SUPPLEMENT ARTICLE

Patient Needs and Point-of-Care Requirements for HIV Load Testing in Resource-Limited Settings

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Medecins Sans Frontieres (MSF) is an international, independent medical nongovernmental organization. One way in which MSF acts to improve patient care is to assist in the identification and development of adapted and appropriate tools for use in resource-limited settings. One strategy to achieve this goal is through active collaborations with scientists and developers, to make some of the field needs known and to help define the medical strategy behind the implementation of new diagnostic tests. Tests used in the field need to be effective in often extreme conditions and must also deliver high-quality, reliable results that can be used in the local context. In this article, we discuss some patient and health care provider needs for human immunodeficiency virus (HIV) load measurement in resource-limited settings. This is just one of the areas in which effective, quality tools are desperately needed, not only by MSF and other international nongovernmental organizations, but also by many other health service providers. We hope that, by clearly defining the needs of patients in MSF clinics—as well as we can assess this—and by explaining why these tools are needed, how they should perform, and how their results can be integrated into a program, we will encourage the development of such tools and hasten their implementation in areas where they are so urgently needed.

VIRAL LOAD TESTS

Why test viral load? Viral load testing can be used to diagnose human immunodeficiency virus (HIV) infection in infants (age, <18 months). A nucleic acid test is required to distinguish between the children who have residual circulating antibodies from their mother and those who are infected with HIV. Polymerase chain reaction (PCR) techniques using dry blood spots have been shown to be accurate, reproducible, and feasible in resource-limited settings [1, 2], but routine implementation has been challenging, because many logistical issues must be addressed, such as sending the sample, receiving the results, and identifying suitable laboratories to perform the testing. A point-of-care (POC) viral load test would help reduce or remove these constraints.

Detection of HIV RNA in infants is usually technically easier than such detection in adults, because viral load is typically very high (>100,000 copies/mL) and the test results do not need to be quantitative. A simple "yes/no" test with a detection threshold of 1000 copies/mL in whole blood samples has been proposed [3].

Viral load is also frequently used to monitor treatment efficacy. In well-resourced settings, viral load measurement every 3–6 months is considered to be the standard of care [4]. The information is used to assess treatment efficacy and adherence and to help in the decision about when to switch to a different, more potent regimen. Although, to date, the World Health Organization does not recommend routine use of viral load testing in resource-limited settings, new 2006 guidelines recognize that "CD4 and plasma HIV-1 RNA testing are not luxuries. They are important tools supporting the delivery of optimal care and, in the setting

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of the public health approach, are invaluable measures of programme monitoring and performance" [5, p 81].

The best way to use viral load information in a context in which therapeutic options are limited has not been fully determined. In resource-rich settings, treatment involves intensive virological suppressive strategies supported by routine use of viral load measurement and unrestricted access to antiretroviral therapy. Clearly, this strategy is not transposable to resource-constrained settings. For a combination of financial, logistical, and human resource–related reasons, most settings cannot perform viral load testing at the present time. Current technologies are very expensive and require delicate instruments, cold chain, and stable electricity, which are not available in areas where the majority of the patients reside. Samples can be shipped; the samples must be received rapidly by the reference laboratory, and many countries have few or no laboratories with the ability to perform testing. In many settings, shipping of samples is not possible and is always a logistical challenge. Because of the challenges in implementing the simpler and better characterized dry spot technique for infant diagnosis, shipping of samples for viral load is unlikely to be feasible or widely used. In addition, the lack of human resources to evaluate and provide treatment for the overwhelming number of patients needing HIV care means that services, when available, are often strained to their limit.

However, in the context of patients receiving chronic, lifelong treatment, often in precarious economic, social, or political conditions, which make adherence or program stability challenging [6], and in settings where therapeutic options are limited, the use of viral load testing is increasingly considered to be critical in establishing whether a patient needs a therapy change [7]. Several monitoring strategies are now being explored that use $CD4^+$ T cell count in combination with clinical and biochemical markers, but these have shown poor predictability of treatment failure. The consensus remains that optimal treatment for patients requires both $CD4^+$ T cell count and viral load measurements [3]. Some researchers have even argued that viral load is of more critical importance than is $CD4^+$ T cell count [8]. Moreover, in settings where human resources are limited, knowledge of a patient's viral load allows the health care provider to perform a "triage," dedicate more time to patients with moderate-to-high viral loads, and refer patients with consistently suppressed HIV RNA to lay counsellors. Patients with elevated viral load early after treatment initiation could be targeted for intensive adherence counselling, preserving the use of the first-line therapy.

Use of viral load testing is further complicated by the limited treatment options available in resource-limited settings. Because viral load tests remain expensive and because of the significantly higher cost of second-line drugs, many programs in developing countries are hesitant to use viral load testing. The use of viral load testing and its integration into patient care is not simple or clear: the number of tests and frequency of testing, the threshold for switching to second-line treatment, and the clinically optimal level of viral suppression need to be analyzed using retrospective cohort data. Care must be taken in designing these studies so that they involve HIV subtypes endemic in the populations, rather than using results of studies performed in other settings or investigating other subtypes.

Viral load testing for adults receiving antiretroviral treatment should not only be seen as addressing when to switch therapy, it should also be considered as a way to decide not to unnecessarily modify a first-line regimen in the context of concomitant infection or $CD4^+$ T cell count decreases, which are usually thought to be poor surrogate markers for treatment failure. Indeed, studies have shown that ~50% of patients who would have had therapy switched on the basis of $CD4^+$ T cell count and clinical condition (as recommended by the World Health Organization) have, in fact, fully suppressed HIV RNA [3].

It is generally accepted that viral load testing is especially important in at least 2 situations: (1) to confirm viral suppression in pregnant women to lower the risk of mother-to-child transmission and (2) in diagnosis during infancy in countries with a high prevalence of HIV infection. However, if a simple, low-cost, and reliable viral load test existed that could be used in countries with a high burden of HIV infection, integration of the test into routine patient care would improve the management of HIV infection, and use of the test in other contexts could be broadened.

Existing viral load technologies in resource-limited settings. Because of the level of sophistication required for viral load measurement, most resource-limited settings do not have access to suitable facilities in the locations where they would be most needed. In remote laboratories, setting up, running, and servicing of simplified machines for $CD4^+$ T cell count measurement are already significant challenges, even in provincial hospitals, leaving machines for viral load measurement almost totally absent from routine equipment lists. Because the medical demand for viral load testing for follow-up of patients is increasing rapidly, some facilities choose to contract out the testing to local laboratories that are sufficiently equipped and supported mostly by overseas academic institutions. This has been the case for MSF projects in such countries as South Africa, Cameroon, Cambodia, and Thailand.

Storage and transportation of samples is still a problem, as are delays for answers from overloaded laboratories. Such qualified laboratories are not available in all settings, and for the most part, viral load testing is simply not feasible under existing conditions. In addition to the high prices charged, it is often difficult to obtain precise and reliable information about the quality assurance procedures implemented in many laboratories, and the reliability of the results can be questionable. In-

ternationally recommended quality assurance procedures (such as those promoted by the World Health Organization) have been sometimes found not to be robust and comprehensive enough for unsupported laboratories [9]. Reagents and equipment are often lacking or expired because of the challenges of ensuring regular and adequate provision of the necessary items. Existing viral load technologies are poorly adapted for use in most resource-limited settings. All of the 4 frequently used systems in high-income countries—the Abbott real-time HIV-1 PCR assay, the Bayer Versant HIV-1 RNA assay (version 3.0; bDNA), the bioMérieux NucliSENS HIV-1QT assay (nucleic acid sequence–based amplification), and the Roche Amplicor HIV-1 Monitor assay (version 1.5; reverse-transcription PCR)—require sensitive equipment, highly trained staff, and good infrastructure, monitoring, and support (Table 1); these conditions are lacking in most countries with a high burden of HIV infection. Moreover, the accuracy of these tests for detection of non-B subtypes has been questioned [10, 11].

Field-appropriate viral load tests: POC and other strategies. How can appropriate, high-quality test results be provided in the most cost-effective way possible? One class of solution is the POC test. POC tests are diagnostic tests that are performed near the patient.

POC tests have the advantage of requiring less laboratory infrastructure, are potentially cheaper, and can be designed to be simple and easy to use and interpret. The quick result and low laboratory burden can help reduce the workload for laboratories and streamline care in settings where large numbers of patients are treated daily. However, in addition to improving the standard of care, a test that can be performed while the patient is at the clinic means that fewer patients are lost to follow-up, and the burden on patients is reduced.

Regardless of the technology solution chosen, the test must perform in local conditions (eg, heat, humidity, dust, and possible lack of laboratory, running water, or electricity) and not be simply imported from resource-rich settings and force-fit to local conditions for want of a better solution. Another important characteristic is that the tools are appropriate to clinical decision making. This means that they deliver a result that is useful for the health care provider to use in making clinical decisions and not results that are ambiguous or unnecessary. Current practice in resource-rich settings is to maintain an

Table 1. Specifications of Current Viral Load Technologies

Specification	Desirable	Acceptable	Current state of the art[a]
Specialized laboratory facilities	No	No	Required
Closed system: amplicon containment to prevent contamination	Yes	Yes	Some
Shelf life	18 Months at 37°C	12 Months at 30°C	3–18 Months at −80°C to 4°C
Cold chain transportation	No	No	Required
Refrigerated storage	No	No	Required
Ease of use			
Sample preparation	Integrated	Stand-alone (<8 steps)	…
No. of steps	<5	<10	>30
Total assay time, h	<2	<3	4–22
Training time	<1 day	<2 days	>1 week
Precision pipetting	No	No	Required
Additional reagents and disposables	No	No	Required
Sample type	Whole blood and plasma	Whole blood and plasma	Plasma and dried blood spots
Lower limit of sensitivity, copies/mL			
Heel or finger prick	1000	4000	Not available
Plasma	500	2000	400
Manufacturing cost per test, US$	<10	<12	Not applicable
Cost per test, US$	Not available	Not available	30–200
Manufacturing cost of equipment for amplification and detection (dipstick reader included; sample preparation optional), US$	<1000	<2000	Not available
Equipment cost, US$	Not applicable	Not applicable	15–60,000
Product licensing			
Qualitative assay	CE mark	CE mark	CE mark and/or FDA approval
Semiquantitative assay	CE mark	WHO, UNDP	CE mark and/or FDA approval

NOTE. FDA, Food and Drug Administration; UNDP, United Nations Development Programme; WHO, World Health Organization.

[a] Currently available HIV nucleic acid–based tests.

undetectable viral load in patients. However, the threshold for undetectable differs depending on the sensitivity of the test used, and the true clinical significance of the viral load information continues to be debated [12–14].

The choice of a cutoff value may depend on the clinical use. The threshold chosen for a switch to second-line therapy has to be specific (eg, switch therapy for all those who need it), whereas a threshold to assess good treatment efficacy despite confounding clinical events or shortly after treatment initiation has to be set very low, to detect problems with treatment adherence. In addition, natural variation in the body can result in a peak of viral load in a single test, implying that repeated viral load testing may be required [13, 15, 16].

Viral load testing: programmatic issues. As experience in running HIV programs increases, MSF has identified a number of contexts in which patients' needs should influence the design of testing strategies and technologies. Some of the undecided clinical and operational issues are:

- Routine viral load testing or testing triggered by a clinical event or immunological failure
- How often should the test be performed? This impacts on the workload at the health care facility or clinic and the overall cost of the program and must be determined in conjunction with the medical program
- How to integrate viral load in the complex algorithm of the decision about when to switch therapy
- The availability of second-line drugs
- Where will patients be followed up and where are the tests to be performed?
- What cost a program can bear relative to the cost of shipping samples or of not offering viral load testing
- Should viral load testing be performed routinely after initiation of antiretroviral therapy to monitor adherence? Is testing only necessary to assess failure based on clinical or immunological grounds?

There is also a crucial but often underappreciated need to prepare the end users and health care systems for emerging tests to ensure good uptake. For example, the introduction of semiquantitative or qualitative viral load testing will require training, information, and follow-up, as well as implementation strategies, pilot projects, and operational research. The development of a test for triage could decrease the time to administration of treatment to the individual patient and significantly reduce the burden on overextended health care systems.

THINKING AHEAD

The international community is well aware of the extent of the HIV epidemic and the urgency for action, and this effort has to be sustained. Can we imagine other models to address this unprecedented global emergency, such as home-based viral load testing, analogous to current diabetes home testing, or community centers with reflex referral? In this reflection, we need to consider the target populations based on the medical needs: how often is testing really necessary? Sustainability is crucial, and solutions that use local resources or develop open-source or adaptable technologies should be favored over commercial solutions. Designing a comprehensive strategy including provision for scale-up, decentralization, and triage would be made significantly easier if such a test was available, even if the test had relatively low sensitivity.

GETTING AHEAD OF THE CURVE

We need to develop technologies to drive better patient care. A POC viral load test is a first step, but we can already aim for a test that would provide not only HIV RNA levels but also the presence or absence of key mutations. Key drug resistance mutations develop when ongoing viral replication occurs under the pressure of drugs. The information provided by such a test will then have a dual purpose if (1) a patient has a detectable HIV RNA level and is infected with virus with a drug resistance mutation (adherence is likely to be good, but treatment is failing), (2) a patient has a detectable HIV RNA level and has no drug resistance mutation (poor adherence), and (3) drug resistance mutations can give information on a more global public health level about which mutations are prevalent in a specific population, with a specific HIV subtype and using specific drugs, and therefore, give information on the usefulness of standardized second-line treatment.

DEFINING THE SPECIFICATIONS AND BUILDING CONSENSUS

We need a broad-based commitment to the development of field-appropriate viral load testing if we hope to develop effective solutions. Developing tests and validating them, as well as ensuring their quality and eventually paying for their manufacture, shipping, and safe and environmentally friendly disposal will take commitment, funding, and collaboration among scientists, medical personnel, national program managers, and all other stakeholders.

CONCLUSIONS

Viral load testing is relevant only if treatments are available and the development of diagnostics and treatments are complementary and crucial. Access to both must also be assured for the optimal long-term management of HIV disease. There is also a need for different tools in different contexts. The specifications of a test are based on the need for a routine test to determine (1) when to switch therapy (eg, higher threshold) and (2) when not to switch therapy (eg, treatment initiation or for assessing adherence when $CD4^+$ T cell count is decreasing). In prevention of mother-to-child transmission programs,

the needs may be slightly different: the goal is to maintain an undetectable viral load in the mother or, in the absence of prophylaxis, to diagnose viral infection in the infant (in whom viral load levels are usually very high). A test used to triage patients would be very useful both for individual care and to relieve some of the pressure on overburdened health care systems.

In parallel, we need to strengthen the use of existing sophisticated technologies at upper levels of care. It is important to have access to reference-level facilities in all countries and to support and maintain the technical and technological capacity of health care systems. A sustainable supply of tests and appropriate quality assurance systems are key.

The impact of a test also depends on preparation of the end users to adopt new technologies and the integration of the test result into patient treatment. Sustainability, affordability, environmental impact, and waste disposal are important factors to be considered early in the development of a test.

We can best hope to develop appropriate viral load technologies through a collaborative, integrated approach. However, many of the issues raised here in relation to viral load testing are relevant to the development of field-adapted diagnostic tools and their integration into health care strategies for a number of other diseases.

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