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Rolling Out Xpert® MTB/RIF for TB Detection in HIV-Infected Populations:An Opportunity for Systems Strengthening

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Abstract

Background—To eliminate preventable deaths, disease and suffering due to tuberculosis (TB), improved diagnostic capacity is critical. The Cepheid Xpert® MTB/RIF assay is recommended by the World Health Organization as the initial diagnostic test for people with suspected HIV-associated TB. However, despite high expectations, its scale-up in real-world settings has faced challenges, often due to the systems that support it.

Opportunities for System Strengthening—In this commentary we discuss needs and opportunities for systems strengthening to support widespread scale-up of Xpert® MTB/RIF as they relate to each step within the TB diagnostic cascade, from finding presumptive patients, to collecting, transporting and testing sputum specimens, to reporting and receiving results, to initiating and monitoring treatment and, ultimately, to ensuring successful and timely treatment and cure. Investments in evidence-based interventions at each step along the cascade and within the system as a whole will augment not only the utility of Xpert® MTB/RIF, but also the successful implementation of future diagnostic tests.

Conclusion—Xpert® MTB/RIF will only improve patient outcomes if optimally implemented within the context of strong TB programs and systems. Roll-out of this technology to people living with HIV and others in resource-limited settings offers the opportunity to leverage current TB and HIV laboratory, diagnostic and programmatic investments, while also addressing challenges and strengthening coordination between laboratory systems, laboratory-program interfaces, and TB-HIV program interfaces. If successful, the benefits of this tool could extend beyond progress

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towards global End TB Strategy goals, to improve system-wide capacity for global disease detection and control.

Background

The 2015 United Nations Sustainable Development Goals include an ambitious plan to end the tuberculosis (TB) and HIV epidemics by 2030.[1] Yet presently, fewer than two thirds of estimated people with TB are notified, and TB remains the greatest cause of morbidity and mortality among people living with HIV (PLHIV).[2] To achieve a world free of TB deaths, disease and suffering by 2035, improved TB diagnostic capacity is critical.[3] Sputum smear microscopy, although widely used, has unacceptably poor sensitivity for detecting *Mycobacterium tuberculosis* (MTB) in PLHIV.[4–5] Bacterial culture – the gold standard for TB diagnosis – is more sensitive, but is costly, technically challenging, and reliant on sophisticated centralized laboratory infrastructure. Moreover, it takes weeks to obtain results, which increases delays in treatment initiation and the period of potential disease transmission or loss to follow-up.[6–7] Efforts have therefore increasingly focused on developing rapid, near point of care (POC) TB diagnostic tools that can be easily utilized in resource-limited settings.[7–9]

In 2010, the World Health Organization (WHO) acknowledged the Cepheid Xpert® MTB/RIF assay as a major milestone in bringing rapid, simple, bacteriologically-confirmed diagnosis of TB disease and rifampicin resistance potentially closer to the patient POC, by strongly recommending it as the initial diagnostic test for people with suspected multidrug-resistant (MDR) or HIV-associated TB.[10–13] A 2014 Cochrane review later determined it to be cost-effective for this indication, and verified that it significantly increases TB case detection compared with smear microscopy in PLHIV. Pooled sensitivity and specificity were 79% and 98% respectively, and sensitivity was higher among smear-positive (97%) than smear-negative but culture-positive PLHIV (61%).[14] In 2010, the United States (U.S.) President's Emergency Plan for AIDS Relief (PEPFAR), U.S. Agency for International Development (USAID), and U.S. Centers for Disease Control and Prevention (CDC) issued a joint commitment to support the rapid and appropriate scale-up of this technology. In 2012, an agreement with Cepheid was negotiated by PEPFAR, USAID, UNITAID and the Bill and Melinda Gates Foundation to reduce the test price by 40% in 145 eligible countries. By December 2014, the public sector in these countries had procured 3,763 Xpert® instruments (17,883 modules) and more than ten million MTB/RIF cartridges.[4,9,15–17]

Despite initially high expectations, however, rapid scale-up of Xpert® MTB/RIF has uncovered limitations, many due not to the test itself, but to the systems that support it. Although initial modelling predicted that accurate same-day diagnosis by Xpert® MTB/RIF could reduce TB mortality by 20–35% by facilitating earlier treatment initiation,[18–19] subsequent studies have failed to show mortality benefit.[9,20–24] In two multicenter randomized-controlled trials from sub-Saharan Africa, while Xpert® MTB/RIF significantly increased the proportion of TB patients starting treatment who had laboratory-confirmed diagnoses, the absolute number of patients initiating treatment remained unchanged. This was likely due to empiric treatment by clinicians with insufficient trust in the negative predictive value of available TB diagnostic algorithms[20,23–29] (although notably, when

Xpert® MTB/RIF was located at the POC instead of a centralized laboratory, the proportion of bacteriologically-confirmed disease was higher, empiric treatment less frequent, and time to treatment shorter).[29–30] While some studies have found that Xpert® MTB/RIF availability reduces time to TB treatment initiation,[21,23,31–33] others highlight persistent delays due to backlogs in machine module availability and inefficiencies in result processing and transfer.[34–36] In one notable success story, decentralized Xpert® MTB/RIF in a multi-country study reduced median time from sputum collection to TB treatment from 56 to 5 days; however this was attributed to efficient specimen transport and result reporting systems.[37] Finally, although predicted to be cost-effective,[13,19,38–42] routinely using Xpert® MTB/RIF requires ongoing investments in trained staff, supplies and infrastructure.[41–42] Results from early programmatic implementation in nine TB REACH countries revealed increased TB case detection, but also multiple challenges including a 10.6% test failure rate (partly due to difficulties maintaining a continuous power supply), heterogeneous result reporting, and difficulties with supply chain management and sputum transport.[42]

These experiences highlight that use of Xpert® MTB/RIF technology itself is merely one component within a cascade of activities that must be successful to ensure that all TB patients are diagnosed and achieve successful and timely treatment and cure (Figure 1). Each process is critical in the programmatic management of TB (and HIV), and weaknesses in any may minimize the realized utility of any new diagnostic. In addition, they must all be supported by adequate funding, coordination and stakeholder engagement, as exemplified by the varied success of Xpert® MTB/RIF implementation thus far. While this technology and newer assays certainly present opportunities for rapid, accurate diagnosis closer to the POC, to maximize their impact in programmatic settings it is crucial that we concurrently optimize other system- and program-related factors necessary for TB diagnosis and treatment. Scale-up of Xpert® MTB/RIF for diagnosis of TB in PLHIV presents a unique opportunity to leverage current TB and HIV laboratory, diagnostic and programmatic investments, and to coordinate with multiple stakeholders to strengthen laboratory systems, laboratory-program interfaces, and TB-HIV program interfaces overall. Investments in evidence-based interventions at each step along the cascade and within the system as a whole will augment not only the utility of Xpert® MTB/RIF, but also the successful implementation of future diagnostic tests (Table 1).

Opportunities for System Strengthening Along the TB Diagnosis and Treatment Cascade

Finding Presumptive TB Patients

WHO recommends Xpert® MTB/RIF as the initial diagnostic test in individuals with suspected HIV-associated (or MDR) TB, which eliminates the additional clinic visit needed to perform sputum microscopy followed by Xpert® MTB/RIF if negative.[11,43] WHO guidelines also recommend that PLHIV be evaluated at every clinical encounter for cough, fever, weight loss or night sweats, with positive symptom screens prompting further diagnostic evaluation; this screening algorithm has a 79% overall sensitivity (90% in clinical settings) and 50% specificity.[44–45] Subsequent Xpert® MTB/RIF diagnostic testing increases case detection sensitivity and specificity further, however to test the maximum number of

PLHIV for presumptive TB, correctly performed symptom screening is often required first. Universal uptake of the recommended screening algorithm will require incorporation into national guidelines and clinician training in most settings, and provides an opportunity for concurrent sensitization to Xpert® MTB/RIF. Importantly, however, reliance on symptom screening before performing a TB diagnostic test can miss asymptomatic patients. The potential role for initial TB screening of PLHIV using Xpert® MTB/RIF (regardless of symptoms) may become cost-effective in high TB-burden settings, especially with the anticipated roll-out of Xpert® MTB/RIF Ultra, which is much more sensitive for smear-negative TB (94% sensitivity reported preliminarily among smear-negative, culture-positive patients).[46] This highly sensitive technology may also empower clinicians to reduce widespread empiric TB treatment among PLHIV in the future.

Case detection of TB among PLHIV can be maximized by strategically placing GeneXpert® machines in facilities and areas with the highest TB and HIV prevalence. However, even under the best programmatic circumstances, clinical screening algorithms alone may be insufficient to identify TB among those who do not seek care, are contacts of known TB patients or are from remote or marginalized populations. Randomized interventions such as TB contact tracing, mobile vans and household TB and HIV counseling and screening reduced TB prevalence in communities in Zambia, South Africa and Zimbabwe,[47–48] and active community-based TB case-finding endeavors have improved TB case detection in other low-income settings.[49–54] Such community-based efforts have great potential to identify additional persons at risk for TB, who can subsequently benefit from diagnostic technologies like Xpert® MTB/RIF.

Collecting Specimens

The sensitivity of smear microscopy for one sputum specimen was 29% in a study of PLHIV with presumptive TB in Thailand and Vietnam, and the incremental yield of two and three sputum specimens was 7% and 2%, respectively.[55] Most TB programs routinely collect and examine at least two specimens per patient, however the collective sensitivity of even three sputum smears remains low, and access to mycobacterial culture is limited in most low-resource settings. Xpert® MTB/RIF offers a useful alternative, with particularly high sensitivity in sputum smear-positive PLHIV (95–99%).[4] In one study of patients with smear-negative TB, sensitivity of Xpert® MTB/RIF for one sample was only 72.5%, but this was increased incrementally with two and three specimens to 85.1% and 90.2%, respectively.[56] In contrast to smear microscopy, however, cost considerations often limit Xpert® MTB/RIF to one specimen per individual. Under such resource constraints (and until the validation and widespread availability of Xpert® MTB/RIF Ultra), the collection of a single sputum specimen must at least be optimized.

Although data regarding the impact of sputum quality on TB diagnosis is sparse and heterogenous,[57] in theory any method that increases quality and bacillary load of a specimen should improve diagnostic yield. Mycobacterial load is the most significant predictor of Xpert® MTB/RIF-positivity in pulmonary specimens and, in lieu of invasive specimen collection methods, patient instruction can increase microscopic detection of TB.[58–61] Additional yield can be achieved by supervised, physiotherapy-assisted collection.[62] Such

simple and low-cost approaches are certainly warranted for all sputum specimen collection; even as more sensitive near-POC diagnostics become available, the quality of sputum samples will remain an important predictor of their diagnostic value.[46] The healthcare worker training necessitated by Xpert® MTB/RIF introduction provides an opportunity to re-evaluate and re-direct specimen collection techniques to the benefit of any sputum-dependent diagnostic assay.

Recent advances in transport media can further improve specimen quality. The PrimeStore Molecular Transport Medium® (Longhorn Vaccines and Diagnostics, San Antonio, TX, USA) inactivates organisms, preserves nucleic acids for molecular detection, and has been shown to enhance TB detection by Xpert® MTB/RIF significantly in samples with low volume and/or bacterial load. Staff familiarity with this medium may facilitate use of other decontaminating transport reagents that preserve organisms for culture.[63–64]

Transporting Specimens

The ability of Xpert® MTB/RIF to detect MTB within two hours is a breakthrough, however reduced turn-around time is not necessarily sufficient to adequately affect time to diagnosis.[65–66] In particular, inefficient specimen collection and transport systems have been associated with increased patient attrition, time to appropriate treatment, and culture contamination rates.[7,67–67] Improving specimen referral and transport systems is a critical cross-cutting area to target in public health laboratory and TB systems strengthening efforts worldwide.[68–69]

Although Xpert® MTB/RIF may not be a classic POC test, several programs are choosing to introduce GeneXpert® machines in high-volume clinics where presumptive TB patients are screened and treated, thereby reducing specimen transport needs. However peripheral, low-volume sites may conversely place machines centrally, which increases demand for efficient specimen transport systems. In addition, WHO recommends that individuals diagnosed with rifampicin-resistant TB have a specimen referred for laboratory culture and conventional drug susceptibility testing (DST), and are monitored by sputum smear and culture.[13] Thus, despite the relative success of moving TB diagnostic capabilities closer to the patient (and even in the context of GeneXpert® Omni, which will likely offer true POC TB diagnosis in the foreseeable future),[70–71] maintaining and strengthening specimen referral and transport systems remains critical. Recently, U.S. Global Health Security Agenda (GHSA) investments in specimen referral systems such as safe, standardized sample packaging and shipping using the existing Ugandan early infant diagnosis (EID) specimen transportation network improved the speed and quality of sample transport to national reference laboratories.[72] The introduction of Xpert® MTB/RIF diagnostic technology to HIV facilities provides a similar opportunity to evaluate specimen transport and referral systems for TB diagnosis and treatment monitoring – as well as for HIV viral load (VL) and EID that are also offered by Cepheid as part of the multi-disease GeneXpert® platform[73] – and to potentially leverage or integrate these systems to ensure timely, safe delivery of biologic specimens to the point of testing.

Testing Specimens

While much excitement surrounding Xpert® MTB/RIF has stemmed from its relative user-friendliness, it does have key and sometimes challenging operational requirements. These include an uninterrupted power supply, stable ambient temperatures, waste disposal mechanisms, and equipment security against theft. Supply chains must be reliable, and control for backlogs in order processing and customs clearance, and limited cartridge shelf life. Modules require annual calibration, machines need routine maintenance, and technical assistance must be readily accessible for trouble-shooting unanticipated challenges.[6,13] Costs for service and maintenance can be prohibitive and planning and resource mobilization must be assured. Early results from Xpert® MTB/RIF implementation in nine TB REACH countries indicated a 42% module failure rate (10.6% MTB/RIF test failure rate), likely due to problems with irregular power, dust build up, overheating and staff quality control.[42,74] Finally, while each module can process a sample within two hours, backlogs can occur if samples exceed available modules, specimens are batched instead of processed as they are received, or throughput through sites remains below instrument capacity due to staffing or time constraints.[10] WHO and others offer recommendations for how to address these issues,[6,11–13,42,75] but implementation of these recommendations requires advanced planning, ongoing coordination, and significant investments in infrastructure.

In addition, Xpert® MTB/RIF scale-up requires investments in labor. In one South African primary healthcare setting, Xpert® MTB/RIF use increased TB screening and rapid detection, but POC placement increased logistical responsibilities for the clinic, requiring two to five staff members to provide same-day diagnostic evaluations for 16 patients per day.[40] In the setting of minimal biosafety concerns, in some cases non-laboratory staff are being trained to run the assay;[23,40,56] this approach may ease some pressures of limited laboratory human resource capacity, however, emphasis must be placed on testing quality.

Continuous quality improvement (CQI) for any diagnostic test is critical for ensuring accuracy and reliability, detecting and reducing errors, and ensuring customer satisfaction.[76] Although CDC currently provides dried tube specimen-based proficiency panels to over 400 Xpert® MTB/RIF testing sites, dried culture spots have been used by the National Health Laboratory Service in South Africa, and other proficiency testing panels have been developed and assessed, comprehensive external quality assessment (EQA) programs for Xpert® MTB/RIF remain limited.[77–79] However, TB laboratories are well-versed in EQA schemes for sputum smear microscopy which, ideally, are run nationally and include blinded re-checking of slides, on-site supervisory visits, panel testing, feedback, and corrective action.[78] These systems are deemed so important that several key WHO laboratory policies are dependent on the presence of a quality-assured smear microscopy network, however these can be costly and logistically difficult to implement and maintain.[81–82] Decentralized Xpert® MTB/RIF testing shares many parallels with smear microscopy networks and thus, as programs build quality assurance systems to support its implementation, they should capitalize on the opportunity to work within and improve existing smear microscopy EQA programs, and to create quality management systems, laboratory and testing site accreditation and certification initiatives. Similarly, as GeneXpert® instruments are placed

within HIV facilities, plans for ensuring the accuracy and reliability of Xpert® MTB/RIF testing should be aligned and/or integrated with systems for HIV-related POC test quality improvement.[76] Finally, EQA programs should include supplementation when possible with continuous performance monitoring via information systems. This has been accomplished with HIV VL testing in South Africa, and remote monitoring is a rapidly growing area of interest, supported by GeneXpert® and other instrument-based tests.[75,78,83] HIV programs offer a well-established model and tools for a stepwise and continuous cycle to plan, implement and sustain quality assurance for POC testing, with emphasis on staff and site certification standards, supervision, and rigorous monitoring and evaluation (M&E).[84] These can be emulated, and strengthened in conjunction with improvements in TB diagnostic testing CQI.

Reporting and Receiving Results

The laboratory-clinic interface is often challenged by lack of effective communication. In many settings, courier systems relied upon to transport specimens to the point of testing are also responsible for delivering test results to clinicians. However, the potential impact of rapid diagnostic tests like Xpert® MTB/RIF to improve clinical care cannot be realized if results are not received and interpreted rapidly.[65] In a 2005 study of smear-positive TB patients who did not initiate treatment, respondents indicated delays in result receipt as a factor contributing to morbidity and mortality.[7]

WHO recommends establishment of rapid reporting mechanisms for Xpert® MTB/RIF results, including electronic systems, especially in the setting of incompletely decentralized Xpert® MTB/RIF availability.[13] This was highlighted in a notable Cambodian study, where transmitting TB case-finding results directly to clinicians by SMS the day they became available greatly shortened TB diagnostic delays.[85] In the previously cited Uganda GHSA project, enhancement of an existing online, open-source communication system to integrate data sources from laboratory, transportation and communication networks allowed real-time tracking of specimens and results.[72] Prevention of mother to child transmission HIV programs provide another example of how currently available technologies such as mobile phones, web-based information systems, and SMS can decrease EID result reporting times.[86] A diverse suite of potential mobile health solutions to expedite Xpert® MTB/RIF test results for clinical and program monitoring are emerging from device manufacturers and third-party innovators, and are increasingly maximizing the use of laboratory data transmission via mobile telephony, data storage in the Cloud, interoperability and encryption,[87] however unique challenges must be anticipated in terms of data ownership agreements, privacy standards, and the need for technological expertise and infrastructure. Coordination with such existing and planned projects may benefit TB, HIV and other programs through cost-sharing and expansion of rapid reporting networks.

Initiating and Monitoring Treatment

Assuming presumptive patient identification and specimen collection, transport, testing, and result reporting all occur in a rapid and high quality manner, clinicians receiving TB diagnostic results are then tasked with making treatment decisions. When Xpert® MTB/RIF (or other genotypic) results are discrepant from phenotypic results, clinicians must be trained

to interpret them and act based on available information.[12–13] This training offers the added opportunity to refresh them on TB diagnosis and management.

After interpreting Xpert® MTB/RIF results, clinicians must then see patients through to treatment completion and cure. Due to improved sensitivity of Xpert® MTB/RIF over smear microscopy, and its capacity to detect rifampicin resistance, increased drug sensitive and MDR TB case detection among PLHIV is anticipated with Xpert® MTB/RIF scale-up. In one South African study, although Xpert® MTB/RIF introduction reduced the time to MDR TB treatment initiation, higher case detection paradoxically increased the waiting list for treatment initiation and admission to a TB specialty hospital.[88] Appropriate planning and resource mobilization is thus critical to accommodate this imminent increase in TB patients, especially for management of MDR TB which requires dedicated facilities or established community-based models of care, specialized staff and stable drug supplies.[6] Many low- and middle-income countries currently have limited capacity to provide quality MDR TB management, and scale-up of its treatment without quality control could fuel development of extensively drug-resistant TB. Since Xpert® MTB/RIF does not distinguish between live and dead bacteria, it cannot be used to monitor disease relapse or treatment failure.[14,89] Conventional TB microscopy, culture and DST are still needed to assess for drug resistance and treatment failure, thus these systems must concurrently be strengthened even as Xpert® MTB/RIF use is scaled-up.[6,13] Conversely, future developments in molecular and phenotypic DST capabilities in response to newly available pharmacotherapy options may benefit from improvements made to the TB diagnostic cascade to accommodate Xpert® MTB/RIF.[90]

Finally, improved TB case detection will increase the number of PLHIV prioritized for antiretroviral therapy (ART) – even in the context of new WHO guidelines recommending ART initiation regardless of immune status – and is also the gateway for other important TB/HIV interventions including TB infection control and preventive therapy.[43,91–92] In many settings, TB and HIV care and treatment are provided at different locations within parallel systems. Linking co-infected patients to both TB treatment and ART therefore requires strengthened coordination and communication between national TB and HIV/AIDS programs and consideration of integrated service delivery.

Supporting the Cascade

Although each element in the cascade between TB symptom identification and successful treatment must be optimized individually to maximize the impact of Xpert® MTB/RIF technology, there are also several overarching requirements. First, it is important that evidence-based recommendations are incorporated into clinical and laboratory guidelines and policies within national TB and HIV programs. A recent survey of 22 high TB burden countries noted that, while 86% had a policy or algorithm to use Xpert® MTB/RIF, most implementation was donor-supported, and not considered sustainable.[75] Adequate funding is clearly crucial, to support initial investments in technology as well as ongoing costs of cartridges, calibration, staff training and supervision. At current concessional prices, a 4-module GeneXpert® machine with a computer costs US$17,000, cartridges $9.98 each, a calibration kit $450, and shipping an average $1,000 ($1 per cartridge). Programs also need

to budget for service, maintenance and extended-warranty costs. [4, 12–13] All things considered, the total costs of investing in Xpert® MTB/RIF technology for the first year are an estimated $61,000 per machine, with subsequent annual running costs of around $32,000.[6] Although shown to be cost-effective in many settings, cost-effectiveness does not necessarily imply affordability, especially in countries with yearly health expenditures often less than $20 per capita.[88] Despite increases in international donor funding for TB programs since 2002, the yearly funding gap was predicted in 2013 to exceed $2 billion by this year.[93] Given limited resources but known benefit, Xpert® MTB/RIF implementation must be prioritized for maximal ease and impact and, most importantly, integrated whenever possible into other systems strengthening efforts currently underway.[6,20,91]

The second critical factor required to support the TB diagnostic cascade is increased local and international stakeholder commitment to TB programs in general, and coordination of efforts between healthcare sectors, facilities and central governments, and healthcare settings and laboratories. Xpert® MTB/RIF has generated significant interest and investment among Ministries of Health, research institutions, and donors. To ensure the success of initial phased implementation projects and national scale-up plans, it is important that tools, innovations and best practices are shared, and that all efforts within countries are coordinated and championed at the ministry level according to national priorities.[94]

Finally, roll-out and national scale-up of projects must be planned in the context of overall TB and HIV programs. In particular, as Xpert® MTB/RIF use is scaled-up, underlying systems must be able to accommodate additional patients expected to be diagnosed using the assay. After stakeholders are coordinated and implementation plans finalized, supplies must be procured, inventories organized, staff trained, and sites prepared for roll-out. Supervision and quality assurance are needed at every step, as is robust M&E – currently not well established – to routinely collect and respond to data on programmatic performance, outcomes and impact, and to assess where instruments are used and where rate- and quality-limiting steps within the cascade are occurring.[94] Like each individual part of the cascade, these efforts should capitalize on M&E systems already in place, or aim to strengthen those that may benefit from additional investments.

Conclusion

In 2012, Loveday, et al assessed a typical patient's journey from diagnosis to treatment in Kwa-Zulu Natal, South Africa, to determine the effectiveness of decentralized care for MDR TB patients. Although both patient- and health system-related factors resulted in ultimately sub-optimal outcomes, most challenges encountered were due to health systems factors, including poor communication of laboratory results, incorrect provider implementation of clinical guidelines, and inadequate integration of TB and HIV services. This "typical journey" highlights the fact that weaknesses at any step in the clinical cascade can compound deficits in others. [95] Conversely, improvements at any step can and should benefit the system as a whole.

Xpert® MTB/RIF is a major diagnostic breakthrough, but will only improve patient outcomes if optimally placed and implemented within the context of strong TB programs

and systems. The roll-out and rapid scale-up of this technology to PLHIV and others in resource-limited settings offers the unique opportunity to address current challenges to maximize impact on the quality of TB programs in general. Ministries of Health, funding agencies and implementing partners should capitalize upon this opportunity by investing in strong, patient-centered health systems, staff and programs, not only to optimize the success of Xpert® MTB/RIF (and other GeneXpert®-supported platforms such as HIV VL testing and EID), but also to allow any future technologies to be seamlessly incorporated and implemented.[74,96] In particular, Xpert® MTB/RIF implementation should be leveraged to strengthen collaborative TB/HIV activities, laboratory networks, and the laboratory-clinic interface. If this is accomplished, the benefits of this diagnostic tool could extend beyond increased TB case detection and treatment, towards achieving global End TB Strategy goals, improving system-wide capacity for disease detection and control, and promoting global health security.

References

1. United Nations. [Accessed February 10, 2016] Sustainable Development Goals. 2015. https://sustainabledevelopment.un.org/sdgs
2. World Health Organization. [Accessed November 4, 2015] Global Tuberculosis Report. 2015. http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1
3. World Health Organization. [Accessed June 10, 2015] The End TB Strategy. 2015. http://www.who.int/tb/post2015_TBstrategy.pdf
4. Vittor AY, Garland JM, Gilman RH. Molecular Diagnosis of TB in the HIV Positive Population. Annals of Global Health. 2014; 80:476–485. [PubMed: 25960097]
5. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of Smear-Negative Pulmonary Tuberculosis in People With HIV Infection of AIDS in Resource-Constrained Settings: Informing Urgent Policy Changes. Lancet. 2007; 369(9578):2042–2049. [PubMed: 17574096]
6. Piatek AS, Van Cleeff M, Alexander H, et al. GeneXpert for TB Diagnosis: Planned and Purposeful Implementation. Glob Health Sci Pract. 2013; 1(1):18–23. [PubMed: 25276513]
7. Squire SB, Belaye AK, Kashoti A, et al. 'Lost' Smear-Positive Pulmonary Tuberculosis Cases: Where Are They and Why Did We Lose Them? Int J Tuberc Lung Dis. 2005; 9(1):25–31. [PubMed: 15675546]
8. Campaign for Access to Essential Medicines, Treatment Action Group, and Partners in Health. [Accessed June 10, 2015] Defining Specifications for a TB Point-of-Care Test: Meeting Report. 2009. http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_event_POC_meetingoutcomes_full_ENG_2008.pdf
9. McNerney R, Cunningham J, Hepple P, Zumla A. New Tuberculosis Diagnostics and Rollout. Int J Infect Dis. 2015; 32:81–6. [PubMed: 25809761]
10. World Health Organization. [Accessed June 10, 2015] WHO Endorses New Rapid Tuberculosis Test: A Major Milestone for Global TB Diagnosis and Care. 2010. http://www.who.int/mediacentre/news/releases/2010/tb_test_20101208/en/
11. World Health Organization. [Accessed June 10, 2015] Roadmap for Rolling Out Xpert MTB/RIF for Rapid Diagnosis of TB and MDR TB: 6 December 2010. 2010. http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf
12. Shinnick TM, Starks AM, Alexander HL, Castro KG. Evaluation of the Cepheid Xpert MTB/RIF Assay. Expert Rev Mol Diagn. 2015; 15(1):9–22. [PubMed: 25373876]
13. World Health Organization. [Accessed June 5, 2015] Xpert MTB/RIF Implementation Manual: Technical and Operational 'How-To'-Practical Considerations. 2014. http://apps.who.int/iris/bitstream/10665/112469/1/9789241506700_eng.pdf

14. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert MTB/RIF Assay for Pulmonary Tuberculosis and Rifampicin Resistance in Adults (Review). Cochrane Database of Systematic Reviews. 2014; 1:CD009593.
15. The United States President's Emergency Plan for AIDS Relief. [Accessed June 11, 2015] US Global Health Programs Welcome World Health Organization Endorsement of Rapid Test for Tuberculosis. 2010. [press release]. http://www.pepfar.gov/press/releases/2010/152541.htm
16. WHO. [Accessed June 9, 2015] TB Diagnostics and Laboratory Strengthening. 2015. http://who.int/tb/laboratory/mtbrifrollout/en/
17. Foundation for Innovative New Diagnostics. [Accessed June 11, 2015] Price for Xpert® MTB/RIF and FIND Country List. 2015. http://www.finddiagnostics.org/about/what_we_do/successes/find-negotiated-prices/xpert_mtb_rif.html
18. Keeler E, Perkins MD, Small P, et al. Reducing the global burden of tuberculosis: the contribution of improved diagnostics. Nature. 2006; 444:49–57.
19. Andrews JR, Lawn SD, Rusu C. The Cost-Effectiveness of Routine Tuberculosis Screening With Xpert MTB/RIF Prior to Initiation of Antiretroviral Therapy: A Model-Based Analysis. AIDS. 2012; 26:987–995. [PubMed: 22333751]
20. Muyoyeta M, Moyo M, Kasese N, et al. Implementation Research to Inform the Use of Xpert MTB/RIF in Primary Health Care Facilities in High TB and HIV Settings in Resource Constrained Settings. PLoS ONE. 2015; 10(6):e0126376. [PubMed: 26030301]
21. Cox HS, Mbhele S, Mohess N, et al. Impact of Xpert MTB/RIF for TB Diagnosis in a Primary Care Clinic With High TB and HIV Prevalence in South Africa: a Pragmatic Randomised Trial. PLoS Med. 2014; 11:e1001760. [PubMed: 25423041]
22. Mupfumi L, Makamure B, Chirehwa M, et al. Impact of Xpert MTB/RIF on Antiretroviral Therapy-Associated Tuberculosis and Mortality: a Pragmatic Randomized Controlled Trial. Open Forum Infect Dis. 2014; 1(1):ofu038. [PubMed: 25734106]
23. Theron G, Zijenah L, Chanda D, et al. Feasibility, Accuracy, and Clinical Effect of Point-of-Care Xpert MTB/RIF Testing for Tuberculosis in Primary-Care Settings in Africa: a Multicentre, Randomised, Controlled Trial. Lancet. 2014; 383:424–435. [PubMed: 24176144]
24. Churchyard GJ, Stevens WS, Mametja LD, et al. Xpert MTB/RIF Versus Sputum Microscopy as the Initial Diagnostic Test for Tuberculosis: a Cluster-Randomized Trial Embedded in South African Roll-Out of Xpert MTB/RIF. Lancet Glob Health. 2015; 3:e450–457. [PubMed: 26187490]
25. Durovni B, Saraceni V, van den Hof S, et al. Impact of Replacing Smear Microscopy With Xpert MTB/RIF for Diagnosing Tuberculosis in Brazil: a Stepped-Wedge Cluster-Randomized Trial. PLoS Med. 2014; 11:e1001766. [PubMed: 25490549]
26. Theron G, Peter J, Dowdy D, et al. Do High Rates of Empirical Treatment Undermine the Potential Effect of New Diagnostic Tests for Tuberculosis in High-Burden Settings? Lancet Infect Dis. 2014; 14(6):527–32. [PubMed: 24438820]
27. Fielding KL, McCarthy KM, Cox H, et al. Xpert as the First-Line in South Africa: Yield, Initial Loss to Follow-up, Proportion Treated (Abstract 96LB). Top Antivir Med. 2014:48–9.
28. Creswell J, Rai B, Wali R, et al. Introducing New Tuberculosis Diagnostics: the Impact of Xpert MTB/RIF Testing on Case Notifications in Nepal. Int J Tuberc Lung Dis. 2015; 19(5):545–551. [PubMed: 25868022]
29. Hanrahan CF, Clouse K, Bassett J, Mutunga L, Selibas K, Stevens W, et al. The patient Impact of Point-of-Care vs. Laboratory Placement of Xpert MTB/RIF. Int J Tuberc Lung Dis. 2015; 19(7): 811–816. [PubMed: 26056107]
30. Van Den Handel T, Hampton KH, Sanne I, Stevens W, Crous R, Van Rie A. The Impact of Xpert MTB/RIF in Sparsely Populated Rural Settings. Int J Tuberc Lung Dis. 2015; 19(4):392–398. [PubMed: 25859993]
31. Yoon C, Cattamanchi A, Davis JL, et al. Impact of Xpert MTB/RIF Testing on Tuberculosis Management and Outcomes in Hospitalized Patients in Uganda. PLoS One. 2012; 7:e48599. [PubMed: 23139799]

32. Van Rie A, Page-Shipp L, Hanrahan CF, et al. Point-of-Care Xpert_MTB/RIF for Smear-Negative Tuberculosis Suspects at a Primary Care Clinic in South Africa. Int J Tuberc Lung Dis. 2013; 17:368–372. [PubMed: 23407225]
33. Kwak N, Choi SM, Lee J, et al. Diagnostic Accuracy and Turnaround Time of the Xpert MTB/RIF Assay in Routine Clinical Practice. PLoS One. 2013; 8(10):e77456. [PubMed: 24204834]
34. Cohen GM, Drain PK, Naubary F, Cloete C, Bassett IV. Diagnostic Delays and Clinical Decision Making With Centralized Xpert MTB/RIF Testing in Durban, South Africa. J Acquir Immune Defic Syndr. 2014; 67:e88–e93. [PubMed: 25314255]
35. McNerney R, Zumla A. Impact of the Xpert MTB/RIF Diagnostic Test for Tuberculosis in Countries With a High Burden of Disease. Curr Opin Pulm Med. 2015; 21:304–308. [PubMed: 25764020]
36. Lawn SD, Kerkhoff AD, Wood R. Location of Xpert MTB/RIF in Centralised Laboratories in South Africa Undermines Potential Impact. Int J Tuberc Lung Dis. 2012; 16:701. [PubMed: 22507934]
37. Boehme C, Nicol MP, Nabeta P, et al. Feasibility, Diagnostic Accuracy, and Effectiveness of Decentralised Use of the Xpert MTB/RIF Test for Diagnosis of Tuberculosis and Multidrug Resistance: a Multicentre Implementation Study. Lancet. 2011; 377(9776):1495–505. [PubMed: 21507477]
38. Vassall A, Van Kampen S, Sohn H, et al. Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis. PLoS Med. 2011; 8(11):e1001120. [PubMed: 22087078]
39. Pantoja A, Kik S, Denkinger CM. Costs of Novel Tuberculosis Diagnostics – Will Countries Be Able to Afford It? J Infect Dis. 2015; 211(S2):S67–77. [PubMed: 25765108]
40. Clouse K, Page-Shipp L, Dansey H, et al. Implementation of Xpert MTB/RIF for Routine Point-of-Care Diagnosis of Tuberculosis at the Primary Care Level. S Afr Med J. 2012; 102:805–07. [PubMed: 23034211]
41. Langley I, Lin H, Egwaga S, et al. Assessment of the Patient, Health System, and Population Effects of Xpert MTB/RIF and Alternative Diagnostics for Tuberculosis in Tanzania: An Integrated Modelling Approach. Lancet Glob Health. 2014; 2:e581–591. [PubMed: 25304634]
42. Creswell J, Codlin AJ, Andre E. Results From Early Programmatic Implementation of Xpert MTB/RIF Testing in Nine Countries. BMC Infect Dis. 2014; 14:2. [PubMed: 24383553]
43. World Health Organization. [Accessed June 17, 2015] WHO Policy on Collaborative TB/HIV Activities: Guidelines for National Programmes and Other Stakeholders. 2012. http://apps.who.int/iris/bitstream/10665/44789/1/9789241503006_eng.pdf?ua=1&ua=1
44. World Health Organization. [Accessed June 17, 2015] Guidelines for Intensified Tuberculosis Case-Finding and Isoniazid Preventive Therapy for People Living with HIV in Resource-Constrained Settings. 2011. http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf?ua=1
45. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a Standardized Screening Rule for Tuberculosis in People Living With HIV in Resource-Constrained Settings: Individual Participant Data Meta-Analysis of Observational Studies. PloS Med. 2011; 8(1):e1000391. [PubMed: 21267059]
46. Alland, D., Rowneki, M., Smith, L., et al. Xpert MTB/RIF Ultra: a new Near-Patient TB Test With Sensitivity Equal to Culture. [Abstract 91]. Paper presented at the 22nd Conference on Retroviruses and Opportunistic Infections; Seattle, WA. Feb 23–26 2015; http://www.croiconference.org/sessions/xpert-mtbrif-ultra-new-near-patient-tb-test-sensitivity-equal-culture
47. Ayles H, Muyoyeta M, Du Toit E, et al. Effect of Household and Community Interventions on the Burden of Tuberculosis in Southern Africa: the ZAMSTAR Community- Randomised Trial. Lancet. 2013; 382:1182–94.
48. Corbett EL, Bandason T, Duong T, et al. Comparison of Two Active Case-Finding Strategies for Community-based Diagnosis of Symptomatic Smear-Positive Tuberculosis and Control of Infectious Tuberculosis in Harare, Zimbabwe (DETECTB): a Cluster-Randomized Trial. Lancet. 2010; 376:1244–1253. [PubMed: 20923715]

49. Miller AC, Golub JE, Cavalcante SC, et al. Controlled Trial of Active Tuberculosis Case Finding in a Brazilian *Favela*. Int J Tuberc Lung Dis. 2010; 14(6):720–726. [PubMed: 20487610]
50. Parija D, Patra TK, Kumar AMV, et al. Impact of Awareness Drives and Community-Based Active Tuberculosis Case Finding in Odisha, India. Int J Tuberc Lung Dis. 2014; 18(9):1105–1107. [PubMed: 25189560]
51. Lorent N, Choun K, Thai S, et al. Community-Based Active Tuberculosis Case Finding in Poor Urban Settlements of Phnom Penh, Cambodia: a Feasible and Effective Strategy. PLoS One. 2014; 9(3):e92754. [PubMed: 24675985]
52. Khan AJ, Khowaja S, Khan FS, et al. Engaging the Private Sector to Increase Tuberculosis Case Detection: an Impact Evaluation Study. Lancet Infect Dis. 2012; 12(8):608–616. [PubMed: 22704778]
53. Yassin MA, Datiko DG, Tulloch O, et al. Innovative Community-Based Approaches Doubled Tuberculosis Case Notification and Improve Treatment Outcome in Southern Ethiopia. PLoS One. 2013; 8(5):e63174. [PubMed: 23723975]
54. Shapiro AE, Variava E, Rakgokong MH, et al. Community-Based Targeted Case Finding for Tuberculosis and HIV in Household Contacts of Patients with Tuberculosis in South Africa. Am J Respir Crit Care Med. 2012; 185(10):1110–1116. [PubMed: 22427532]
55. Monkongdee P, McCarthy KD, Cain K, et al. Yield of Acid-Fast Smear and Mycobacterial Culture for Tuberculosis Diagnosis in People with Human Immunodeficiency Virus. Am J Respir Care Med. 2009; 180:903–908.
56. Boehme C, Nabeta P, Hillemann D. Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. N Engl J Med. 2010; 363:1005–15. [PubMed: 20825313]
57. Ho J, Marks GB, Fox GJ. The Impact of Sputum Quality on Tuberculosis Diagnosis: a Systematic Review. Int J Tuberc Lung Dis. 2015; 19(15):537–544. [PubMed: 25868021]
58. Theron G, Peter J, Calligaro G, et al. Determinants of PCR Performance (Xpert MTB/RIF), Including Bacterial Load and Inhibition, for TB Diagnosis Using Specimens From Different Body Compartments. Sci Rep. 2014; 4(5658)
59. Alisjahbana B, Van Crevel R, Danusantoso H, et al. Better Patient Instruction for Sputum Sampling Can Improve Microscopic Tuberculosis Diagnosis. Int J Tuberc Lung Dis. 2005; 9(7):814–817. [PubMed: 16013780]
60. Khan MS, Dar O, Sismanisis C, Shah K, Godfrey-Fausett P. Improvement of Tuberculosis Case Detection and Reduction of Discrepancies Between Sputum-Submission Instructions: A Pragmatic Randomised Controlled Trial. Lancet. 2007; 369(9577):1955–1960. [PubMed: 17560448]
61. Khan MS, Dar O, Sismanidis C, Shah K, Godfrey-Faussett P. Improvement of Tuberculosis Case Detection and Reduction of Discrepancies Between Men and Women by Simple Sputum Submission Instructions: a Pragmatic Randomised Controlled Trial. Lancet. 2007; 369:1955–1960. [PubMed: 17560448]
62. Bell DJ, Dacombe R, Graham SM, et al. Simple Measures Are as Effective as Invasive Techniques in the Diagnosis of Pulmonary Tuberculosis in Malawi. Int J Tuberc Lung Dis. 2009; 13(1):99–104. [PubMed: 19105886]
63. Daum LT, Fourie PB, Peters RPH. Xpert MTB/RIF Detection in Mycobacterium Tuberculosis From Sputum Collected in Molecular Transport Medium. Int J Tuberc Lung Dis. 2016; 20(8): 1118–1124. [PubMed: 27393549]
64. Maharjan, B., Shrestha, B., Weirich, A., Stewart, A., Kelly-Cirino, C. [Accessed July 22, 2016] A Novel Sputum Transport Solution Eliminates Cold Chain and Supports Routine Tuberculosis Testing in Nepal. [published online ahead of print April 27 2016]. J Epidemiol Glob Health. 2016. http://www.jegh.org/article/S2210-6006(16)30008-9/fulltext
65. Pascopella L, Kellamn S, Ridderhof J, et al. Laboratory Reporting of Tuberculosis Test Results and Patient Treatment Initiation in California. J Clin Microbiol. 2004; 42(9):4209–4213. [PubMed: 15365013]
66. Yagui M, Perales MT, Asencios L, et al. Timely Diagnosis of MDR-TB Under Program Conditions: Is Rapid Drug-Susceptibility Testing Sufficient? Int J Tuberc Lung Dis. 2006; 10(8): 838–843. [PubMed: 16898366]

67. Paramasivan CN, Narayana AS, Prabhakar R, Rajagopal MS, Somasundaram PR, Tripathy SP. Effect of Storage of Sputum Specimens at Room Temperature on Smear and Culture Results. Tubercle. 1983; 64(2):119–124. [PubMed: 6412408]
68. Nkengasong JN, Nsubaga P, Nwanyanwu O, et al. Laboratory Systems and Services Are Critical in Global Health: Time to End the Neglect? Am J Clin Pathol. 2010; 134(3):368–373. [PubMed: 20716791]
69. Shinnick TM, Iademarco MF, Ridderhof JC. National Plan for Reliable Tuberculosis Laboratory Services Using a Systems Approach. MMWR Morb Mortal Wkly Rep. 2005; 54(RR05):1–12. [PubMed: 15647722]
70. Cepheid and FIND. [Accessed November 24, 2015] World's Most Portable Molecular Diagnostics System Unveiled at AACC. Jul 28. 2015 http://ir.cepheid.com/releasedetail.cfm?releaseid=924108
71. Drain P, Garrett NJ. The Arrival of a True Point-of-Care Molecular Assay- Ready for Global Implementation? Lancet Glob Health. 2015; 3(11):e633–634.
72. Borchert JN, Tappero JW, Downing R, Shoemaker T, Behumbiize P, Aceng J, et al. Rapidly Building Global health Security Capacity – Uganda Demonstration Project, 2013. Morb Mortal Wkly Rep. 2014; 63(04):73–76.
73. Cepheid. [Accessed February 12, 2016] Cepheid Solutions: CE-IVD Tests. 2015. http://www.cepheid.com/en/cepheid-solutions-uk/clinical-ivd-tests/virology
74. UNITAID. 2014: Tuberculosis Diagnostics Technology and Market Landscape. 3. Geneva, Switzerland: World Health Organization; 2014.
75. Pai M, Schito M. Tuberculosis Diagnostics in 2015: Landscape, Priorities, Needs and Prospects. J Infect Dis. 2015; 211(S2):S21–8. [PubMed: 25765103]
76. Parekh BS, Kalou MB, Alemnji G, Ou CY, Gershy-Damet GM, Nkengasong JN. Am J Clin Pathol. 2010; 134:573–584. [PubMed: 20855638]
77. Klein, K., Degruy, K., Hatcher, C., Alexander, H. A Pilot Proficiency Testing Program for Xpert MTB/RIF Using Dried Tube Specimens. [Abstract OA-410-05]. Presented at the 46th Union World Conference on Lung Health; Cape Town, South Africa. Dec 5, 2015;
78. Scott L, Albert H, Gilpin C, Alexander H, Degruy K, Stevens W. Multicenter Feasibility Study to Assess External Quality Assessment panels for Xpert MTB/RIF Assay in South Africa. J Clin Microbiol. 2014; 52(7):2493–2499. [PubMed: 24789182]
79. Scott LE, Gous N, Cunningham BE, et al. Dried Culture Spots for Xpert MTB/RIF External Quality Assessment: Results of a Phase 1 Pilot Study in South Africa. J Clin Microbiol. 2011; 49(12):4356–4360. [PubMed: 21976767]
80. Association of Public Health Laboratories, Centers for Disease Control and Prevention, International Union Against Tuberculosis and Lung Disease, and World Health Organization. [Accessed June 22, 2015] External Quality Assessment for AFB Smear Microscopy. 2002. http://www.aphl.org/AboutAPHL/publications/Documents/External_Quality_Assessment_for_AFB_Smear_Microscopy.pdf
81. World Health Organization. [Accessed June 22, 2015] TB Diagnostics and Laboratory Strengthening – WHO Policy: Reduction of Number of Smears for the Diagnosis of Pulmonary TB, 2007. 2015. http://www.who.int/tb/laboratory/policy_diagnosis_pulmonary_tb/en/
82. World Health Organization. [Accessed June 22, 2015] Same Day Diagnosis of Tuberculosis by Microscopy. 2011. http://whqlibdoc.who.int/publications/2011/9789241501606_eng.pdf?ua=1
83. Cepheid. [Accessed June 22, 2015] RemoteXpert Program. 2014. http://www.stoptb.org/wg/gli/assets/documents/M6/Colla%20-%20Cepheid_RemoteXpert.pdf
84. World Health Organization. [Accessed February 12, 2016] Improving the Quality of HIV-Related Point-of-Care Testing: Ensuring the Reliability and Accuracy of Test Results. 2015. http://apps.who.int/iris/bitstream/10665/199799/1/9789241508179_eng.pdf?ua=1
85. Lorent N, Choun K, Thai S, et al. Community-Based Active Tuberculosis Case Finding in Poor Urban Settlements of Phnom Penh, Cambodia: A feasible and Effective Strategy. PLoS One. 2014; 9(3):e92754. [PubMed: 24675985]
86. President's Emergency Plan for AIDS Relief. Early Infant Diagnosis: Improving PMTCT and Pediatric HIV Programs. Final Meeting Report from PEPFAR Annual Meeting; August 18, 2010; 2010. http://womenchildrenhiv.org/pdf/vc-10-07/Report_EID.pdf

87. GxAlert. [Accessed February 12, 2016] GxAlert. 2016. http://www.gxalert.com/

88. Padayatchi M, Loveday M, Naidu N. Drug-Resistant Tuberculosis Control in South Africa: Scientific Advances and Health Systems Strengthening Are Complementary. Expert Opin Pharmacother. 2014; 15(15):2113–6. [PubMed: 25226528]

89. Lawn SD, Mwaba P, Bates M, et al. Advances in Tuberculosis Diagnostics: the Xpert MRB/RIF Assay and Future Prospects for a Point-of-Care Test. Lancet Infect Dis. 2013; 13:349–61. [PubMed: 23531388]

90. Wells WA, Boehme CC, Cobelens FGJ, et al. Alignment of New Tuberculosis Drug Regimens and Drug Susceptibility Testing: A Framework for Action. Lancet Infect Dis. 2013; 13:449–58. [PubMed: 23531393]

91. Date A, Modi S. TB Screening Among People Living With HIV/AIDS in Resource-Limited Settings. J Acqui Immune Defic Syndr. 2015; 68:S270–3.

92. World Health Organization (WHO). [Accessed September 30, 2015] Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. 2015. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf

93. Floyd K, Fitzpatrick C, Pantoja A, Raviglione M. Domestic and Donor Financing for Tuberculosis Care and Control in Low-Income and Middle-Income Countries: An Analysis of Trends, 2001–11, and Requirements to Meet 2015 Targets. Lancet Glob Health. 2013; 1:e105–15. [PubMed: 25104145]

94. Alexander, H. Scaling Up Xpert MTB/RIF as Part of HIV Care: Progress, Challenges, and the Way Forward?. Talk presented at the 19th Core Group Meeting of the Global TB/HIV Working Group; February 2014;

95. Loveday M, Padayatchi N, Brust J, Voce A, Wallengren K. The Treatment Journey of a patient With Multidrug-Resistant Tuberculosis in South Africa: Is It Patient Centred? Int J Tuberc Lung Dis. 2013; 17(10 0 1):56–59. [PubMed: 24020603]

96. Kik SK, Denkinger CM, Jefferson C, Ginnard J, Pai M. Potential Market for Novel Tuberculosis Diagnostics: Worth the Investment? J Infect Dis. 2015; 11(S2):S58–66.

Significance of Work

Scale-up of Xpert® MTB/RIF for diagnosis of tuberculosis (TB) in people living with HIV presents a unique opportunity to leverage TB and HIV laboratory, diagnostic and programmatic investments, as well as to coordinate and strengthen laboratory systems, laboratory-program interfaces, and TB-HIV program interfaces overall. In this commentary, we discuss this opportunity as it relates to each step within the cascade from TB diagnosis to successful treatment.

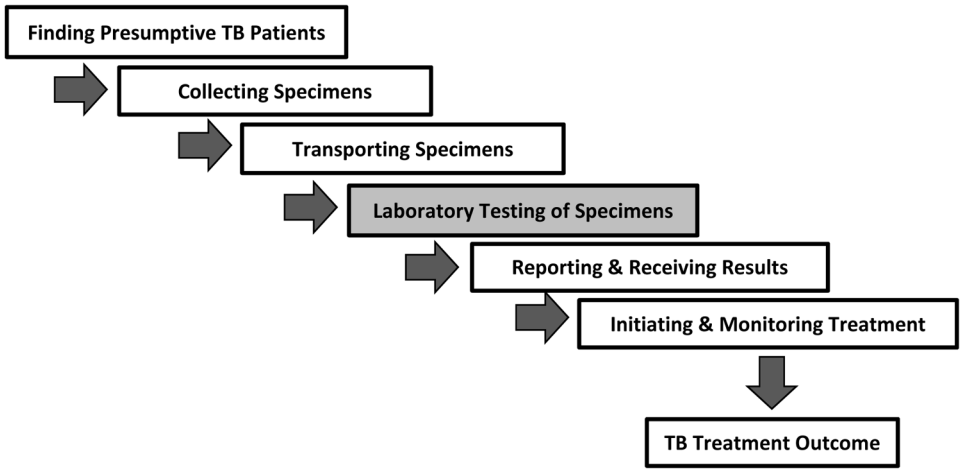

Figure 1.
Key steps in the cascade from TB diagnosis to successful treatment

Table 1

Summary of Challenges and Opportunities Along the Cascade

Cascade Step	Challenges	Opportunities for System Strengthening
Finding Presumptive TB Patients	• Correct and routine TB symptom screening • Identification of potential TB patients among those who do not seek care	• Incorporation of TB symptom screening algorithm into guidelines and clinician curricula provides an opportunity for concurrent Xpert® MTB/RIF training • Initial screening of PLHIV using Xpert® MTB/RIF may become cost-effective in high burden settings (especially when Xpert® MTB/RIF Ultra is available) • Community-based TB case-finding can identify more people who might benefit from Xpert® MTB/RIF
Collecting Specimens	• Low sensitivity of sputum smear microscopy • Access to mycobacterial culture	• Xpert® MTB/RIF is a useful alternative to smear microscopy • Simple, low-cost approaches to improve mycobacterial load in sputum specimens would improve yield for any sputum-dependent diagnostic assay, and can be taught alongside Xpert® MTB/RIF roll-out
Transporting Specimens	• Centrally-placed machines • Efficient transport needed to support DST and monitoring for Rifampicin-resistant patients	• Improving specimen referral/transport systems would strengthen other public health and laboratory efforts • Opportunities exist to improve these systems in partnership with the U.S. Global Health Security Agenda or HIV programs (e.g for assays such as HIV VL and EID)
Laboratory Testing of Specimens	• Multiple operational requirements for Xpert® MTB/RIF scale-up	• Investments in infrastructure, supply chain and human resources would benefit other facilities/programs • Quality assurance systems can work with existing smear microscopy and/or HIV-related EQA/CQI programs, and create laboratory site accreditation initiatives and continuous performance monitoring
Reporting and Receiving Results	• Result reporting to clinicians often relying on courier systems	• Electronic platforms can allow real-time specimen tracking and results reporting for multiple diseases • Mobile health solutions projects could benefit other programs via cost-sharing and expanded rapid reporting networks
Initiating and Monitoring Treatment	• Proper and timely use of Xpert® MTB/RIF results by clinicians • Increase in diagnosed TB, MDR TB and TB/HIV due to Xpert® MTB/RIF scale-up	• Training clinicians to interpret/use Xpert® MTB/RIF results can allow concurrent refreshers on TB diagnosis and management • Advance planning and resource mobilization needed to accommodate an increase in diagnosed TB and MDR TB patients would benefit overall health systems and future DST capabilities • Increased coordination between TB and HIV/AIDS programs and quality of care for co-infected patients
TB Treatment Outcomes	**Supporting the Cascade:** • Incorporate evidence-based recommendations into clinical and laboratory guidelines and policies • Secure adequate funding to support initial investments in technology and ongoing costs • Coordinate collaboration between local and international stakeholders, facilities and laboratories • Provide supervision, quality assurance, and robust M&E at every step of Xpert® MTB/RIF implementation • Champion Xpert® MTB/RIF roll-out at the Ministry level in the context of overall TB/HIV programs • Integrate Xpert® MTB/RIF implementation when possible into other systems strengthening efforts	**Table 1:** **Summary of Challenges and Opportunities Along the Cascade**