

Increased access to diagnostic tests for HIV case management

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Introduction

Expansion of HIV case management through antiretroviral therapy has far outpaced access to diagnostic monitoring of HIV patients in resource-limited settings. As a result, the need to expand access to CD4 and viral load testing in resource-limited settings is growing.¹⁻⁵ A substantial number of new technologies for CD4 and viral load testing are now being developed.⁶⁻⁹ To ensure that they meet growing needs, the global health community must consider the diversity of health systems into which new technologies will be introduced.¹⁰

Current efforts to develop CD4 and HIV viral load technologies primarily focus on technologies for settings with relatively high HIV-prevalence rates. The reality, however, is that the need for CD4 and HIV viral load testing is not confined to high-prevalence or high-infrastructure settings. Such needs are apparent in many low-resource settings. The specific circumstances of these settings—including disease prevalence and infrastructure—must be considered during the development of appropriate diagnostic interventions. Product requirements may vary according to the best strategies for a given setting. An understanding of the specific settings into which new technologies will be introduced is crucial for targeting new technologies for maximum impact.

This paper presents a model that allows comparison of these issues and explores four possible scenarios in which these tests could be performed:

1. Highly centralized laboratory testing
2. Moderately centralized laboratory testing
3. Decentralized laboratory testing
4. Point-of-care testing

For each scenario, we describe some of the implications of each testing system.

The intersection of technologies and systems

Diagnostic technologies can influence laboratory systems. Some new technologies may support centralized testing, for example, whereas others may facilitate highly decentralized networks of testing labs. Still other technologies may facilitate testing at the patient's bedside. In addition, the laboratory systems that emerge from new technologies will have different cost and benefit profiles that depend on the specific circumstances of each region in which they are implemented.

The current standard of care in the developed world is to monitor patients' CD4 and viral load counts three to four times per year. It is reasonable to expect that much of the developing world will be able to deliver this level of care in the next 20 years. As we work toward this goal, it is useful to evaluate very different approaches to testing (e.g., at the central lab, at a decentralized lab, and at the point of care). Recent cost-effectiveness studies suggest that CD4 testing is a cost-effective intervention but that viral load testing may not be cost-effective, especially in the absence of second-line antiretroviral drugs. Yet arguments for implementing viral load testing are extremely compelling,¹ and

countries are implementing costly viral load testing as part of their national HIV case-management programs.

Whereas CD4-testing platforms have been adapted to some extent to suit moderately centralized lab testing models, viral load testing remains limited to highly centralized facilities. One of the major cost drivers for viral load testing is throughput,¹¹ or the number of specimens tested per viral load run. Additionally, viral load testing is a relatively complex method requiring specialized skills to ensure accurate results.

The model system

To facilitate discussion about testing systems and how new technologies will fit into them, we have defined a model health system onto which we impose four alternative testing scenarios with varying degrees of decentralization. The model reflects observations of testing systems in various regions.¹²

The model is composed of a population (country) serving 10 million residents served by a public health system which has four tiers of health care facilities, ranging from basic primary care clinics to Tier 3 hospitals with sophisticated laboratory and medical equipment (Table 1). It assumes that 70 percent of HIV-positive patients are receiving comprehensive care, management, and treatment (CCMT) through the public health care system. In addition, it also assumes that each patient receives a viral load and CD4 test three times per year.

As noted earlier, consideration of specific local conditions is essential to the success of technology development efforts. However, preliminary discussions can be facilitated by defining some general characteristics of labs in low-resource settings. To ensure that readers consider a common set of issues, our model requires us to make generalizations. We attempt to account for some regional diversity by plotting the impact of varying disease prevalence on test throughput at various system levels, but conducting formal studies on implementation in different regions will be important next steps.

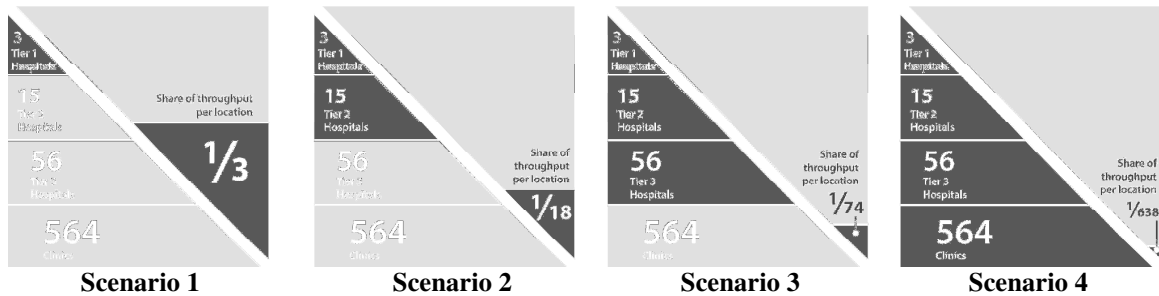
Table 1. Four tiers of health facilities in model system

Facility type	Number in model population	Laboratory capabilities	Notes
Tier 3 hospital	3	<ul style="list-style-type: none"> • Highly sophisticated laboratories. • Generally housed in a university or teaching hospital. • Specialized laboratories available (e.g., virology, hematology). • Each lab is outfitted with state-of-the-art equipment. 	Currently, most viral load testing takes place in Tier 3 hospitals. CD4 testing typically is performed in Tier 3 and 2 hospitals.
Tier 2 hospital	15	<ul style="list-style-type: none"> • Staffed by multiple laboratory technicians. • May have some specialized diagnostic equipment for performing ELISA, CBC, blood gas analysis, CD4 counts, etc. 	
Tier 1 hospital	56	<ul style="list-style-type: none"> • Rudimentary laboratory often staffed by a single laboratory technician. • Capable of performing microscopy, agglutination tests, and other tests that do not require equipment. • Each lab is equipped with a centrifuge to separate plasma and sera from blood. Blood is often centrifuged prior to sending specimens on to Tier 2 or 3 hospitals. 	Expansion to these levels could represent a significant expansion in access to testing and also could pose significant challenges.
Clinic	564	<ul style="list-style-type: none"> • The only diagnostic tests performed on site are rapid tests. • Rapid HIV tests are typically performed by nurses or community health workers. • Patients are generally referred to the nearest Tier 1 hospital for other tests. • In some cases, specimens may be collected at the clinic and sent to the Tier 1 hospital for testing. 	

Applying the model

Below, we describe four alternative scenarios to perform viral load and CD4 tests via the public health system described by the model. Figure 1 provides an overview of the four scenarios and is followed by descriptions of each scenario and its implication, including throughput considerations, potential benefits and limitations, and technology development efforts that could strengthen the systems.

Figure 1: Illustration of the four scenarios



Scenario 1: Highly centralized testing

In Scenario 1, tests are performed only in the three Tier 3 hospitals. The hospitals are served by a strong logistical network that ensures the specimens can be efficiently transported from peripheral clinics to the nearest Tier 3 hospital.

This type of system is common for viral load testing in the developing world, primarily due to assay complexity and the need for specialized equipment. As less complex assays emerge, it will be important to evaluate the value and challenges of moving these assays out of highly specialized laboratories to lower-level laboratories.

Throughput

Throughput considerations are important when evaluating equipment and volume (unit) needs. As shown in Table 2, an instrument with a daily throughput of 500 specimens would be sufficient in a region with an HIV prevalence rate of 2 percent, but it may be excessive in a very low-prevalence environment. Conversely, higher-throughput equipment or multiple units would be required in higher-prevalence areas.

Table 2. Daily testing volumes in each laboratory—highly centralized testing

	HIV prevalence								
	0.5%	1%	2%	4%	8%	12%	16%	20%	24%
Tests per lab per day	96	192	384	767	1,534	2,301	3,068	3,836	4,603

As the daily throughput increases and necessitates additional equipment and staff, laboratory systems managers must evaluate whether to increase the capacity of the central laboratory or to extend testing capability to lower-level laboratories. Laboratory

managers must also weigh the risks and benefits of equipment with very high throughput versus multiple pieces of equipment with lower-throughput capabilities.

Benefits

- Several economies of scale can be achieved through centralized testing.
- A relatively small staff of highly skilled technicians, equipped with high-throughput testing equipment, can process a very large volume of tests. The value of minimizing the labor per test is generally considered quite high—both because of cost savings and because hiring and retaining qualified laboratory staff is a challenge.
- Staff can be trained and dedicated to a single type of testing. This specialization will likely improve quality and efficiency.
- Implementation of sound quality assurance and quality control (QA/QC) practices is easier with a small number of laboratories.
- Recruiting staff might be easier, since reference laboratories are often located in desirable locations, such as large cities and offer more avenues for professional development.
- Equipment service and maintenance are much easier.
- Reagent procurement and supply logistics are restricted to a few focal points and thus are greatly simplified.

Limitations

- The added time required to transport specimens from remote laboratories to the Tier 3 laboratory increases turnaround time and also poses challenges to ensuring specimen quality.
- The logistics of delivering undeteriorated specimens in the cold chain (especially for CD4 testing) can be a significant challenge and cost burden to the collection site. This often translates to a burden for the patient, who must be at the clinic on particular days and times so specimens can reach the testing laboratory without deterioration.
- A highly centralized system suffers significantly if a single laboratory becomes temporarily nonoperational. Backlogs can increase rapidly, which can ultimately increase turnaround times for the whole system and potentially delay timely dissemination of results.

Technology developments

- **Increased access to molecular assays.** Equipment for performing viral load and CD4 tests in large laboratories is becoming increasingly automated, and there is potential for increasing the number of tests per assay run, simplifying use, and ensuring that the tests are increasingly robust. Although molecular assays are financially out of reach for most settings today, they should become more accessible as more molecular

technologies compete for the same market; as technologies other than real-time polymerase chain reaction (RT PCR) and transcription mediated amplification (TMA)—such as loop-mediated isothermal amplification (LAMP), helicase-dependent amplification (HDA), and recombinant protein amplification (RPA)—are developed;¹³⁻¹⁸ and as novel biomarkers for HIV infection, viral load, proviral DNA, and CD4 levels are identified.

- **New collection and extraction methods.** Collection and extraction of the total nucleic acids (NAs) from a specimen will facilitate quantitative detection of HIV and generate a substrate for a variety of molecular-based targets and assays that, in the future, will be more sensitive, less affected by inhibitory compounds, and able to produce results faster than current methods.¹⁹⁻²² Some current methods permit multiplexing of the specimen to simultaneously determine the presence/absence of more than one agent. (For example, the Procleix[®] Ultrio[®] by Gen-Probe is an HIV-, HBV-, and HCV-based assay that is highly automated when used in conjunction with the Tigris[®] system. This method is essentially hands-free after sample tubes have been loaded. It has the capacity to test 1,000 samples in 14 hours.) In addition, technology may permit cross-referencing of a specimen's estimated values by more than one method/assay, which would further validate results. Automated testing also would improve QC within the test regimen. Finally, an improved design could reduce equipment costs; lower requirements for power, footprint, physical robustness, faster run times, and multiplexing; and reduce waste.
- **Increased specimen stability.** A number of efforts to improve the stability of blood specimens collected in the field for transit are under way. The use of commercially produced stabilizers such as Cyto-Chex BCT and Transfix have been reported to preserve the CD4 antigen from internalization and decay for extended periods (at least one week) when kept in the cold chain.^{23;24} These or improved formulations may improve stability during shipping prior to flow cytometric analysis.^{25;26} Technology solutions for stabilizing RNA include RNA-stabilization reagents, plasma-separation tubes, Flinders Technology Associates (FTA) cards, and dried blood spots.²⁷⁻²⁹

A move from cell-based testing to NA-based approaches would be ideal for resource-limited settings with wide geographical ranges, as the cold chain would no longer be required. The ability to collect large numbers of stabilized samples fits into a scheme in which large, centralized laboratories are capable of high-throughput processing. Another benefit of an NA approach is the extra samples available for further testing (e.g., for QC, genotyping, or screening for drug-resistance markers).

- **Improved sample collection.** Developers are working to improve sample collection by using bar-coded collection vessels with matching patient data sheets. Attendant paperwork with the matching codes could either be shipped with samples or stored at the point of care. Accessioning samples would be extremely fast for high-throughput processing, analysis, and reporting. Data collection and results storage/reporting are currently entirely *in silico* at this level. Such improvements would reduce error rates

and the high costs associated with errors in high-throughput screening (e.g., invalidation of entire run data and repeat testing or sampling).

Scenario 2: Moderately centralized testing

In Scenario 2, tests are performed in Tier 2 and 3 hospital labs. As with highly centralized testing, strong logistical networks are required to transport specimens over long distances from the point of sample collection to the laboratory. Since the skills required to perform a CD4 test are currently lower than those needed to test viral load, and because CD4 specimens are very time-sensitive, many low-resource settings currently deploy CD4 in this type of testing system.

Throughput

The daily throughput requirements for this testing system (Table 3) are dramatically lower than those for the highly centralized testing network. Thus, appropriate technologies for this testing system may be different than those for highly centralized laboratories.

Table 3. Daily testing volumes in each laboratory—moderately centralized testing

	HIV prevalence								
	0.5%	1%	2%	4%	8%	12%	16%	20%	24%
Tests per lab per day	16	32	64	128	256	384	511	639	767

Benefits

- As with highly centralized testing, significant economies of scale can be achieved with this testing system, but only in high-prevalence regions.
- The time to transport the specimen from the point of collection to the laboratory can be reduced to an average of 24 to 48 hours, ultimately reducing turnaround time and making testing of time-sensitive specimens (such as CD4) feasible.
- A testing system based on a distributed network of laboratories is less susceptible to catastrophic failure due to a single laboratory going off-line.

Limitations

- Specimen transport time is still a significant contributor to turnaround time. As an average specimen requires 24 to 48 hours to travel to the laboratory, there is little hope of delivering a result within 24 hours. The empirical value of reduced turnaround time will vary from test to test and is difficult to quantify. However, clinicians generally place a high value on reduced turnaround time for all tests.
- In low-prevalence settings, the throughput may not be sufficient to justify the capital costs of installing equipment and training staff in 18 laboratories.
- In low- to medium-prevalence settings, having specialists for a specific test may not be feasible.

- More robust supply chains for reagents and stronger instrumentation-support services are required.
- QA/QC is more challenging to sustain.
- Infrastructure requirements—such as regular power supply, water quality, and supply of disposables—begin to be less reliable. This translates to products that must be more self-contained.

Technology developments

Compared with top-tier facilities, the reduced human and material resources of the Tier 2 hospital setting place greater constraints on the complexity and number of tests that can be performed. Assays are less automated, but they still incorporate internal QC where possible.

- **Microcapillary flow cytometry.** Current forms of microcapillary flow cytometry may still prevail for CD4/CD8 assays. This type of assay can still perform relatively high levels of testing to routinely screen 50 to 100 samples per day, with more than one machine to reduce the impact of machine failure. Such equipment is easier to use than that for flow cytometry, gives accurate results, requires minimal maintenance, and produces minimal amounts of waste from typically small specimens (10 μ L). The development of equipment that is cost-effective at throughput levels in the range of 50 to 100 has been reported.³⁰⁻³²
- **Transport and stability.** Similar issues regarding transport and stability of cells remain within this scenario. A rapid cold chain (i.e., less than 24 hours to testing) is still needed, or stability reagents are required (although current reagents reduce the levels of CD4 presented by cells).
- **NA testing.** Some NA testing may be possible if specimen-preservation technologies are comparable to those in the Tier 1 hospitals. The development of new NA assays and technologies will be of special benefit to lower-tier laboratories. Sample collection with NA stability must be developed concurrently with it.
- **Lyophilized reagents.** Lyophilized reagents and controls are necessary for this scenario to succeed. They add great value to QC and reduce the need for cold-chain storage of reagents. It is possible to manually prepare smaller numbers of specimens for NA testing (50 per day) with a single trained operator. The use of NA technologies would permit the relatively straightforward transfer of remaining specimens to the higher-tier laboratory for repeat testing of positive samples.
- **Training and software issues.** The lyophilized reagent format with preprogrammed equipment (e.g., assay protocols) facilitates a low-complexity training regime and requires less specialization of staff. However, training concerns regarding the use of computer software associated with microcapillary flow cytometry (such as Microsoft Excel) have been reported. This challenge could affect reporting formats and results for other diagnostic equipment.³³

Scenario 3: Decentralized laboratory testing

Under Scenario 3, tests are performed in all hospital laboratories (Tiers 1, 2, and 3), bringing the number of testing sites in our model population to 74 and representing a significant shift from the previous two scenarios.

Currently, CD4 and viral load tests are generally not performed in Tier 1 hospital labs because of the test's complexity. These labs are generally staffed by one or two generalist lab technicians and outfitted with very basic equipment. Significant improvements to existing viral load and CD4 platforms would be required to facilitate their use in these laboratories. Alternatively, in high-prevalence regions, specialized HIV labs could be established in parallel to existing hospital laboratories.

Throughput

With 74 testing labs online, the average daily volume at each would be less than 200 in a region with an HIV prevalence of 24 percent. In regions with low prevalence rates, the number drops to less than 20 per day, which calls into question whether decentralized testing would be cost-effective in low-prevalence areas and what types of technologies would make it cost-effective.

Table 4. Daily testing volumes in each laboratory—highly decentralized testing

	HIV prevalence								
	0.5%	1%	2%	4%	8%	12%	16%	20%	24%
Tests per lab per day	4	8	16	31	62	93	124	155	187

Benefits

- The most significant benefit would be the average of a one-day turnaround time and the potential for same-day turnaround of specimens collected in Tier 1 hospitals. The transport of specimens from clinics to the Tier 1 hospital would likely occur on the same day.
- Each CCMT site could be outfitted with a laboratory. Currently, CCMT sites often reside in Tier 1 hospitals but not in clinics. Thus, many patients requiring testing would present to the CCMT site for testing. Urgent matters identified in the CCMT clinic could be informed by stat testing of viral load and CD4.

Limitations

A Tier 3 laboratory would be severely tested in a scenario in which the laboratory was required to test 200 specimens per day. Robust equipment, constant cold-chain storage for reagents and specimens, and adequate numbers and retention of trained staff would all be great challenges in this setting.

In addition:

- Ensuring QA/QC would be much more challenging in this decentralized system as compared with centralized systems.

- Service and maintenance of complex equipment would be spread over a large geographical area and therefore pose a greater challenge.
- Labor and equipment costs would be much higher than with centralized testing. For example, in a region with an HIV prevalence of 2 percent, six technicians in a central lab outfitted with two high-throughput (250 tests/day) instruments could likely perform the same number of tests as 24 technicians with 24 low-throughput (20 tests/day) instruments in 24 locations.
- Recruiting could be a challenge. Finding skilled labor for the current, relatively small number of central testing facilities already poses a challenge in many areas, and this system would require expanding the workforce further. Recruiting skilled labor to some of the remote areas where Tier 1 hospitals are located would also be difficult.
- Ensuring supply-chain logistics of reagents and supplies to serve a widely distributed network of testing sites would be difficult.

Technology development

- **Low test volume of CD4 counting.** Novel developments in HIV diagnostics will have the greatest impact at this level, since current test methods are time consuming. A number of low-cost and relatively accurate tests have been described, including Dynabeads[®] by Dynal Biotech,^{19,20} Cyto-Spheres by Beckman-Coulter, and RosetteSep[®] by StemCell Technologies.³⁴⁻³⁶ To be effective, CD4 counting methods using microscopy should only screen low numbers of specimens for counting, as increases in test-volume errors attributed to laboratorian fatigue are inevitable. The development of novel assays with minimal user training/input at low test volumes will benefit the Tier 3 laboratories.
- **Small batch viral load testing.** User-friendly, small-batch PCR instruments are currently under development for applications in the developing world such as nucleic acid testing in small medical clinic. These technologies might be promising when applied to low resource settings. Their cost-effectiveness would rely heavily on minimizing the cost of standards required to generate quantitative results.

Scenario 4: Point-of-care testing

In Scenario 4, each clinic is outfitted with point-of-care CD4 and viral load testing. These tests are very easy to use; nurses, community health workers, and others capable of performing a rapid HIV test have no problem performing them. A handheld instrument may be required to perform the test.

An alternative to performing quantitative tests at the point of care is providing semi-quantitative test results that are used to identify patients most at risk of treatment failure. High-risk patients are then referred to hospitals for quantitative testing.

Throughput

Throughput calculations assume that 80 percent of tests are performed in clinics and that the other 20 percent are evenly distributed among all hospitals. This scenario leads to extremely low test volumes in both hospitals and clinics.

Table 5. Daily testing volumes in each laboratory–point-of-care testing

	HIV prevalence								
	0.5%	1%	2%	4%	8%	12%	16%	20%	24%
Tests performed per day per lab:									
Hospital labs	1	2	3	6	12	19	25	31	37
Clinic labs	0	1	2	3	7	10	13	16	20

Benefits

The greatest benefit of this testing system is its ability to provide same-day results. Same-day results can decrease loss to follow-up, allow early identification of treatment failure, and reduce cost to patients. These benefits are augmented by clinicians' ability to act on the information.

Limitations

- QA/QC oversight would be extremely challenging. QA would need to be seamlessly incorporated into the testing technologies.
- Because equipment maintenance and service would be difficult, there is a strong argument for using tests that do not require equipment. Currently, however, most technology-development efforts for point-of-care CD4 and viral load testing have some reliance on equipment.
- The workload of already-overburdened health care workers in clinics would increase. Many clinics see 60 to 100 patients per day and are staffed by two to six nurses and health care workers. In high-volume, understaffed clinics, test quality could suffer, as would the morale of clinicians who have had a substantial new element added to their workload.
- Supply-chain logistics of reagents and supplies for a widely distributed network of testing sites would pose significant challenges. Thermostable reagents, appropriately packaged supplies, and/or fully integrated lab-on-card systems would be necessary to support point-of-care testing.

Technology development

- **Point-of-care tests.** There have been many proposals to optimize, validate, and manufacture inexpensive, easy-to-use, and accurate point-of-care devices. These proposals typically focus on an effective device for CD4 measurement, which would have immense value for antiretroviral therapy programs in rural areas.^{37,38} Currently, testing at the point of care is limited to lateral flow devices. Significant effort has been invested into developing point-of-care CD4 tests,^{7,8} and many more potential

methods have been proposed.³⁹⁻⁴⁴ None of the latter appears close to clinical evaluation, however.

- **Thermostable reagents.** Developments in thermostability are finding application in vaccines and could be applied to diagnostic reagents.
- **Minimally instrumented systems.** Advances in microfluidics, micro-electro-mechanical systems (MEMS), and nanotechnologies show promise for self-contained, minimally instrumented point-of-care diagnostic systems. These approaches require greater investment.
- **Specimen collection.** Specimen collection for highly decentralized systems is critical. There is a need for robust data collection and sample stabilization.
- **Data reporting.** Investment in cellular networks to permit data exchange of results between point-of-care and higher-tier facilities may improve reporting and data collection for population-based studies.

Summary and discussion

Table 6 provides a summary of the daily testing volumes that are discussed in each of the scenarios above.

Table 6. Summary of daily testing volumes in each laboratory under the four scenarios

	HIV prevalence								
	0.5%	1%	2%	4%	8%	12%	16%	20%	24%
	Test volume needed								
Tests per day	288	575	1,151	2,301	4,603	6,904	9,205	11,507	13,808
	Test throughput								
Highly centralized lab testing	96	192	384	767	1,534	2,301	3,068	3,836	4,603
Moderately centralized lab testing	16	32	64	128	256	384	511	639	767
Highly decentralized lab testing	4	8	16	31	62	93	124	155	187
Point of care:									
Hospital labs	1	2	3	6	12	19	25	31	37
Clinic labs	0	1	2	3	7	10	13	16	20

As the table shows, the importance of throughput for viral testing works against decentralizing viral load tests unless the setting has a high HIV prevalence and optimal specimens/run throughputs are sustained. In addition, barriers such as QA/QC, sustainability, technical complexity of the test, and staff requirements also serve as challenges to decentralizing the viral load test.

It is also apparent that a highly centralized laboratory testing system will provide technology developers and users with the most monolithic target solution over a range of HIV-prevalence rates, since optimal throughput can easily be attained in all settings. In the absence of further technology development in specimen preservation and transportation, however, the reach of centralized testing will always be compromised,

particularly for patients in remote settings. So while centralized testing is likely the most cost-efficient testing system for complex quantitative tests such as CD4 counts and HIV viral load tests, decentralization will be required to extend the reach of these tests to patients in more remote settings.

Decentralization of testing, even if only to Tier 2 laboratories, would create a range of throughput capacity needs with varying infrastructure requirements and different product profiles. For example, based on throughput alone, products that meet the needs of a clinic performing point-of-care testing in a setting with 20-percent HIV prevalence may meet the needs for a Tier 2 laboratory in a 0.5-percent HIV prevalence setting. Similarly, testing technologies developed to meet the needs of a Tier 1 or 2 laboratory in a setting with an HIV prevalence of 12 percent or higher may also benefit more centralized testing systems in low-prevalence settings.

A portfolio of technologies will be required to address the diversity of needs found throughout the developing world. Based on our analysis, we believe that investment in the following developments is justified and would provide the potential for highest impact:

- Stabilized reagents, including internal controls in commercial tests, so test shelf life is extended.
- Stabilized standards for both CD4 and viral load tests to ameliorate procurement and supply-chain challenges.
- Specimen-stabilization technologies that reduce the stringent requirement for cold-chain systems in specimen shipment.
- Identification of novel biomarkers that are more amenable to simpler diagnostic platforms and serve as proxies for CD4 counts and viral load.
- Low-throughput diagnostic platforms. Delinking throughput from the cost-per-viral-load test result is a fundamental challenge that must be addressed.
- Point-of-care tests that can either serve as triaging tools or are accurate enough to inform treatment-management decisions.
- Specimen and results tracking technologies and systems that are less prone to user error (such as barcoding systems).

Accurate definition of the product specifications for these products will require detailed studies of landscape and user requirements and the identification of operational strategies for the introduction of these technologies. These activities should be coupled with the evaluation of the cost and health impact of specific technologies in a given setting. Finally, a similar discussion will be required regarding technology needs for drug resistance surveillance and management.

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