

Scale-up of Routine Viral Load Testing in Resource-Poor Settings: Current and Future Implementation Challenges

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Despite immense progress in antiretroviral therapy (ART) scale-up, many people still lack access to basic standards of care, with our ability to meet the Joint United Nations Programme on HIV/AIDS 90-90-90 treatment targets for HIV/AIDS dependent on dramatic improvements in diagnostics. The World Health Organization recommends routine monitoring of ART effectiveness using viral load (VL) testing at 6 months and every 12 months, to monitor treatment adherence and minimize failure, and will publish its VL toolkit later this year. However, the cost and complexity of VL is preventing scale-up beyond developed countries and there is a lack of awareness among clinicians as to the long-term patient benefits and its role in prolonging the longevity of treatment programs. With developments in this diagnostic field rapidly evolving—including the recent improvements for accurately using dried blood spots and the imminent appearance to the market of point-of-care technologies offering decentralized diagnosis—we describe current barriers to VL testing in resource-limited settings. Effective scale-up can be achieved through health system and laboratory system strengthening and test price reductions, as well as tackling multiple programmatic and funding challenges.

Keywords. viral load; virological; resource-limited settings; antiretroviral therapy; monitoring.

Immense progress in the scale-up of antiretroviral therapy (ART) has been made over the past decade in low- and middle-income countries (LMICs), with 15 million people now receiving life-saving treatment. However, many still lack optimized standards of care. Revised World Health Organization (WHO) treatment guidelines [1, 2]—which recommend starting treatment earlier—have intensified the need for more effective treatment monitoring and adherence support to reduce morbidity and mortality and to prevent new infections, with improvements in diagnostic capacity therefore a key component of scale-up. Indeed our ability to meet 2 of 3 of the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 treatment targets for HIV/AIDS depends on diagnostics (<http://www.unaids.org/en/resources/documents/2014/90-90-90>).

Viral load (VL) testing is the gold standard in human immunodeficiency virus (HIV) treatment monitoring and ensures widespread and well-established benefits in terms of the timely monitoring of treatment adherence and efficacy, and in diagnosing and minimizing treatment failure in those on ART [3–6]. WHO recommends that all LMICs phase in VL monitoring,

testing all patients at 6 months after ART initiation, and then at least every 12 months [1, 2]. This approach aims to ensure early indication of when enhanced adherence support is needed and when a person needs a treatment switch. Because most countries can only afford to offer first- and second-line ART, this represents an important step toward achieving equity in treatment approaches in developed and developing countries. An international VL implementation task force, led by the Diagnostics Access Initiative members, has developed a VL toolkit aimed at guiding ART programs to scale up VL testing, which was released in draft form this year. Other toolkits and guidance are already in circulation to support clinical decision making (<http://samumfsf.org/blog/portfolio-item/viral-load-vl-toolkit/>) [7]. Use of VL testing will prolong the use of first-line regimens, preventing drug resistance from developing, and thus ensuring the longevity of treatment programs globally [5]. Advantageously, it also requires that clinicians see patients less often because treatment monitoring can be simplified to an annual clinical visit for those who are virally suppressed, reducing visit burden on both patients and healthcare workers [6, 8].

Despite widespread and routine use of VL testing in wealthy countries, its cost and complexity, among other issues, have presented major barriers to its scale-up and use in LMICs (<http://samumfsf.org/blog/portfolio-item/viral-load-vl-toolkit/>) [6, 9–11]. Where VL testing does exist, a lack of awareness among both clinicians and patients as to the importance and benefits of VL testing means it may be underused.

Yet developments in the field of diagnostics are rapidly evolving [12]. Newer laboratory-based tests are becoming increasingly automated, reducing the level of laboratory infrastructure,

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skill, and hands-on time required, and there have been rapid developments in implementation of dried blood spots (DBSs) for sample transportation and point-of-care (POC) technologies that are designed to be simple to use and can be performed by any healthcare worker, thus decentralizing VL testing [10]. In this Viewpoint, we discuss the current status quo globally with regard to implementation of VL testing in LMICs, summarize the latest technological advances, and address current and future programmatic and pricing challenges in global scale-up.

IMPLEMENTATION TO DATE: A LONG WAY TO GO

Routine VL testing is not yet widely available globally, with some countries still not recommending routine VL testing at all in their national guidelines, or recommending it only in the case of suspected treatment failure (Médecins Sans Frontières [MSF] Access Campaign: <http://msfaccess.org/HIV-HCV-diagnostic-product-guide-2015>) [13]. The latest implementation data show access to VL testing to be highly variable—mostly severely limited—with considerable variations in the approaches to monitoring encountered (MSF Access Campaign) [13, 14]. Information compiled from the International Association of Providers of AIDS Care database show that although 47 of 54 LMICs have guidelines in line with latest WHO recommendations to ensure routine VL testing, the reality is that only a handful are implementing VL testing (MSF Access Campaign: <http://msfaccess.org/HIV-HCV-diagnostic-product-guide-2015>). Six countries recommend VL testing only in the case of suspected treatment failure: mandatory in Morocco, Myanmar, and South Sudan (if the test is available), and optional in Haiti, India, and Zimbabwe. India and Zimbabwe only recommend targeted VL testing and it is only optional to confirm treatment failure. Most countries are also still recommending routine immunological treatment monitoring, with only 8 countries reporting that they have dropped routine CD4 testing post-ART initiation (Cameroon, Kenya, Malawi, Namibia, South Africa, Swaziland, Thailand, and Uganda).

A recent survey by WHO [15] targeting 122 LMICs found that only 20% of ART patients receive VL testing. In the LMICs surveyed, there were only 2 VL instruments, on average, per 8706 people on ART, with 10% of these machines not in operation because they had not yet been installed or required repair, or due to lack of reagents and the absence of staff training. Findings from an in-depth qualitative survey of experts based in India, Kenya, Malawi, South Africa, and Zimbabwe (March–May 2014 [14]) found that in Malawi, with >400 000 patients on ART, only 37 000 received a VL test in 1 year (2013 data [14]). This suggests that VL implementation currently falls well short of guidelines and limits the public health impact of these programs [1, 2]. Respondents cited financial constraints as a key reason for incomplete or slow implementation [14]. In addition, insufficient and overburdened healthcare professionals, poor training and lack of knowledge, and weak

transport and laboratory systems were all considered barriers to scale-up of VL testing [11, 16–18]. Furthermore, access to testing is higher in central and urban areas compared with more remote areas [16, 17]. LMICs, however, have strong ambitions to expand VL testing, with many countries having scale-up plans in place. India now plans to expand from 9 to 30 laboratories with VL testing capacity. These countries face immense funding and implementation hurdles that may mean it is hard to put new guidelines into practice. Many of these same barriers were documented with CD4 and early infant diagnostic (EID) scale-up, and those involved in VL scale-up should consider the lessons learned [16–19]. Countries were able to improve coverage using various models, such as the hub-and-spoke system [19]. Although there has been significant expansion in CD4 and EID capacity in resource-poor settings, this does not always translate to access, particularly for lower-level health facilities. Also, turn-around time and loss of samples or results remain problematic [20], and more work is needed in this area.

CURRENT VL TESTS AVAILABLE AND IN THE PIPELINE

Several promising laboratory-based VL technologies and simple POC tests are expected to become available soon for use in LMICs [5, 12, 21]. POC testing will not necessarily be a magic bullet and will most likely complement—not replace—conventional testing platforms. One of the key problems with current POC tests is that most of them are still plasma based for VL testing, which is inconvenient due to the continued need for trained phlebotomists and electrical centrifuges for plasma separation, both limited in LMICs. POC implementation will still require training of staff, implementation of quality control mechanisms, and operational research to assess POC performance and the benefits of POC testing over and above conventional testing.

Context-based decisions will need to be made in terms of whether to use decentralized POC tests, or centralized DBS-based laboratory tests. One survey found that across LMICs, VL laboratory-based technology performed an average of 5 tests (range, 1–191) per machine per day, despite most platforms having a nominal capacity of at least 90 tests per day, suggesting that VL technology faces the double challenge of limited numbers of VL tests due to high reagent costs and costs per test being considerably higher than they would be if platforms were efficiently used [15]. Decisions on where to place VL testing must take several factors into account, including patient volume and characteristics (eg, to what degree transient, remote, or stigmatized populations are linked to the healthcare system); cost per test and anticipated levels of instrument usage, which can yield different cost efficiencies; human resource skill level and task-shifting policies and consequences; and the time to a results-based intervention [13]. Throughput needs should also take into account likely scale-up of diagnostics in the immediate future. Laboratory-based VL testing may make more sense, for

example, in high-prevalence settings with existing sample transport systems, particularly if people are already enrolled in care and the aim of the VL test is to confirm that treatment is working effectively.

In other contexts, POC testing will be an important catalyst in promoting adoption of VL, ensuring better patient outcomes, and enabling vulnerable patient groups and those in rural areas to be reached more effectively. However, careful consideration will need to be given to ensuring quality control and performing cost-effectiveness analysis of true POC testing, and operational research to assess which technologies could be adapted to which contexts is needed [22–24]. If countries are to better optimize the mix of POC and laboratory-based tools, they will need to increase the functioning of their referral networks, including sample and results delivery (to clinics and patients) through preexisting referral networks and other electronic and mobile solutions [25, 26]. This will not only decrease the cost per result through reduced transport costs and reductions in missing data, but also improve service delivery by providing rapid results and better linkage to care. The Global Fund's Procurement Strategy for VL and EID now places a welcome emphasis on supporting significant investments in laboratory systems and sample transport networks and people (<http://www.theglobalfund.org/en/procurement/viral-load-early-infant-diagnostics/>).

HOW LOW CAN WE GO: DECREASING PRICES

Although prices have continued to come down for VL testing, with the entry of new products and manufacturers to the market, there is still considerable room for price decreases and numerous price-decreasing mechanisms that could and should be adopted [27]. The market is still dominated by a handful of suppliers [15], and incentives and/or procurement flexibility will be needed to ensure new manufacturers can enter the market to drive prices down. There remains a considerable gap between the real costs of manufacture and the actual prices paid by countries for reagents and consumables—as well as shipment, customs charges, tax, service, and maintenance, etc—demonstrating the potential for further price decreases. One study found that the costs associated with intellectual property are significant, with royalty payments for some VL technologies accounting for a considerable portion (19%–63%) of the total manufacturing costs [21]. Intellectual property should, ideally, be licensed at low or no cost when the final products are sold to LMICs, and any cost saving should be passed on to purchasers. Global health actors will need to better support strategies, such as pooling patents from third parties, royalty-free patents, or reasonable royalties, to ensure affordability.

What remains clear is that there are major pricing discrepancies globally. An analysis from the Global Fund's Price and Quality Reporting Tool found that VL reagent costs alone varied from \$13.13 to \$43.34 between countries [13]. Publicly available data put the costs for reagents and consumables

negotiated by the Clinton Health Access Initiative in Kenya at only US\$10.50 per test, suggesting considerable flexibility on price and the need for greater transparency between governments and other purchasers to ensure that more programs are able to access the best prices. In high-volume situations, donors and affected governments should encourage competition between contractors and negotiate for lower prices (including for maintenance) and better services. In Brazil, Kenya, and South Africa, for example, as a result of competition at the tendering stage and negotiation, the selling price per laboratory-based test has now dropped to around US\$10.00, which includes the cost of instrument rental and service and maintenance (although not human resources or transport services). The South African tender also included provisions to create a global price ceiling, which allows 83 countries to access one company's reagents for <\$9.40 per test (<http://www.theglobalfund.org/en/procurement/viral-load-early-infant-diagnostics/>). As an extension of this price ceiling, Roche Molecular Diagnostics offers ex-works pricing for both VL and EID at \$9.40 per test, including reagents and proprietary consumables, for LMICs eligible under their Global Access Programme (http://molecular.roche.com/GlobalAccessProgram/Documents/GAP_Country_List_15July2015.pdf).

Furthermore, moving to pooled procurement and to instrument rental options rather than purchasing expensive equipment that does not allow for flexibility in platform choice in the future are options that ensure better prices and service agreements for LMICs. For example, the Global Fund, the US President's Emergency Fund for AIDS Relief, and high-volume countries such as South Africa currently have the opportunity to pool volumes, which will increase purchasing power, allow for more attractive split tenders, and result in lower prices. Future tenders should include the option for manufacturers of polyvalent platforms to submit bundled pricing discounts across disease testing platforms (tuberculosis, HIV, hepatitis B virus, and hepatitis C virus, etc), as Abbott Molecular has done in the recent Global Fund tender, and the tender criteria should be transparent. Last, negotiations with manufacturers for large volumes, optimizing throughput (efficiency) of each instrument, and considering the use of open, multimanufacturer platforms to further stimulate choice and competition, should further reduce the cost per test [27]. It will be useful for manufacturers to have 18-month forecasting estimates to be able to better plan manufacturing need and improve efficiency and, therefore, more easily offer price reductions. Driving down the costs of reagents and consumables offers the greatest potential for overall VL cost reductions, contributing to >60% of VL testing costs according to a comprehensive costing survey across sites in 6 countries (Kenya, Thailand, Lesotho, Malawi, Swaziland, and Zimbabwe) [28]. These fully loaded costs ranged from \$21.56 to \$44.07 and included costs attributed to human resources, sample collection, reagents and consumables,

Table 1. Challenges and Solutions in Viral Load Implementation

Challenges	Proposed Solutions
Poor adherence to current WHO guidelines on VL testing	Countries should incorporate routine VL monitoring into their national guidelines and may need external support to do this
Funding shortfalls for routine VL monitoring scale-up	Donors and national governments must prioritize VL testing and scale-up in their budgets
High costs for VL tests, reagents, and consumables	Decrease the cost of products through a variety of mechanisms (eg, pooled procurement, competition, negotiation, and pricing transparency)
Weak health and laboratory systems in low- and middle-income countries	Strengthen health and laboratory systems globally, addressing human resource and training issues: 15% of an HIV program budget should be earmarked for laboratory/diagnostics
Weak transport systems and networks for delivering results	Strengthen these systems, using approaches such as e- and m-health solutions, and more convenient sample strategies such as dried blood spots
Low levels of staff training and quality assurance	Laboratories should work toward becoming accredited, such as via the Stepwise Laboratory Improvement Process Towards Accreditation program ^a , and follow the new WHO guidelines on ensuring the quality of HIV-related POC testing, ^b and implement quality assurance/quality control and proficiency testing
Lack of awareness among patients and clinicians as to the benefits of VL testing	Education empowerment work, adopting community-centric strategies
Lack of civil society mobilization on the issue of VL testing and access to diagnostics	Encourage their involvement in advocating for rapid and appropriate scale-up of VL testing, adopting lessons learned from antiretroviral therapy scale-up
Poor awareness among program managers as to the wider benefits of VL scale-up to health-system strengthening and cost reduction	(i) Program managers should consider polyvalent technologies to enable testing for multiple disease and bundled pricing, and multimanager platforms sourcing products from multiple suppliers to bring costs down through competition (ii) Program managers should consider a leasing or reagent rental option and bundled pricing across diseases, to allow flexibility to adopt newer and more efficient technologies as and when they come to the market and to ensure all-inclusive services, and bundled pricing across diseases to leverage price gains made for HIV
Limited local and national guidance on supporting patients with a low VL	Introduce community-centric models of care that allow people to receive treatment in the community and not visit the clinic more than once a year.
Centralized or decentralized?	When deciding between a centralized laboratory-based approach and a decentralized or near-POC approach, take several factors into account, including patient volume and characteristics, cost per test, throughput per site, anticipated levels of instrument usage, human resource skill level, and task-shifting policies
Could a phased implementation approach be an option?	Yes, for example using VL testing on selected higher-risk populations. This is considered to represent suboptimal use of VL testing but could be considered to kick-start scale-up

Abbreviations: HIV, human immunodeficiency virus; POC, point-of-care; VL, viral load; WHO, World Health Organization.

^a Available at: <http://www.afro.who.int/en/clusters-a-programmes/hss/blood-safety-laboratories-a-health-technology/blt-highlights/3859-who-guide-for-the-stepwise-laboratory-improvement-process-towards-accreditation-in-the-african-region-with-checklist.html>.

^b Source: WHO and US Centers for Disease Control and Prevention. Handbook for improving the quality of HIV-related point-of-care testing. Ensuring the reliability and accuracy of test results. In press.

equipment, laboratory, quality control, results delivery, and costs due to machine failures [28].

PROGRAMMATIC CHALLENGES REMAIN

What is now clear is that diagnosis and monitoring is key to early and accurate disease detection and ensuring treatment efficiency, and thus our ability to tackle HIV/AIDS in LMICs (<http://www.unaids.org/en/resources/documents/2014/90-90-90>). In our view, Governments should be looking at allocating up to 15% of total HIV program budget on facility-level costs that should go toward laboratory testing, including training and support for laboratory personnel.

Of key importance is the need for governments and donors to prioritize the strengthening of health and laboratory systems globally [10, 15]. Maintaining a strong workforce, training them in delivering new tests and task shifting—policies that allow nonphysicians, including nurses and trained lay workers to administer testing and treatment—is a crucial first step.

MSF's survey highlighted that all 5 countries reported insufficient personnel availability, with overburdened and inadequate numbers of healthcare professionals in front-line facilities, as well as insufficient training and a lack of up-to-date knowledge [14]. Sufficient laboratory technicians must be trained if we are to increase capacity.

Investments in VL sample transport, laboratory tools, reporting tools, databases, and human resources can be leveraged to benefit other diseases too, accelerating diagnostic access overall and health systems strengthening [7, 28]. As countries consider which platforms to select, polyvalency—the capacity to run assays for other diseases on the same platform—should be considered. This approach reduces overall large upfront costs, because a different machine does not need to be purchased or rented for each different disease, and facilitates standardized human resource training, service and maintenance, and procurement [28]. Program managers should consider a leasing or reagent rental option, to allow flexibility to adopt newer and more

efficient technologies as and when they come to the market and to ensure an all-inclusive contract.

Improving sample transport—for example, by strengthening transport networks—to ensure the prompt delivery of results to people is also crucial. The use of DBSs has greatly simplified sample transport to the laboratory from remote sites, and new advances in DBS technology will undoubtedly increase accuracy [7,29]. Despite the fact that more data are needed to inform next steps to scaling up DBS at the present time, what is clear is that in many current settings DBS is the only option for ensuring scale-up of VL testing. Use of pooled samples, whereby DBS samples (either via a fingerprick or phlebotomy) from multiple people (eg, minipools of 5 samples) are mixed together and 1 test is conducted on the pooled sample, has been shown in several studies to reduce costs related to VL monitoring, particularly where a high percentage of patients' VL is suppressed [29]. In Malawi, using a cost of US\$30 per VL, DBS pooling reduced the number of tests performed by 30%, saving \$207 000 per year. As prices for VL testing continue to drop, the cost-effectiveness of pooling samples may decline. Pooling is only useful if it saves money, so countries will need to make their own decisions according to test volume and failure rate.

Where it is not feasible to fully introduce routine VL testing, a phased implementation approach could be a positive first step in facilitating logistical and technical laboratory capacity, and could be established before widespread scale-up [6,8]. One possible approach is to prioritize particular higher-risk patients—for example, to use VL just to confirm clinical or immunological treatment failure before switching ART—or to perform routine VL specifically for children and adolescents, or pregnant and breastfeeding women. Although these approaches represent suboptimal use of VL testing, they allow phasing in of VL testing while capacity is built for universal access to routine monitoring.

Last, programs need to consider an education and counseling component, because VL testing can function as a motivator for adherence [30] and informed patients can further create a demand for VL testing.

CONCLUSIONS

Recent years have seen increased and welcomed commitment toward improving both the quality and outcomes of ART programs, with data showing that it is both medically important and operationally feasible to implement VL testing in LMICs. There have been calls to divert funds from CD4 testing to VL testing [31,32]; treatment initiation for all HIV-infected people has now been recommended by WHO in its 2015 guidelines, in response to the recent Strategic Timing of AntiRetroviral Treatment trial results [33], continuing preferably with routine VL monitoring but with CD4 testing now reserved for measuring immunosuppression to inform the need for prophylaxis and to screen for opportunistic infections. Table 1 summarizes key next steps in the global implementation of VL testing.

What is now becoming clear is that VL testing has numerous cost benefits for HIV programs, facilitating a reduced number of clinical contacts and opportunities for further task shifting, as well as reducing the cost of drugs by preserving first-line ART and reducing transmission [34,35]. VL monitoring integrated with intensive adherence support programs has been shown to be successful in increasing adherence to ART, thus preventing a treatment switch [3,36]. Additional research is needed to optimize the package of adherence support and visit spacing linked with routine VL monitoring. Training for clinicians, to be better able to provide optimal care, as well as people living with HIV/AIDS to know how to best monitor their health, is increasingly becoming important. Since civil society have advocated for many of the most important tools and policies that have improved the HIV response globally, their voice will now be more important than ever in demonstrating demand and ensuring the rapid and appropriate scale-up of VL testing.

Notes

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