

EDITORIAL

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Viral-load point-of-care technologies to achieve an AIDS-free generation

“Implementing point-of-care technologies is not only a smart strategic investment but also a game changer as it can help overcome some of the individual, organizational and societal barriers that prevent people infected with HIV to receive timely and appropriate treatment.”

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Ending the AIDS epidemic requires not only political commitment and financial resources but also innovative solutions. New point-of-care (POC) technology to detect HIV viral load promises to be a game changer in the diagnosis and monitoring of HIV infection. Poverty and distance from healthcare facilities often place people infected with HIV beyond the reach of life-saving care. Viral-load POC testing brings diagnosis and monitoring of antiretroviral therapy (ART) treatment closer to the patient – even in remote regions of sub-Saharan Africa where HIV prevalence is high and resources are scarce – which means more rapid results and potentially improved treatment and prevention outcomes.

The value of POC testing is underscored by UNAIDS suggesting the possible end to the AIDS epidemic by 2030 if three 90–90–90 ambitious targets are achieved by 2020: 90% of all individuals living with HIV know their status; 90% of all individuals diagnosed with HIV receive sustained ART and 90% of all individuals receiving ART have viral suppression [1]. Achieving the third target requires universal access

to viral-load testing. This is in line with the most recent WHO ART guidelines, which recommend the use of viral-load testing to monitor treatment success and identify its failure [2]. The WHO defines treatment failure as a persistently detectable viral load exceeding 1000 copies/ml during two consecutive viral-load measurements, within a 3-month interval and after at least 6 months of using ART [3]. Viral load should be tested 6 months after initiating ART and then at least every 12 months to detect treatment failure.

High-income countries already use routine viral-load monitoring to detect early treatment failure and inform decisions on switching patients to second-line ART. By contrast, in resource-limited settings, treatment failure is still defined by clinical criteria and CD4 cell counts, parameters that are poorly correlated with viral load. Without access to viral-load testing, individuals may be unnecessarily switched to more expensive second- and third-line treatments.

Simple and affordable POC technologies to detect viral load are in development. These innovations are expanding access to

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“The unique advantages of point-of-care and conventional centralized systems call for an integrated approach that ensures a greater impact, quality and effective use of both systems.”

critical diagnostic services and optimizing treatment monitoring for individuals living with HIV [4]. However, ensuring that all of the estimated 15 million individuals currently receiving ART, regardless of location (urban or rural), are monitored by viral-load testing will require careful planning and efficient financial investments – in the expansion of conventional laboratories, the creation of laboratory networks and the deployment of POC technologies. While regularly monitoring millions of ART patients seems a daunting task for governments and donors, it also opens interesting market opportunities for companies developing affordable monitoring platforms.

Conventional laboratory testing for viral load, which typically occurs at a central facility to which all tests from a particular region are sent for processing, has certain advantages. Collecting and batching tests produce economies of scale that reduce the cost per test. Today, the price per viral load test at central conventional laboratories can range widely (US\$10–60) depending on the manufacturer and country [5]. In addition, it is easier to manage and assure quality of centralized laboratory testing than of a more decentralized testing method. However, in settings where healthcare infrastructure and transportation are poor, conventional testing – with its long delays in sending specimens to the lab, receiving results at the facility and then notifying the patient of the results and providing any necessary follow-on treatment – can result in large numbers of patients lost to follow-up [6].

Avoiding losing patients to follow-up and maintaining their viral load at undetectable levels is critical not only to avoid treatment failure in the patient but also to reduce the risk of transmission at the individual and the community level. Monitoring to ensure that ART is working, in other words, suppressing the virus, is important for minimizing viral transmission. Several research studies in recent years have confirmed that ART has HIV prevention benefits. Evidence from discordant couples shows that ART is 96% effective in preventing transmission to an uninfected sexual partner [7]. The large, observational ‘PARTNER study’ provides encouraging insight into the risk of transmitting HIV sexually. When a person’s viral load was undetectable, there was no HIV transmission even when couples failed to use condoms [8].

Maintaining individual viral load to undetectable levels is critical for reducing the risk

of transmission at the individual as well as the community level. Measuring viral load can also inform public health officials on the risk of transmission at the community level. Community viral load (CVL) is a metric aggregating the viral load for a community. ‘The central hypothesis underlying the use of CVL is that as ART coverage increases, greater numbers of HIV-infected persons will be virologically suppressed, leading to reduced CVL and consequently, reduced incidence of HIV infection in the general population’ [9].

WHO recommends that all newborns exposed to HIV receive early infant diagnostic screening within the first 2 months of life. However, only half of newborns exposed to HIV receive this screening, contributing to a major gap in HIV treatment access. Only 32% of infants [10] living with HIV received ART in 2014. Recent data from four countries report that almost 75% of all HIV-positive infants were not on treatment at 1 year of age; a significant contributor to this result was that 51% of conventional laboratory early infant diagnosis (EID) patients never received their test results [10]. Without knowing the HIV status of a child, it is impossible to offer life-saving treatment. It is equally important to engage mothers infected with HIV in treatment and prevention strategies to ensure that their children remain free of HIV infection and that mothers stay alive and well. Without treatment, half of all children born with HIV will die by the age of two, and the majority will die by the age of five. In order to eliminate mother-to-child transmission, it is critical to prevent new HIV infections among women of reproductive age, especially among adolescents and young women, and among their children.

EID of HIV among infants born to mothers infected with HIV has been scaled up using dried blood spots (DBS). The main advantage of DBS is that it solves the problem of storage and shipment of samples where infrastructure is poor. DBS can be stored for weeks at ambient temperature without clinically significant degradation of nucleic acids. Virological testing for infant HIV diagnosis can be accomplished through an HIV nucleic acid test (NAT) that targets viral RNA or proviral DNA using commercially available assays or laboratory-developed tests [11]. However, central laboratories enable large-volume NAT, but transporting specimens and reporting results can result in turnaround times of 1–3 months, loss to follow-up and missed opportunities for diagnosis and timely treatment.

The unique advantages of POC and conventional centralized systems call for an integrated approach that ensures a greater impact, quality and effective use of both systems.

Real-world examples show how countries in Africa are expanding EID and viral-load monitoring using conventional laboratories as well as POC. In Uganda, monitoring for virologic failure has emerged as an urgent issue with reports of 11.6% of patients showing evidence of drug resistance. In response, the Ministry of Health is leveraging their successful EID sample transport system to expand access to routine viral-load monitoring for the more than 500,000 patients receiving ART [12]. Uganda scaled up EID using DBS in rural settings through the national postal courier system. An analysis of 19 hubs serving 616 health facilities transporting DBS showed improved access to EID from 36 to 51%, transportation costs reduced by a dramatic 62% and turnaround times cut almost in half (by 46%) [13]. However, a main limitation of DBS among treated patients is the contribution of cell-associated and proviral DNA that reduces the specificity of the test on this type of sample, which may lead unnecessary treatment switch.

In Kenya, a sophisticated transportation system for viral-load testing was implemented in the Kisumu region: blood samples are sent to regional hubs, where they are centrifuged and then sent to a central laboratory at the Kenya Medical Research Institute (KEMRI). Last year, the KEMRI lab processed more than 30,000 viral-load tests using this sample referral system. However, this system requires plasma specimens to be separated within 6 hours of whole-blood collection and a reliable cold-chain system for plasma transportation and storage to centralized facilities. With only one laboratory processing viral-load tests for the entire country, backlogs further delay the reporting of test results [14].

Conventional viral-load testing is usually performed in plasma; however, technologies that use whole blood, such as DBS and POC tests, become less reliable at thresholds lower than 1000 copies/ml. Thus, the threshold for semiquantitative POC-positive results is currently set above 1000 copies/ml. The POC-SAMBA system (simple amplification-based assay semiquantitative test for HIV-1) currently performs HIV diagnosis through an isothermal nucleic acid amplification method similar to NASBA, coupled with lateral flow detection in an integrated cartridge combined with a benchtop instrument. The performance

of these tests is under evaluation; however, the POC SAMBA reports good performance in distinguishing viral loads above and below 1000 copies/ml. Using samples from patients in the UK, Malawi and Uganda, SAMBA showed an accuracy of 96.9% (95% CI: 94.9–98.3%) as compared with the COBAS AmpliPrep/COBAS TaqMan HIV-1 test [15].

POC technologies that can move HIV viral-load monitoring out of the central laboratory are in different stages of development, and the WHO has proposed an evaluation framework named ASSURED (affordable, sensitive, specific, user friendly, rapid and robust, equipment free and deliverable to end users) to evaluate their effectiveness and feasibility for scale-up. The cost per test is expected to vary between US\$3 and US\$15, and the price of the instrument between US\$1000 and US\$15,000 [5].

As with other innovations, there will be challenges to implementing POC viral-load technology in resource-limited settings. POC requires staff training and time to operate the machine, thus the output is limited to three to four tests per hour; therefore, it is generally believed that the technology is resource consuming, but without actual data on its full cost–effectiveness, it is impossible to make accurate, detailed plans for implementation and operations. POC testing will require coordinated procurement to ensure adequate supplies, consumables and reagents are available at each facility and developing countries already struggle with maintaining adequate quantities of testing supplies and reagents for conventional laboratory testing. POC machines require regular calibration, maintenance and repair. A recent study assessing a POC CD4⁺ machine reported that 12.7% of test results were invalid across different countries, settings and users. Although most errors were attributed to the operator, the possibility of invalid results needs to be factored into the costs of POC technologies [16]. Health providers will still need to ensure that patients act on the test results – initiating and adhering to treatment – even when there is no delay in getting test results. Providers also will need to keep accurate, up-to-date patient records because if they fail to track patient viral load consistently, the benefits of POC testing are minimized [17].

Still, the benefits of POC viral-load technology seem to outweigh the implementation challenges. The obvious advantage is the close proximity to where a patient is receiving care; shortening the turnaround time for test results from weeks to

hours allows for making immediate clinical management decisions and taking action during the same patient visit – thus increasing appropriate treatment initiation and reducing loss to follow-up, especially in remote (and often poor) regions. For example, the implementation of POC CD4⁺ in Mozambique reduced loss to follow-up between testing and treatment from 64 to 33%. Moreover, the proportion of patients initiating ART doubled, and the median time to start ART was cut in half [18]. The technology saves costs by enabling local facilities to diagnose and monitor disease without the support of a central laboratory. It tends to shift testing from highly trained laboratory technicians to less expensive nonlaboratory staff, and it saves on specimen transport costs. By providing proper virological confirmation of treatment failure, it also has the potential to prevent unnecessary and costly switches to second- and third-line treatment and contribute to better health outcomes. A recent analysis to achieve sustainable HIV treatment in Africa calls for a more efficient and viral-load-informed differentiated care. Patients with suppressed viral load would visit the clinic less frequently, thus allowing providers to focus on patients with unsuppressed viral load, and to promote adherence and timely switching to second-line regimens [19].

Scientific innovations coupled with strategic implementation of new technologies are showing remarkable progress and allow us to envision that the end of the AIDS epidemic is within our reach. We have the technology to dramatically reduce the number of new HIV infections and virtually eliminate infections in newborns. Implementing POC technologies is not only a smart strategic investment but also a game changer as it can help overcome some of the individual, organizational and societal barriers that prevent people infected with HIV to receive timely and appropriate treatment. Through shared global responsibility and smart, science-based investments, we can save millions more lives and achieve an AIDS-free generation [20].

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