Review Article

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HIV testing in developing countries: What is required?

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HIV diagnostic and follow up testing are usually done in laboratory settings. However, in developing countries there is a need to decentralize testing as the majority of the population lives in rural settings. In developing countries stringent quality assurance (QA) practices, which include appropriate training, development of standard operating procedures, maintenance of operator proficiency, routine use of quality control (QC) specimens, standardized data management, equipment calibration and maintenance, and biohazard safety with proper disinfection/disposal procedures are not routinely followed to ensure reliability of results and a safe work environment. The introduction of point-of-care testing technologies involving the use of non-laboratorians in routine testing has further increased the complexity of QA. Therefore, a careful approach towards improvement of laboratories that encourages best practices, coupled with incentives, and review of government policies in point-of-care testing is needed to improve quality of testing as decentralization takes place. Development of a functional laboratory tiered network that facilitates communication, referral, training and problem solving could further enhance confidence in laboratory testing. There is also a need for special considerations in implementing a step-wise approach towards quality improvement, strengthening of the supply chain management, human capacity development, infrastructure upgrade, and strong public private partnerships to ensure long term sustainability of these efforts.

Key words Accreditation - developing countries - diagnostics - HIV - point of care testing - quality control - rapid tests

Introduction

Developing countries currently bear the brunt of HIV and AIDS infection, in addition to the burden of economic hardship and other diseases. In response to this, support for health systems in developing countries has become a major focus of many donors, including the Global Fund for AIDS, Tuberculosis and Malaria, the World Bank, the US President's Emergency Plan for AIDS Relief (PEPFAR), the Global Health Initiative (GHI), bilateral government support, and private foundations[1-3]. Though these programmes have helped in increasing the number of people who have access to HIV/AIDS testing and counselling, prevention, care, and treatment services, there are concerns about the inadequacy of sufficient laboratory infrastructure as well as the fragile quality of laboratory services in the majority of the existing laboratories[4]. This inability of the laboratory infrastructure to fully support the developing country's needs has been the subject of many discussions with the recommendations to review and propose guidelines for setting up more effective laboratory services and systems[5]. In particular, attainment of quality laboratory services in developing countries has been hampered

by several factors which include lack of laboratory supplies and essential equipment, limited numbers of skilled personnel, lack of educators and training programmes, lack of decentralized laboratory systems, and standard laboratory testing menus[6,7]. The outcome has been the establishment of laboratory facilities without consideration of tiered standardized integrated structures that will ensure quality improvement, capacity building, referral systems and sustainability. As a result, the accessibility of laboratory testing and the quality of available services remain a serious challenge. Consequently, clinicians in developing countries lack confidence in the laboratory results available and often rely on clinical diagnosis and empirical treatment instead of laboratory-confirmed diagnosis. It is, therefore, imperative that laboratory systems be strengthened within broader efforts toward health systems strengthening. This article highlights some of the challenges being faced in the course of decentralization of testing facilities in developing countries and some thoughtful considerations for improving infrastructure and quality systems.

Current HIV testing technology and testing needs in developing countries

HIV testing technologies include HIV serology covering diverse methods such as enzyme immunoassay (EIA), HIV rapid tests, agglutination tests, and Western blot (WB) to detect presence of HIV antibodies. Other tests include DNA polymerase chain reaction (PCR) for early infant diagnosis, and viral load, haematology, clinical chemistry, and genotyping for clinical monitoring of patients.

Most testing sites in developing countries use venous blood sample for initial screening. Depending on the country's national algorithm and location of testing, a combination of two or more tests is used to confirm and release results. In either circumstance, it is recommended that the test kits used should first be evaluated or validated in country to ensure that they perform optimally in terms of their sensitivity and specificity.

HIV rapid tests are now routinely used in most developing countries at thousands of testing sites that may also include testing for pregnancy, syphilis or malaria to make the package more cost-effective (integrated counselling and testing centres). Such facilities provide appropriate counselling for both positive and negative clients and are integral components of overall HIV prevention, care and treatment efforts. Number of facilities providing HIV testing and counselling has increased to more than 100,000 in 2009, as per WHO compiled data from more than 100 countries (*www.who.int/hiv/topics/vct/data/en/*). The HIV testing and counselling (HTC) sites can be a part of the hospital or clinic setting, can be free-standing or in mobile vans to reach rural areas which otherwise will not have accessible testing. Recently, there is a drive to reach larger populations via house-hold based testing and counselling where nurses and counsellors team up to offer testing and counselling to multiple members of the same household. Staff performing the test should be well trained not only in the execution of the test but also in pre- and post-test steps that cover quality assurance measures to ensure accuracy of results and safety of the personnel.

The test kits in use should be approved by a stringent regulatory authority available in the country. The performance characteristics of the tests, not the cost alone, should drive the decision to use any particular HIV test kits. In some countries, the national algorithm is developed to further confirm all HIV reactive samples from EIA and rapid test with the Western blot. While this may add value to the quality of testing, the WB technology is expensive, time consuming, and may lead to some indeterminate results which further compound the diagnosis and challenge of improved turn around time[8]. Because of this, WB should be used to resolve cases of discordant results from ELISA or rapid testing particularly in circumstances where repeated sample draw and testing have not resolved this problem. Many countries have adopted two-test algorithm, without the use of WB for HIV diagnosis. It should be noted that alternative algorithms have been proposed in the United States that do not involve WB[9,10]. Although the positive predictive value (PPV) of two-test algorithm is good in high prevalence population, WHO recommends three-test serial algorithm in low prevalence population to increase PPV. However, this leads to additional challenges of procuring and stocking test kits that are not often used, especially at low volume testing sites.

The HIV diagnostic testing is usually performed in serial or parallel strategies that include two or more tests. WHO recommends serial algorithm in most situations to conserve resources and cost, especially if the prevalence of HIV is not high. However, parallel testing would be an acceptable option in a high prevalence and high volume situations to facilitate

rapid diagnosis. The additional cost of parallel testing is offset by added personnel time when conducting serial testing. Parallel testing should be routinely done when women present late during delivery to facilitate intervention and in emergency situations. Serial testing on the other hand poses other challenges since it may require the need to follow up participants for a second sample draw in case the first sample is positive particularly in circumstances where only a finger prick sample was collected.

It is important to ensure that there are provisions for referral services in all settings where HIV diagnosis is taking place. These include referrals for medical, mental health and social services for individuals receiving HIV-positive confirmatory test results. It is absolutely necessary that the national reference laboratory in developing countries should have capacity to support referral to provide these services for patients diagnosed at the national reference laboratory level and those referred from the various regional, provincial and community testing sites. For persons infected with HIV, routine monitoring of CD4 counts provides important information on their immune status, and may be used to determine the patient's treatments, response to therapy and disease progression. Also viral loads are a prognostic marker for disease progression and outcome of antiretroviral therapy. The presence of chemistry and haematology platforms are also very important as these provide valuable information particularly on organ functions, hence monitoring HIV viral load along with CD4 T-lymphocyte counts, chemistry and haematology parameters will allow physicians to determine the effectiveness of the antiviral therapy to suppress HIV-1 replication. It is recommended that there should be capacity for measuring these parameters at all referral centres. Different technologies are available for measuring these parameters; what matters most is the ability of the facility to afford the complex technologies, trained manpower and the availability of quality assurance systems in place to guarantee quality testing. More recently, cheaper, less complicated and user friendly point-of-care (POC) technologies have been evaluated and recommended for use in resource-limited settings[11,12]. It is suggested that referral settings with less capacity should consider using the POC testing platform. In fact, as laboratory support moves from the national to provincial and community levels, there is evidence that the ability to support complex testing platforms is weakened; hence the POC will be most useful at these levels.

Point-of-care (POC) testing

Developing countries continue to be home to more than half of the estimated 33 million people living with HIV and AIDS worldwide[13]. At the same time, they face substantial challenges in the provision of laboratory facilities to quickly diagnose and treat those infected with the pandemic. These challenges are usually at all levels of the tiered laboratory structure, though at varying degrees and would require solutions from different perspectives[14,15]. Therefore, it is important that the national public health laboratory of each developing country should be strengthened to serve the urban population and act as the referral centre for quality assurance and more complex testing. A greater proportion of the population in developing countries live in the rural and community settings with complete lack of laboratory infrastructure including a lack of electricity to support sophisticated equipment functioning and cold chain for reagents storage. When HIV testing services are available at the national level in developing countries, access is a huge challenge; this could be due to the unaffordable cost of these services on the part of the users, stigmatization of coming to the central laboratory for testing, long distances from the rural community where they live to the central laboratory, or complete unawareness on the need for them to know their HIV status[16].

Further, because of the long turn around time for release of HIV testing results, a significant proportion of the people being tested in developing countries do not return for their results, greatly affecting current efforts to scale up access to HIV diagnosis and treatment. Due to these challenges, it is strongly recommended that HIV testing at the community levels should consider the use of diagnostic tests which are user-friendly, simple to operate, and affordable. The POC platforms that are modern, accurate, reliable, as well as mobile techniques with highest quality and best performance, will be very suitable. Although earlier rapid tests required use of serum or plasma specimens, most rapid tests now can use whole (unprocessed) blood from finger prick. The pre-filter on the rapid testing device traps the cells allowing plasma to separate. There are more than 50 rapid tests in the market. It is important to select pre-qualified or validated tests[17]. Some rapid tests can also be performed with oral fluid (OF) specimens. Usually an absorbent pad is used to collect oral fluid (saliva) specimens and soaked into a buffer to release antibodies. OF based testing cannot only simplify testing but can reduce the biohazards associated with

finger prick and lancet that require disinfection/disposal of contaminated products.

The HIV and AIDS clinical monitoring POC for CD4, viral load, haematology and clinical chemistry have been evaluated and recommended for use in resource limited settings as well[11,12,16]. These systems have greatly revolutionized the monitoring of treatment for HIV/AIDS patients. Some are conducted in a disposable microfluid biochip in conjunction with portable analyzers. Their advantages over other technologies include clinical decisions made at point-of-care, test performed with minimal training, expensive equipment not required, intensive sample preparation and acquisition eliminated, reagent use minimized, thus reducing costs significantly. Also minimal blood volumes are used requiring minimal expertise and eliminating the risk of transporting potentially infectious materials. In addition, some of these are portable and battery operated; very suitable for rural settings where electricity is a major challenge.

The shift in HIV testing from the central laboratory to community testing in developing countries has not been welcomed from several levels; the laboratory staff who traditionally and over the years have been the only people involved with HIV testing see this either as a threat to their sole authority or as a means of rendering them unemployed. Secondly, existing policies in some countries allow point-of-care testing but results require further confirmation before a final diagnosis is made, especially in HIV positive cases. This is compounded by the introduction of task shifting to allow for lay counsellors, nurses or non-laboratorians to be involved in point-of-care testing. In Zimbabwe for example, the initial national policy mandated that HIV testing could be performed only by trained laboratory technicians. Following an evaluation that demonstrated the ability of trained nurse counsellors to correctly perform rapid HIV testing in the absence of supervision from laboratory technicians[18], a new policy was adopted that allowed non laboratory personnel to be trained and certified to perform rapid HIV testing. A similar evaluation of voluntary counselling and testing (VCT) counsellors in Botswana demonstrated that concordance among rapid tests in the algorithm was equivalent whether testing was performed by laboratory or non-laboratory personnel[19]. It is recommended that once HIV rapid testing is being implemented at sites, initial prospective data should quickly be collected and presented to policy makers to show evidence that results obtained are comparable to the EIA based algorithm. There is also a need for policy change to allow non-laboratorians to be involved in POC testing

Expansion of HIV testing

In the midst of in country's reluctance to accept point of care testing, are the private sectors, local non-governmental organizations, and international donor partners who see the need to introduce HIV rapid testing and scale up testing to the community and hard to reach populations[20,21]. This calls for the need for a more concerted action including donor harmonization and to implore a step-wise approach in the roll out of HIV rapid testing to the community as well as in the implementation of quality assurance programmes to ensure the quality of community HIV rapid testing.

It is recommended that government should organize a stakeholders meeting on HIV diagnosis. This should lead to more concrete discussions with the ultimate aim of forming a nationally recognized HIV testing committee or working group. This committee has generally been seen to play an important role in other settings particularly in creating more awareness, developing standard manuals and policies relating to HIV diagnosis including rapid testing, and assisting countries in evaluation/validation and proposing national testing algorithms. The next step should be for the committee to put in place guidelines for development of nationally accepted HIV testing algorithms to be used both at the central level for testing and confirmation, that will also serve as the gold standard as well as the point of care HIV rapid testing algorithm to be used in the community or at VCT sites.

Once the algorithm at the central or national laboratory is developed, the committee should embark on strategies to roll out HIV rapid testing or POC to the various provider initiated counselling and testing (PICT) or VCT sites. This should start with the identification and training of trainers (TOT) to help ensure rapid tests function as expected in settings of their intended use. The World Health Organization (WHO) has developed guidelines for country-based evaluation and implementation of rapid HIV testing, that advocate for the implementation of the algorithm with a system of continuous quality assurance that optimally includes training, supervision, and competency assessment of personnel who perform the tests; site visits to observe testing; and external quality assurance based on retesting a proportion of specimens by reference laboratories[22-25]. It is absolutely necessary that all these steps should be followed to ensure effective implementation. Proper

documentation to ensure compliance and capturing of data generated during this exercise is very important. Key documents would include standard operational procedures (SOPs) that cover all activities to be carried out at various testing sites, forms and records to include the HIV rapid testing and quality assurance logbooks for recording all test results and quality assurance activities[17]. There is also the need for a site assessment tool to be used to assess various sites to ensure that they are ready for rolling out HIV rapid testing and a procedural manual that clearly describes the entire process.

National Quality Assurance (QA) programme

Accuracy and reliability of diagnostics and clinical monitoring of testing is very critical to the success of HIV and AIDS programmes. The expanding HIV testing in developing countries has not kept pace with quality assurance (QA) programmes to monitor the performance of these tests, raising concerns about test accuracy. In order to ensure reliability and reduce errors to a minimum, a quality system that addresses all aspects of testing in the laboratory is essential. This involves the implementation of a quality system in all laboratories and testing sites, and should apply to all testing activities, including simple-to-perform or POC tests.

Because of a lack of trained manpower in developing countries, it is common to see testing laboratories using unqualified or untrained staff with minimal in house training and no certification to perform key laboratory tests meant for patient care. This should be strongly discouraged as it may constitute a significant source of laboratory errors. It is recommended that there should be well defined career profile and requirements for laboratory testing staff with adequate training, competency assessment and certificate programmes to guarantee the quality of results being released by laboratories. Staff's knowledge and awareness on the need to use equipment that are well maintained, strictly follow laboratory SOPs as stated, documentation, and participation in all QA programmes to include quality control (QC) and external quality assessment (EQA) is important.

Apart from running internal quality control (IQC) samples alongside the patient samples, it is very important that testing laboratories should also participate in EQA programmes that provide additional and external checks to the performance of the laboratory. EQA programmes operate through a combination of three approaches that include participation in external proficiency testing (PT) programmes, supervisory site visits by external experts, and retesting a subset of specimens in another competent laboratory or site at a higher level[12]. Considering the nature and complexity of EQA to include the need for follow up supervision to resolve non-conformances, it is recommended that countries should set up functional EQA programmes to be co-ordinated at the national level with the capacity to either produce or procure proficiency testing panels to distribute to the other laboratories.

One of the key challenges in running PT programmes in developing countries has been that of the cost and distribution to include the issues of maintaining cold chain, packaging and shipment with maximum safety to laboratory staff and people involved in the shipment exercise. To overcome these challenges, CDC recently developed the dried tube specimen (DTS) based PT that is simple to prepare and ship to testing sites to support HIV serology testing with maximum safety[17,26]. There are also the DTS and dried blood spot PT panels as well to support viral load testing and PCR-based early infant diagnosis, respectively, that national EQA programmes could use to support their menu. The National EQA programme may also have the additional responsibility of producing and distributing PT panels to add to these ones and to support other testing platforms such as haematology and clinical chemistry. Where they do not have capacity to produce these PT panels, they could procure from other international sources and ensure in country co-ordination in the distribution of panels, collection and analysis of results and feedback to laboratories with appropriate guidance based on their performance. A multifaceted approach to include enhanced communication at all levels is encouraged.

Need for Integrated Tiered Laboratory Network

Public health laboratories in developing countries should operate in a tiered network according to their capacity and location where laboratories with the most capacity usually located in the capital city are designated as the national reference laboratories that provide training and referral services to other laboratories with lesser capacities and located at the regional or provincial levels. Similarly these regional or provincial laboratories should provide referral services to the community level laboratories with much lesser capacity and sample volume.

Laboratory procedures such as ELISA, Western blot, CD4 and PCR require sophisticated equipment that should be routinely calibrated and maintained for optimal performance. Laboratory technicians using these equipments require high skills and should perform preventative maintenance. Molecular testing often requires separate areas in the laboratories for sample preparation, amplification and detection to prevent cross-contamination. In general, infrastructure and capabilities are inadequate at the lower level of laboratories to perform complex testing. This highlights the need to have a strong network of laboratories where clients and/or specimens can be referred to from low tier to higher level laboratories for more complex form of HIV testing (*e.g.* serology confirmation, CD4, early infant diagnosis, viral load). A laboratory network can provide a forum for national proficiency testing programme, training, update on availability of new technology or tests (*e.g.* new testing platform, oral fluid based testing, *etc.*), and annual meeting of laboratory professionals to exchange information; thus providing continuing education and competency enhancement. The network can also facilitate laboratory accreditation and help improve quality of testing in a gradual but systematic manner.

In general, the operation of most public health laboratories in developing countries do not follow this pattern giving room for laboratories with less capacity being unable to function well or carrying out tests that would otherwise have been referred to other levels. There is a need for the formation of a tiered network of testing facilities operating under common principles and procedures with a rational distribution of testing capacity. Such a network should include government-run and private units that are commonly integrated with hospitals and clinics, and clearly define different levels or tiers; depending on whether the tests are conducted in health centre facilities and whether the network includes reference laboratories. There is also a need to establish standardized test menus, service delivery and technology across the network to promote more efficient and cost-effective operation and management of the network.

A functional network should result in efficient communication across different levels of laboratories. This communication can be enhanced with a well-organized annual meeting of laboratory professionals at different levels. Training of laboratory technicians by national and regional reference laboratory in new and complex methodology or POC tools should be integral component of laboratory network.

Implementation of quality management system and accreditation

The procedures-activities, mechanisms, actions that a laboratory uses to achieve and demonstrate control over its operating system constitute the quality management system (QMS), while accreditation provides verification that laboratories are adhering to established quality and competence standards deemed necessary for accurate and reliable patient testing and the safety of staff and the environment. The implementation of sustainable QMS and laboratory accreditation has been a big challenge particularly in developing countries because of lack of resources[27]. This has negatively affected the quality of test results. Adherence to laboratory quality improvement standards and participation in accreditation programmes can improve operational efficiency and customer service and reduce rates of laboratory errors.

Generally, laboratories in developing settings have been under-resourced and marked by poor performance. This has fostered distrust in laboratory data among clinicians and helped to reinforce cycles of underinvestment in laboratory systems[15]. Because of these challenges particularly in resource limited settings, the outcome of the WHO and the U.S. Centers for Disease Control and Prevention (CDC) joint conference on laboratory quality systems (held in Lyon, France in April 2008), recommended that countries with limited resources consider taking a staged approach, where principal requirements for all are stated in the national laboratory standards as minimum requirements, while more advanced and national reference laboratories are encouraged to aim at meeting internationally accepted standards such as ISO 15189[28]. This declaration provides a framework to ensure that laboratories without adequate resources should adhere to minimum standards that guarantee the quality of their results. We greatly recommend that HIV testing laboratories in developing countries should have adequately budget and the minimum quality standards in their testing facilities are adhered to.

A staged approach implies that laboratories should develop strategies to facilitate the implementation of their quality systems. The step-wise approach in implementing QMS and laboratory accreditation has been shown to be very useful in several resource limited settings. One of such evidence based approaches is the CDC and WHO-Afro step-wise process for QMS and accreditation that has greatly improved laboratory systems in Africa[27]. This scheme enables laboratories

in resource-limited settings to have some level of QA and to eventually reach international standards (*e.g.* ISO 15189) in a step-wise manner and become accredited by national or regional accreditation bodies. HIV testing facilities in developing countries should consider using such approaches to strengthen their quality systems. Establishing affordable, scalable, and effective laboratory accreditation schemes to ensure quality of laboratory tests and bridging the gap between clinicians and laboratory experts on the use of test results is absolutely important.

Sustainability of testing processes in developing countries

Health systems sustainability is currently a serious challenge in developing countries. This has stemmed from the fact that either countries completely lack the resources or manpower to sustain the infrastructure and systems implemented or there are not enough advocates and buy in at the policy level on the need to plan and budget adequately to ensure long term sustainability. In general, laboratories in developing countries operate without any co-ordinated systems such as the establishment of laboratory strategic plans, tiered laboratory networks, referral and back-up systems, and training and career profiles for laboratory personnel[29]. It is recommended that HIV testing laboratories in developing countries should ensure that these systems are in place to ensure sustainability.

Recurrent challenges within testing laboratories in developing countries that must be considered and addressed include implementation of supply chain management systems (SCMS) to include procurement, reagent inventory and stock maintenance, cold chain and establishment of equipment service contracts to ensure uninterrupted, timely and quality testing[7]. Because of the financial involvement and benefits derived from SCMS, there seems to be an unending contention in developing countries among the laboratories and financial services of various institutions on who manages the SCMS; in general, where the laboratory does not have total control, SCMS challenges are usually huge. It is recommended that the laboratories should have total control over the management of the SCMS. Participation in external quality assurance programmes conducted by WHO and/or CDC is encouraged, particularly with the supply of the panels for HIV serology and DNA PCR for early infant diagnosis. Laboratories are minimally able to function through these programmes, however, their participation in other procured panels from commercial institutions to support other testing platforms still remains a challenge. This could also be addressed through the institution of a functional SCMS. It is recommended that testing facilities in developing countries should enroll and participate in the free of charge EQA programmes as well as address their needs to participate with other procured panels through their SCMS.

Other key issues include lack of capacity to recruit and retain staff as some developing countries either do not have the competent staff or key competent staff have left the country for better paying jobs. This in fact has left some laboratories in developing countries well equipped but without competent personnel to supervise and provide testing. Some of these challenges have come from the fact that these laboratories were established through donor funds without due consideration of in country capacity and structure to ensure long term sustainability; these traditionally stop functioning as soon as the funds dry up or the project comes to an end. It is suggested that before HIV testing is implemented in developing countries, there is a need to establish a laboratory operational budget that will clearly address the key operational issues including staff retention and source of funding by all interested parties. Where donor funds are involved, the governments or institutions should work out a long-term sustainability plan beyond the life of the funds to ensure uninterrupted testing; in fact a co-ordinated partnership between the private and public health sector (public-private partnership) is needed to achieve long-term sustainability. There is also the need for laboratories to consider the use of point-of-care testing that is inexpensive and simple to operate, particularly in situations where there is no evidence of long-term sustainability of more complex platforms.

Conclusions

HIV testing technologies in developing countries range from complex methods to simple POC testing platforms. Continued support of HIV testing in developing countries and adoption of appropriate POC technologies, in support of HIV programmes (prevention, care, treatment, and surveillance), will be critical to turn the tide of HIV pandemic. Quality assurance, including proficiency testing programmes, should be an integral component of all forms of testing to ensure confidence in laboratory results and improve patient care, including programme outcome. Development of a functional laboratory network that facilitates communication, referral testing, training and quality improvement among laboratories and testing sites would be important for overall improvement of laboratory services beyond HIV.

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