recommendations, and linking laboratory testing to clinical care.

Legal issues governing conducting and reporting laboratory tests may prevent the implementation of POC technologies. In many countries, nonlaboratory personnel cannot perform even the simplest laboratory tests (eg, dipstick urinalysis), which disincentivizes the adoption of POC tests designed for use in the field by clinical staff.

Access to appropriate diagnostic assays is essential to provide effective and high-quality clinical care. However, international and national guidelines often lack clarity around how tests should be used, leaving interpretation up to the clinician. This can become an impediment to delivery of services. A good example is the guidance for discretionary use of HIV-1 viral load to confirm treatment failure of patients on ART. If clinicians interpret this to mean that viral load testing is a necessary prerequisite before starting costly second-line drugs, then poor access to viral load may in turn limit access to treatment. Such conditional recommendations without clear interpretation make it difficult for national programs to allocate resources to laboratory testing or for manufacturers to estimate need and therefore determine the types of tests that might best serve the market.

All of this is compounded by an inconsistent regulatory environment (see Palamountain et al, this issue). In some settings

there are strict national-level regulations and well-described standards that manufacturers and tests must meet. In other settings, national governments might use the reference standards of international regulatory agencies or have no defined policies whatsoever to determine what types of diagnostic assays are acceptable for use. For manufacturers, such inconsistencies make the process of seeking regulatory approval complex and unpredictable, and for national programs, a lack of alignment between normative and regulatory guidance makes it hard to put newer technologies in place.

Too often, test results do not translate into care decisions. The recent increase in access to DNA polymerase chain reaction for diagnosis of HIV in infants is a case in point. Unprecedented scale-up of infant diagnosis has been achieved over the past 5 years, and currently an estimated 400 000 infant diagnosis tests are performed annually [37]. However, despite clear guidance from WHO that all HIV-infected infants be treated immediately, program reviews suggest that less than half of all HIV-positive infants are referred to ART treatment centers. Irrespective of the nature of the diagnostic test, whether laboratory based or POC, it is essential that testing and service delivery are linked in the care and treatment program.

LABORATORY STRENGTHENING TO SUPPORT DECENTRALIZED POC DIAGNOSTICS

In recent years, international aid programs to combat HIV, tuberculosis, and malaria have increased investment in developing countries [38]. Conventional centralized testing is typically more efficient, with higher throughput, and is easier to manage and quality assure than highly decentralized testing. However, significant gaps exist because conventional testing often cannot reach patients living in remote areas and the delay required to send specimens to a laboratory results in loss to follow-up [39]. Centralized tests typically require multiple component products; for example, even simple staining tests or CD4 count tests require >10–15 individual products [40].

Insufficient access to health services in resource-limited settings is a major factor impacting expanded treatment. Access to adequate laboratory services is particularly deficient and often nonexistent in rural settings. In addition, poor laboratory results reduce confidence in diagnostic testing by the healthcare providers [41]. The strengthening of laboratory systems in resource-limited settings is therefore becoming an important priority. The implementation of POC testing will place significant demands on the laboratory systems required to ensure high-quality and reliable testing.

For a successful laboratory strengthening program, it is important to address several factors [42]. Collaborations are essential, and building alliances to develop local capacity and ownership is imperative for sustainability. With both NGOs and government organizations, the first step is to plan strategically and create a budgeted operational plan. Following this, the program must, through local leadership, use the plan to introduce technology, improve and maintain infrastructure, implement quality programs, and develop human resources. The establishment and implementation of laboratory networks is an important step in understanding the country disease burden and ensuring the quality of results as countries implement EQA programs.

In developing economies, maintaining adequate quantities of testing stocks at each site will require enhanced, interactive, and highly responsive supply chains. The supply chain management system of essential health commodities experiences problems leading to stockout and expiry of essential reagents [43], and POC systems are not likely to be the exception. In fact, improved diagnostic capacity is expected to increase the number of individuals on treatment, placing increased pressure on tenuous health systems. To realize the impact of POC devices, it is important to address factors responsible for drug stockouts and expiry, such as inaccurate supply quantification and forecasting, prolonged procedural requirements, and delay in ordering supplies. As testing becomes more dispersed, it will become important to implement systems that check in with test operators on a regular basis and ensure that testing is still being done, that there are adequate supplies of consumables, and that the instruments are in working condition.

Point-of-care diagnostic devices (as all laboratory equipment) require regular calibration, maintenance, and repair, regardless of ease of use. Manufacturers of POC systems should develop local capacity for technical assistance where possible because transporting equipment or technical staff is not cost effective in the long run. The use of modular diagnostic equipment with interchangeable internal components makes repair simpler and reduces the number of parts that need to be stocked. Although many diagnostic companies prefer to switch out rather than repair diagnostic machines, many devices are purchased through government programs that do not allow switch-outs.

POINT-OF-CARE DIAGNOSTICS: HIV OPERATIONAL CHALLENGES

Notwithstanding the fact that the majority of HIV rapid tests are easy to perform and appropriate for nonlaboratory settings, implementation and rapid growth of HIV rapid testing has created challenges and raised concerns about the accuracy and reliability of POC diagnostics [44]. These concerns include those associated to both the test (eg, rapid growth of testing not keeping pace with external quality assurance programs) and testers (eg, lack of sufficiently trained personnel to perform accurate POC diagnosis) [45]. Poor-quality test kits and inconsistent test kit lots, which are not evaluated routinely by qualified laboratories, impact accuracy. As an example, WHO, in the last quarter of 2011, discovered unacceptably high rates

of invalid results of certain lots of SD Bioline 1/2 3.0 manufactured by Standard Diagnostics from the Republic of Korea [46, 47]. Consequently, on 20 December 2011, the US Agency for International Development removed this test from the list of approved diagnostics, and the US President's Emergency Plan for AIDS Relief (PEPFAR) advised its country teams to cease procurement and to quarantine unused stocks [48]. As a result of this delisting, countries have been forced to revise their testing algorithms to assure continuity of testing services. In addition to the evaluation of the diagnostic device, test operators should undergo a comprehensive hands-on training that focuses on following the manufacturer's instructions in test procedures, allowing for accurate interpretation of test results [49]. Despite best efforts to provide extensive training, high attrition rates and personnel turnover can still lead to severe capacity challenges, including inadequate documentation [50]. Systematic approaches to improve test accuracy during the scaling-up of POC HIV rapid testing have included the use of validated kits [48], extensive training with an emphasis on quality, use of standardized logbooks, proficiency testing, new kit lot verification, and postmarket surveillance [51].

POC DIAGNOSTICS: TUBERCULOSIS OPERATIONAL CHALLENGES

Over the past decade, tuberculosis case detection and treatment rates have improved dramatically, and tuberculosis mortality has declined as a result [52]. Further improvements, however, will likely require the use of better diagnostic tools. There are still significant unmet needs in developing countries; >3.5 million tuberculosis cases were undiagnosed and untreated in 2009 [52]. Although new diagnostic tools developed globally over the past several years may help close this gap, adoption and implementation of these tools remains a substantial challenge in many high-burden countries. The Stop TB Partnership Research Movement, with funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), identified key areas in which knowledge gaps hamper effective implementation of tuberculosis control [53]. Ministries of health, through their national tuberculosis and HIV control programs, must create an environment that can rapidly integrate new diagnostics, develop new policies for diagnostic testing, and scale up the new technology countrywide [52, 54].

Countrywide tuberculosis control is exceedingly complex, requiring coordination of numerous financial, technical, and implementing partners, public and private agencies, powerful professional organizations and advocacy groups, and research/training institutes [54, 55]. All stakeholders have a vested interest in tuberculosis control, and their buy-in is critical to the rapid uptake of new diagnostics, but staffing to coordinate these stakeholders at the national level is often grossly inadequate. Challenges include lack of strong national regulatory frameworks; lack of accountability, transparency, and commitment; weak capacity of program managers to effect change; inadequate infrastructure, equipment, and staff; and severe financial limitations. A potential solution to individual country regulatory agencies is the adoption of regional regulatory bodies, which can assess how effective technologies are and make recommendations for use.

The adoption and development of a new policy to introduce a new TB diagnostic in a country is a complex and time-consuming process (see Cobelens et al, this issue). Countries must adapt global recommendations to national needs and resources and conduct analyses to look at the needs and evidence for change, risks, and benefits of new diagnostics and capacity of the current environment to adopt, introduce, and implement the new tuberculosis diagnostic [54].

The successful introduction and implementation of new tuberculosis diagnostics challenges every technical facet of a national tuberculosis control program, from registration of products to guideline development to dissemination of materials and training of staff. Given the association and high burden of HIV/tuberculosis coinfection in many resource-limited settings, implementation of a new tuberculosis diagnostic entails coordination with HIV programs and integration into HIV diagnostic infrastructure. Operationally, program managers must phase out existing tools; ensure availability of new tools in both public and private sectors; adapt procurement, distribution and inventory management plans; and revise monitoring and evaluation systems.

LOOKING AHEAD: MODELS TO INFORM THE IMPLEMENTATION OF POC DIAGNOSTICS

Given that the challenges outlined above are substantial, developers and public health officials must project the cost and public health impact of introducing POC tests before investing in their development. Mathematical models—including dynamic transmission models [56] and economic models [57]—are well suited to this purpose. Existing analyses have evaluated multiple applications of rapid HIV testing [58–60], but unfortunately, extension of these methods to novel POC diagnostics for HIV and tuberculosis has been limited [61, 62]. As such, decisions regarding the development and implementation of such tests are often made without a formal framework for incorporating existing evidence and prevailing knowledge.

Modeling the impact and cost effectiveness of POC tests for HIV and tuberculosis is limited not just by the paucity of available evidence but also by methodological challenges [63]. Perhaps greatest among these is the difficulty of estimating the operational and clinical impact of POC tests after implementation in the field. Not only is the accuracy of POC tests often lower in the field than in the laboratory [64, 65],

but implementing POC diagnostics can alter healthcare processes and workflows beyond simply increasing sensitivity, specificity, or access to services. For example, integrated HIV testing and POC CD4 testing may raise the initial CD4 count at diagnosis [66], increasing demands on ART programs, and rapid tuberculosis diagnosis with drug susceptibility testing may reduce loss to follow-up and time to diagnosis of drug resistance [24], making certain laboratory infrastructure unnecessary and increasing demand for second-line tuberculosis therapy. Models of POC diagnostics' cost effectiveness and impact must account for these operational realities.

Ultimately, a new generation of translational models must be developed to inform test developers and healthcare decision makers of the likely epidemiologic and economic impacts of POC diagnostics before these tests are fully implemented and to update these estimates as operational data accrue. These models must account for the operational realities of POC testing [67], incorporate a variety of outcomes (including economic, public health, and patient centered), and be made accessible to decision makers across a spectrum of local conditions. Only by creating such models can POC diagnostics for HIV and tuberculosis be developed and implemented in a rational, evidence-based fashion.

LESSONS LEARNED

Because care and treatment programs have shown great success in an emergency phase, there is a renewed impetus for ensuring sustainability and that investments are efficient and have a measurable impact on disease burden. An example of such a smart investment is found in the experience of PEPFAR's supply chain management system shifting from mainly air freight to predominantly sea freight. Transportation savings are achieved through extended forecasts and synchronized planning, but the magnitude of savings far outweighs the effort expended. For example, shipping commodities equivalent to 2 containers costs approximately $20 000 by sea freight (8–10 weeks' lead time) compared with >$230 000 by air freight (2–3 weeks). As of June 2011, PEPFAR's intentional shift from air to sea freight has resulted in $52 million in savings through December 2010 (unpublished data). These savings (equal to a year's supply of antiretrovirals for 575 000 persons) represent funding that can be reallocated to service expansion. Another important and tangible spillover effect is noted in the overall technical capacity building that such advance planning entails.

Important avenues to pursue with regard to diagnostics include:

- Further leveraging of pooled procurement mechanisms, such as PEPFAR's supply chain management system and GFATM's voluntary pooled procurement (VPP) program, applying value-for-money criteria to the laboratory sector. The VPP mechanism is a strategic initiative established by GFATM for the recipients of its grants to leverage GFATM's market influence in order to achieve better prices for quality health products and to enhance the long-term sustainability of the market. It also aims to address some of the procurement problems faced by recipients, such as long processes and stockouts caused by delays in procurement.
- Further development of multipartner collaborations such as the Coordinated Procurement Planning (CPP) initiative. The goal of the CPP initiative is to help countries, donors, and implementing partners improve procurement and supply management planning to support the continuous availability of antiretrovirals and other essential medicines and medical commodities required by HIV/AIDS patients. The CPP initiative originated out of a PEPFAR implementers' meeting to ensure that commodities are available for uninterrupted ART services; efforts are focused on strengthening country-level coordination and information sharing among funders and technical agencies to avert stockouts and improve procurement effectiveness.
- Evaluating lessons learned through the Foundation for Innovate New Diagnostics experience in deriving best price models with Xpert.

CONCLUSIONS

Point-of-care testing will reduce many technical and operational challenges associated with laboratory-based testing but will create others as more patients are tested and require treatment and quality assurance becomes more distributed. As new POC devices are deployed, it will be important to find the right balance between POC and conventional testing to achieve the greatest benefit from each type of technology. Striking this balance is not simple and requires consideration of the distribution of test demand across different sites, all-inclusive testing costs (ie, including facility, staff, and overhead costs), human resource and infrastructure requirements, maintenance, quality monitoring, supply chain needs, and potential patient benefits (Table 3). For example, despite the benefits of POC testing, conventional laboratory capacity may be more cost effective or better suited to high volume testing in urban areas with stable infrastructure and transportation systems. Centralized referral networks may be more cost effective than widespread peripheral distribution of POC instruments, especially because peripheral facilities may have low patient volumes. To assess the optimal balance between POC and centralized laboratory testing, market researchers should evaluate the number of affected clinics, existing laboratory infrastructure and human resources, and the volume of patients seen at each level.

New testing platforms can also be slow to implement on a national scale, so conventional laboratory platforms are likely to remain the primary diagnostic systems for years after competing POC technology is initially introduced. There are

Table 3. Current Implementation Obstacles for Introducing New Diagnostic Tools in Resource-Limited Settings and Possible Solutions

Issues	Challenges	Potential Solutions
Laboratory strengthening	Lack of human resources and infrastructure; rudimentary laboratory network	Develop a national laboratory strategic plan that includes funding support from the national budget; utilize telecommunication network to link devices with central laboratory facility
Regulatory	Lack of international guidelines that translate to local needs; lack of transparency, accountability, commitment and policy at the country level; inconsistent regulatory environment	Develop regional bodies to compile available data and guidance; make recommendations based on feasibility studies to meet regional needs; accelerate WHO prequalification of new diagnostics
Quality control	Lack controls to ensure the assay is functioning properly and guarantee validity of test performance	Include internal process controls in the assay; use standardized connectivity methods to transmit data to central laboratory facility
Quality assurance	Lack controls to ensure the sample is processed correctly; more costly to implement; may require temperature controlled storage of QA reagents; relatively short shelf life	Develop new models to incorporate sample processing; use standardized connectivity methods to transmit data to central laboratory facility; centralize procurement
Supply chain management	Inadequate supply of reagents; need to abrogate stockouts and use of expired reagents	Institute programs to accurately forecast supply needs; link with connectivity to monitor use; follow up with warm lines; centralize procurement; develop distribution network; evaluate and release test lots at a central facility
Maintenance and repair	Lack of qualified human resources to perform routine maintenance and repair of equipment in the field	Include modular design for easier repair; develop local capacity; institute switchout programs (if possible)
Training and retention	Lack of sufficient training for the appropriate persons performing assays; high turnover of staff	Develop training requirements that are dictated by where testing will be conducted such as secondary (hospitals), tertiary (clinics), or health outposts; provide performance incentives; secure funding to increase wages

Abbreviations: QA, quality assurance; WHO, World Health Organization.

significant barriers to new test adoption, including the large cost of switching from one test platform to another and quality assurance coverage. To be made efficient, decisions about how to deploy POC diagnostics require modeling of their projected impact and cost effectiveness under local conditions. In the end, ongoing dialogue and compromise across a broad partnership of stakeholders is required if we are to fulfill the promise of POC diagnostics for combating the dual epidemics of HIV and tuberculosis.

Notes

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