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REVIEW

Point-of-Care HIV Viral Load Testing: an Essential Tool for a Sustainable Global HIV/AIDS Response

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SUMMARY The global public health community has set ambitious treatment targets to end the HIV/AIDS pandemic. With the notable absence of a cure, the goal of HIV treatment is to achieve sustained suppression of an HIV viral load, which allows for immunological recovery and reduces the risk of onward HIV transmission. Monitoring HIV viral load in people living with HIV is therefore central to maintaining effective individual antiretroviral therapy as well as monitoring progress toward achieving population targets for viral suppression. The capacity for laboratory-based

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HIV viral load testing has increased rapidly in low- and middle-income countries, but implementation of universal viral load monitoring is still hindered by several barriers and delays. New devices for point-of-care HIV viral load testing may be used near patients to improve HIV management by reducing the turnaround time for clinical test results. The implementation of near-patient testing using these new and emerging technologies may be an essential tool for ensuring a sustainable response that will ultimately enable an end to the HIV/AIDS pandemic. In this report, we review the current and emerging technology, the evidence for decentralized viral load monitoring by non-laboratory health care workers, and the additional considerations for expanding point-of-care HIV viral load testing.

KEYWORDS AIDS, HIV, differentiated care, point-of-care, viral load

INTRODUCTION

Currently, over 20 million people living with HIV (PLHIV), mostly in low- and middle-income countries (LMICs), are receiving antiretroviral therapy (ART) (1). The World Health Organization (WHO) recommends that all PLHIV be offered ART, regardless of CD4 count, which means that almost 20 million more people still require treatment (2). In the absence of a cure, the goal of providing ART is to achieve HIV virological suppression, which has been defined as an HIV viral load (VL) of <1,000 copies/ml. PLHIV who achieve virological suppression have more robust immune reconstitution, better clinical outcomes, and lower mortality rates (3). Furthermore, PLHIV who maintain an undetectable viral load have effectively no risk of sexual transmission to an HIV-negative partner, which has become the message of the U = U (Undetectable = Untransmittable) campaign (4).

The Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the 90-90-90 project to achieve the following goals by the year 2020: (i) identify 90% of all PLHIV, (ii) initiate 90% of all PLHIV who know their status on ART, and (iii) maintain viral suppression among 90% of all PLHIV receiving ART (5). To reach these targets, coordinated efforts are required to diagnose PLHIV and initiate ART, as well as to provide ongoing care for those already on ART. Innovative models of care delivery and patient monitoring, including advanced diagnostic tools, provide opportunities to further accelerate progress toward high levels of HIV viral load suppression.

Despite scale-up of routine viral load monitoring in LMICs, viral load test results do not always lead to appropriate clinical action, including adherence counselling and follow-up viral load testing, to improve the HIV cascade of care. In Swaziland, one-third of PLHIV with viremia (>1,000 copies/ml) received appropriate adherence counseling (6, 7). In South Africa, fewer than 20% of PLHIV with viremia (>1,000 copies/ml) received a follow-up viral load test within 3 months (8, 9). A separate study in four South African provinces reported a median time from viremia (>1,000 copies/ml) to confirmation of virological failure of 30 weeks (interquartile range [IQR], 17 to 53 weeks), and the median time from viremia to ART regimen switch was 68 weeks (IQR, 35 to 124 weeks) (10, 11). While these problems may reflect broader weaknesses in the public health systems, point-of-care (POC) VL testing could expedite detection of viremia, thereby increasing viral resuppression and reducing community viral loads.

Diagnostic POC tests have rapidly emerged and are expanding into laboratories and clinics in high-income countries and in LMICs (12). In recent years, several POC HIV viral load tests have become available, and more are expected soon (13). These new technologies have the potential to decentralize and expand viral load coverage, enhance efficiency in health care services, and improve viral suppression. POC HIV viral load assays are important to measure individual treatment success as well as monitor the overall progress in achieving the goals of the HIV care and treatment. However, several important technological challenges and clinical research questions remain. In this review, we highlight the existing technologies for POC HIV viral load testing, the existing evidence for decentralized testing by health care workers within HIV programs, and evidence from modeling and cost-effectiveness studies.

TABLE 1 Ideal product attributes for POC HIV viral load test

Domain	Optimal criteria
Goal	Quantification of HIV RNA viral load copies/ml
Limit of detection	200 HIV RNA viral load copies/ml
Precision	Less than 0.3 $\log_{10}$ HIV viral load copies/ml, as compared to reference gold standard test
Time to results	Less than 30 min total
Throughput	Minimum of 15 tests per 8-h workday
Equipment	Small, portable, and robust, with uninterrupted power supply for use in primary health care clinics at a wide range of temperatures
Sample specimen	Finger capillary whole blood (maximum, 200 μl) or heel stick for young children; dried blood spot would be acceptable
Simple operation	The device should be capable of being used by health care workers, including technicians, nurses, and physicians, after a minimal amount of training
Quality control	Internal full positive and full process negative controls to monitor individual test results
Patient identification	Results can be easily linked to a specific patient
Data export for quality assurance	Full data export over mobile phone network with computer or tablet interface

TECHNOLOGIES FOR POC HIV VIRAL LOAD TESTING

Requirements of an Ideal POC HIV Viral Load Test

A variety of molecular platforms exist for accurate, high-throughput HIV viral load testing, but they require sophisticated laboratory infrastructure and highly skilled laboratory technicians. The logistical requirements to reliably transport samples to centralized laboratory facilities, which include scheduling specimen pick-up and maintaining sample integrity, can also present challenges. POC assays may allow testing outside of centralized laboratories but face a variety of constraints (12). In more remote clinical settings with fewer resources, the assays must remain functional under extreme environmental conditions (e.g., high temperature, humidity, and dust), have minimal reliance on a power supply, allow for simple sample collection, and feature automated equipment to allow for operation by users following minimal training (13–15).

In 2013, the International Diagnostics Centre presented a draft target product profile (TPP) review for a POC HIV viral load test (16). We have modified those criteria to make them more appropriate for emerging technologies (Table 1). In brief, test results should be rapid, accurate, and unambiguous, in order to be actionable during the patient visit and archivable to a centralized management system to record and monitor test volumes, results, and error rates (17–19). A POC HIV viral load assay must provide information on the level of viremia consistent with clinical standards for indicating virological failure, the threshold of which is currently defined by the WHO as 1,000 RNA copies/ml (2). Given the availability of newer medications with greater efficacy for maintaining viral suppression, newer POC HIV viral load assays should achieve a lower limit of quantification, 200 copies/ml. In addition, any POC HIV viral load assay must be easy to use by local health care workers with a minimal amount of training. With POC viral load testing, it is crucial that diagnostic accuracy is established in a wide range of HIV subtypes that represents global HIV subtype diversity. Finally, the capital equipment, consumables, and service conditions must be affordable to resource-limited HIV programs that are funded by governments in LMICs and global donors.

Currently Available Tests

We provide an update to a prior landscape review with details on POC HIV viral load tests, describing three products that are commercially available and one project near commercialization in India, Africa, and South America by Molbio Diagnostics (Table 2 and Fig. 1) (14). We excluded the COBAS Liat system (formerly the IQuum Liat HIV viral load assay), which demonstrated good diagnostic accuracy in two validation studies (20, 21), as the technology has been acquired by Roche and further development has been postponed. Among products from six companies that were previously described as being in the early to middle development stages (14), only one product (Molbio Diagnostics; Goa, India) is still being actively advanced (22, 23).

m-PIMA by Abbott. The Alere q instrument and assays were recently rebranded to m-PIMA after the acquisition of Alere by Abbott (Abbott Park, IL, USA). The instrument

TABLE 2 Point-of-care HIV viral load assays that are commercially available or in late development[a]

Manufacturer	Assay	HIV type(s)	Amplification/detection	Analytic sensitivity (copies/ml)	Testing time[b] (min)	Sample type and vol	Instrument dimensions	Test instrument	WHO PQ, CE-IVD	Marketed
Abbott Inc. (formerly Alere)	m-PIMA (formerly Alere q HIV-1/2 Detect)	HIV-1 groups M/N and O, HIV-2[c]	RT-PCR/real time with competitive reporter hybridization	800–1,000	<70	Plasma, 50 μl	220 by 200 by 310 mm; weight, 7.8 kg	1 unit	Yes, yes	Only in nonregulated markets
Cepheid	Xpert HIV-1 Viral Load	HIV-1 groups M, N, and O[d]	RT-PCR/real time with molecular beacons	40	90	Plasma, 1 ml	102 by 305 by 298 mm; weight, 8.2 kg	1 unit	Yes, yes	Yes
Diagnostics for the Real World	SAMBA I PSQ	HIV-1	NASBA/ICS	1,000	90	Plasma, 200 μl	Display module: 215 by 170 by 180 mm Assay module: 190 by 330 by 330 mm Display module: 2.1 kg Assay module: 9.9 kg	2 units	No, yes	Yes
Diagnostics for the Real World	SAMBA II WBSQ	HIV-1	NASBA/ICS	1,000	90	Blood, 120 μl	Display module: 215 by 170 by 180 mm Assay module: 190 by 330 by 330 mm Display module: 2.1 kg Assay module: 9.9 kg	2 units	No, yes	No
Molbio Diagnostics	TrueNat HIV Viral Load	HIV-1, group M	RT-PCR/real time with conventional TaqMan probes	500	55	Plasma, 500 μl Blood, 250 μl	240 by 300 by 120 mm; weight, 3 kg	2 units	No, no	No

[a]Abbreviations: WHO, World Health Organization; PQ, prequalification; CE-IVD, Conformité Européene *in vitro* diagnostic; TAT, turnaround time; PSQ, plasma semiquantitative; WBSQ, whole-blood semiquantitative; RT-PCR, reverse transcription PCR; NASBA, nucleic acid sequence-based amplification; ICS, immunochromatographic strip.

[b]Testing time does not include time for plasma separation.

[c]Limits of detection for m-PIMA: HIV-1 group M, 342 copies/ml (95% CI, 279 to 451) and 595 IU/ml (95% CI, 487 to 785); HIV-1 group O, 228 copies/ml (95% CI, 187 to 295); HIV-2 group A, 364 copies/ml (95% CI, 292 to 484) and 200 IU/ml (95% CI, 160 to 260).

[d]Diagnostic sensitivity at limit of detection with WHO 3rd International Standard, 18.3 copies/ml; diagnostic specificity, 100% (95% CI, 96.7 to 100.0); limit of quantitation, 40 copies/ml.

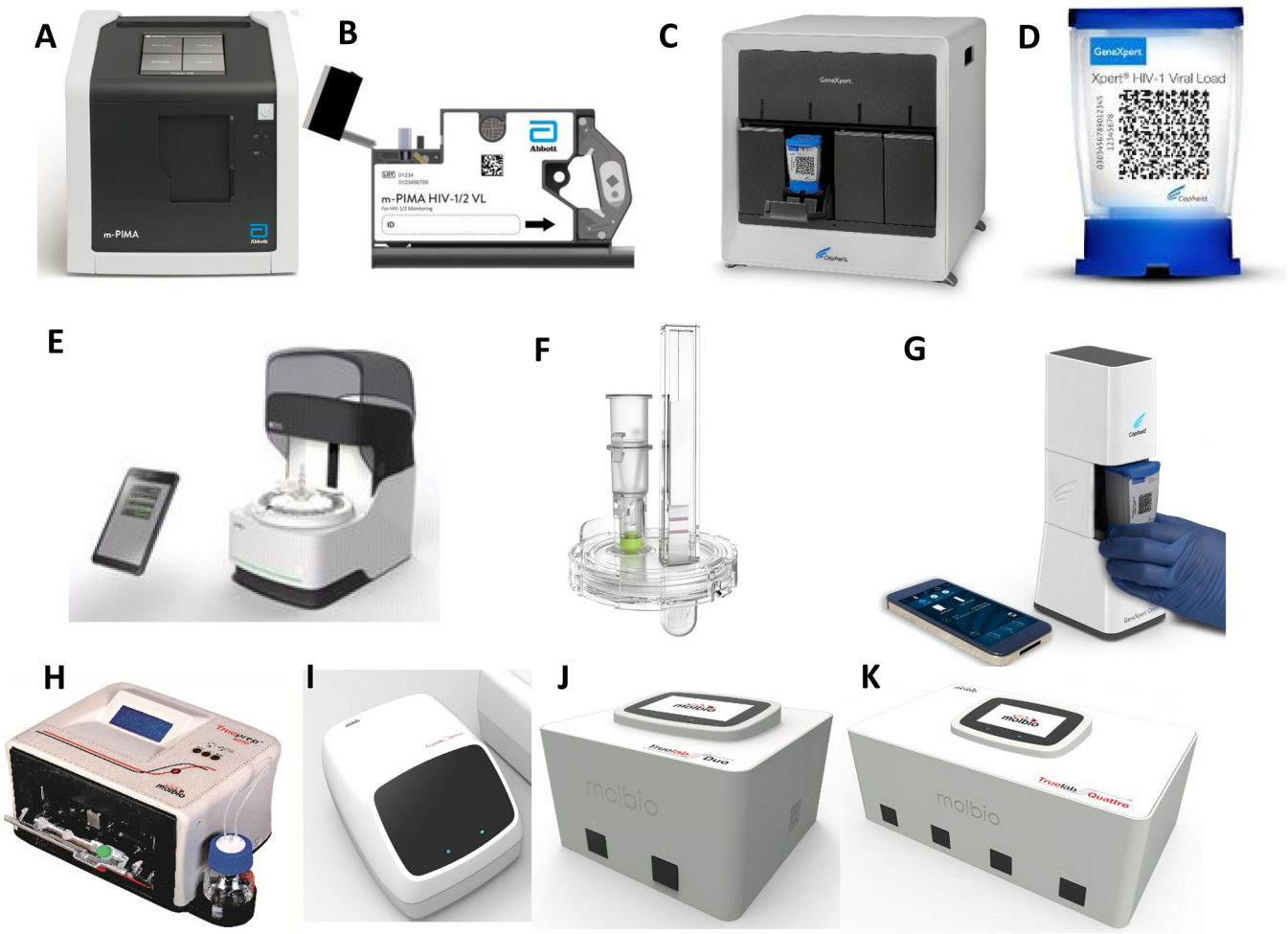

FIG 1 Point-of-care HIV viral load equipment and test cartridges currently marketed (A to F) or in development (G to K). Attendant key equipment for some devices, such as modems, barcode scanners, or printers, is not included. (A) The Abbott m-PIMA analyzer; (B) the Abbott m-PIMA HIV-1/2 test cartridge; (C) the Cepheid GX4 instrument; (D) the Cepheid Xpert HIV-1 viral load test cartridge; (E) the DRW SAMBA II test module with controller; (F) the DRW SAMBA II plasma semiquantitative test; (G) the Cepheid Omni instrument and controller; (H) the Molbio Diagnostics Trueprep sample preparation device; (I to K) the Molbio Diagnostics Truelab amplification instruments in Uno (I), Duo (J), and Quattro (K) module formats. (Images are reprinted with permission of the respective manufacturers.)

is a rugged, battery-powered instrument designed for fully automated processing to enable testing outside of a laboratory (Table 2) (24). The technology uses real-time reverse transcriptase PCR (RT-PCR) monitored via competitive reporter hybridization to the amplified target sequence and can quantify HIV-1 RNA from groups M, N, and O, in addition to HIV-2. The m-PIMA is the only POC assay to measure HIV-2 viral load. The lower limit of quantification is 800 to 1,000 copies/ml. The test cartridge contains all required reagents and has a capillary port to introduce 50 μl of plasma that must be separated from venous or capillary whole blood. Such a step requires a refrigerated centrifuge and adds further 15 to 20 min to the test processing time, with a refrigerator required to store the samples prior to adding to the test cartridge. The cartridge is sealed and inserted into a single-module automated instrument that contains internal quality control measures, and the total time to result is approximately 70 min, excluding plasma separation. Abbott has a qualitative HIV-1/2 test, the Alere q HIV 1/2 Detect qualitative viral load assay for EID (early infant diagnosis), that had received WHO prequalification (PQ) status in 2016 for the diagnosis of HIV-positive children and adults using whole blood (25). In an early study comparing the whole-blood Alere q NAT POC viral load against the Roche Cobas Ampliprep/Cobas TaqMan v2 using plasma, the Alere q had a mean bias of 0.86 log copy/ml, a Pearson coefficient of 0.59 (confidence

interval [CI] not provided), and a sensitivity and specificity to detect a viral load >1,000 copies/ml of 96.8% (95% CI, 92.1% to 99.1%) and 47.8% (95% CI, 42.2% to 53.4%), respectively (24). These results reflect the difficulty of separating cell-associated DNA from whole-blood specimens. More recent evaluations of the quantitative m-PIMA HIV-1/2 viral load assay remain unpublished; the assay received CE-IVD marking in December 2018 and is currently undergoing review by the WHO PQ program (26).

GeneXpert by Cepheid. Cepheid produces the Xpert HIV-1 viral load assay, which has received WHO PQ and CE-IVD marking (Table 2) (27). The assay requires 1 ml of plasma, and a 15- to 20-min blood fractionation step using a refrigerated centrifuge is necessary prior to testing (28). The assay uses real time RT-PCR with molecular beacons to target RNA from HIV-1 group M (including subtypes A, B, C, D, F, G, H, J, K, CRF01_AE, CRF02_AG, and CRF03_AB), group N, and group O (http://www.cepheid.com/en/cepheid-solutions/clinical-ivd-tests/virology/xpert-hiv-1-viral-load). On-cartridge sample processing and test analysis are automated, with the total machine processing time, not including plasma separation, taking approximately 90 min. The cartridge can be used in GeneXpert machines, which also run similar cartridge tests for tuberculosis (TB), sexually transmitted infections (STIs) and other infections (30). The machines require temperatures below 30°C and dust-free environments, which restrict their use to controlled settings (31, 32). While they may be considered near POC, several modifications using batteries and even solar panels have enabled its implementation outside of traditional laboratories (33, 34). Cepheid has been developing the Omni, a battery-powered mobile instrument capable of processing a single test cartridge at the clinical point of care (30). Test cartridges for the Omni are fitted with a near-field communication chip, instead of a barcode, to activate the instrument. In July 2018, Cepheid launched the GeneXpert Edge for decentralized testing while working to fix production issues for Omni, which can be battery operated and controlled via tablet instead of computer.

A variety of studies conducted in high- and low-income settings have compared the diagnostic accuracy of the Xpert HIV-1 viral load assay to those of conventional laboratory assays, including the Abbott RealTime HIV-1 m2000rt (Abbott Molecular) (35–40), Roche COBAS AmpliPrep/COBAS TaqMan (Roche Diagnostics) (41–44), NucliSENS EasyQ HIV-1 v2.0 (bioMérieux) (45), and Versant HIV-1 RNA 1.5 assay (Siemens HealthCare Diagnostics) (46). In a recent meta-analysis of these studies, the pooled Pearson coefficient was 0.94 (95% CI, 0.89 to 0.97; $n = 8$ studies) and the pooled Spearman coefficient was 0.96 (95% CI, 0.86 to 0.99; $n = 3$), demonstrating good correlation with laboratory reference results (50). The Xpert HIV-1 had a mean bias of within 0.35 log copy/ml of the reference viral load assays. Variability in viral load thresholds meant that pooling of results for sensitivity and specificity was not performed. However, for WHO prequalification, the Xpert HIV-1 viral load assay had 94% sensitivity and 99% specificity for detecting HIV viral loads of >1,000 copies/ml (27). In one study, the Xpert HIV-1 did not detect a viral load in one patient with high titers of an HIV-1 CRF02_AG subtype variant, which had a 25-nucleotide insert that was not matched to reference wild-type sequences (42). The concordance between the Xpert HIV-1 and the reference Roche TaqMan 2.0 was high among other patients with CRF02_AG subtype, which is predominant in West Africa (42). The authors of the meta-analysis noted that the Xpert HIV-1 assay could be of significant value to decentralized HIV viral load testing due to its accuracy, ease of use, and relatively low infrastructure requirements (50). The Xpert HIV viral load assay, used in mobile community-based clinics in Botswana, showed high levels of agreement across a broad range of HIV-1 RNA values with the Abbott m2000sp/m2000rt comparator and that its use in rural communities (after home-based collection of venous blood) was feasible (38). However, to date there are no published studies demonstrating whether it is feasible to provide same-day, true POC viral load results using the Xpert HIV-1 in programmatic settings in LMICs. Instead, the need for centrifugation may prevent the Xpert HIV-1 from being used as a true POC test. Currently, there are three ongoing trials

of this assay being conducted in the United States and/or sub-Saharan Africa (NCT03187964 [47], NCT03533868 [48], and NCT03066128 [49]).

SAMBA by Diagnostics for the Real World. Diagnostics for the Real World (DRW) has developed a simple amplification-based assay (SAMBA) for semiquantitative HIV viral load measurement, called SAMBA semi-Q (https://www.drw-ltd.com/copy-of-samba-overview). The SAMBA I system has a semiautomated format with separate sample preparation, amplification, and detection units capable of processing four samples simultaneously (Table 2). The SAMBA II system is a fully automated modular system, comprised of a tablet-based controller module and up to four processing units per controller. The sample extraction, amplification and detection components are contained within a single sealed cartridge. The SAMBAs use nucleic acid based-sequence amplification (NASBA) (52), an RNA-based isothermal amplification method to amplify HIV-1 RNA, detecting the single-stranded NASBA amplicons via sequence-specific oligonucleotide capture followed by colorimetric detection on a nitrocellulose strip (53). The time to process a specimen is approximately 90 min. The test result is visually scored on a lateral flow assay (LFA) format with a viral load threshold of 1,000 copies/ml. The SAMBAs currently use plasma, adding 15 to 20 min to the test processing time and requiring a refrigerated centrifuge, although a whole-blood testing format is in development (54, 55). The SAMBA I semi-Q prototype assay had a reported 96.6% (CI not reported) concordance with the Roche COBAS AmpliPrep/COBAS TaqMan (57). In a later study, the SAMBA HIV-1 Semi-Q on the SAMBA I demonstrated 98.1% (95% CI, 96.5% to 99.1%) concordance with the Roche TaqMan 2.0 assay (56). However, in these two analyses, any result on the Roche TaqMan 2.0 that was between 500 and 2000 copies was automatically considered concordant with the SAMBA result, which may have biased the concordance results. In a separate analysis, the SAMBA HIV-1 Semi-Q on the SAMBA II was found to have 98.0% (95% CI, 94.3% to 99.6%) concordance with the Abbott RealTime assay (56).

Molbio Diagnostics. Molbio Diagnostics intends to launch an HIV viral load device in 2019 (Table 2). According to the manufacturer, the technology uses real-time RT-PCR and can quantify HIV RNA from HIV-1 group M with a lower limit of quantification, 500 copies/ml. The testing process is fully automated using tabletop-based battery powered instruments, but sample preparation and subsequent amplification and detection occur in two separate instruments (22, 23). The total time to test results is approximately 55 min, which includes a 20-min sample preparation step to process either whole blood or plasma, though a further 15 to 20 min is required to first separate the plasma. The amplification and detection of the RNA extracts are performed on a test chip containing all necessary reagents. The current equipment is a single-, two-, or four-module instrument that uses an Android software platform for processing test chips, storing data, and communicating results and test location via mobile telephone networks (Fig. 1). Currently, there are no published evaluations of the Molbio assay.

Technologies To Advance Next-Generation Tests

While several commercial near-POC HIV viral load tests are available or in late-stage development, further innovation is required to reduce test time, enable the use of whole blood as a starting sample, lower the costs of capital equipment and disposable test cartridges, and improve assay sensitivity and quantitative accuracy. HIV viral load testing is a complex, multistep process requiring sample collection, blood fractionation, viral lysis, RNA extraction, amplification, and detection, and communication of test results (Fig. 2). Sample preparation is a significant challenge for "sample-to-answer" viral load tests requiring automation of blood fractionation, virion lysis, and nucleic acid extraction prior to downstream amplification and detection.

POC viral load testing should be conducted on whole blood, via either venipuncture (0.2 to 2 ml), heel prick, or finger prick sampling ($<$200 μl) (58, 59). Plasma separation has been used to remove red blood cells and peripheral blood mononuclear cells (PBMCs) that can inhibit nucleic acid amplification tests or cause spurious results by inclusion of proviral DNA (60, 61). Several equipment-free solutions for integrated

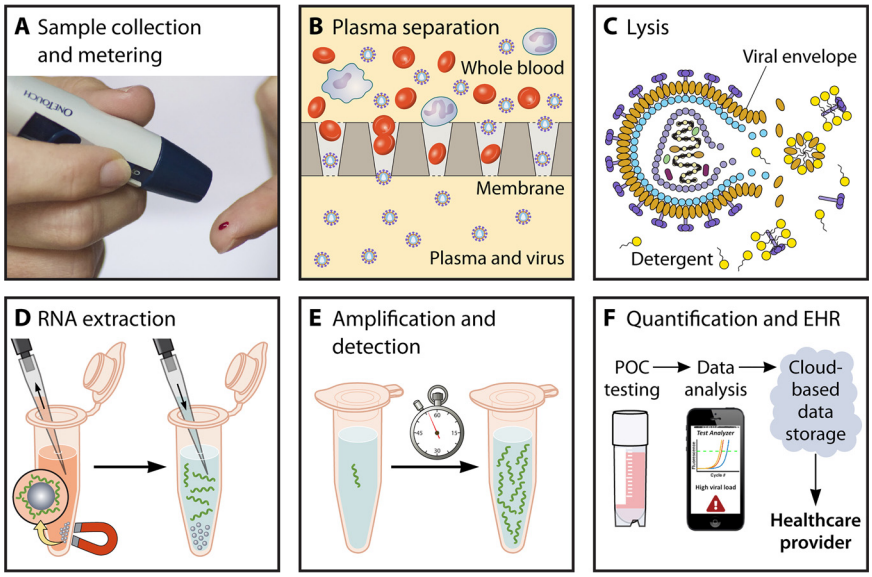

FIG 2 Examples of various steps which must be integrated into potential POC HIV viral load tests. (A) Sample collection should be simple to perform and provide precise volume metering. (B) Membrane-based plasma separation to exclude proviral HIV DNA in PBMCs. (C) Viral lysis using a detergent to denature the viral envelope and release HIV RNA. (D) Magnetic bead-based RNA extraction to purify RNA from blood-related inhibitors and lytic agents. (E) Amplification of nucleic acids to detectable concentrations. (F) Algorithm and device to provide quantitative results and communicate results to electronic health records (EHR).

plasma separation have emerged to eliminate additional user steps (62). Sedimentation techniques often require microchip fabrication and struggle to process volumes greater than 5 to 10 μl of undiluted blood (63–65). Other techniques using separation membranes, which can be sized to process large sample volumes, are easier to integrate in paper-based assays (66–70).

A crucial step is thorough lysis of the HIV virion, which degrades the lipid and protein viral envelope that encapsulates RNA strands. Lysis can be achieved by heating, detergents, enzymes, or chaotropic salts (71–74). After virion lysis, efficient isolation of highly purified HIV RNA is required, as even trace amounts of inhibitors can significantly affect performance of quantitative amplification. Solid-phase, silica-based extraction methods are used in gold standard tests (75) and have been translated into POC microfluidic or paper-based formats (76–78). Silica-based extraction requires exchanges of wash and elution buffers, a task difficult to automate in simple POC devices. Several single-step nucleic acid purification strategies have been developed in paper-based devices, such as chitosan-coated membranes (79) and electrophoretic separation of nucleic acids from blood (69). Despite these recent advancements in sample preparation techniques, automating HIV lysis and RNA extraction from blood samples remains a formidable challenge (80–83).

Real-time PCR has long been the staple of nucleic acid amplification testing (NAAT), including most of the current gold standard viral load tests (74). PCR assays are difficult to implement in POC devices due to the significant power demands of thermocycling and the need for highly purified nucleic acids. Other options may include isothermal amplification techniques, such as loop-mediated isothermal amplification (LAMP) (84, 85), helicase dependent amplification (86), and recombinase polymerase amplification (87). Isothermal assays do not require thermal cycling and therefore have reduced power demands and require less time for amplification. While isothermal methods are convenient for POC implementation, few assays have demonstrated reliable quantitative results (88–90). For researchers developing HIV viral load isothermal amplification assays, the primary challenge remains demonstrating quantitative accuracy comparable to that of real-time PCR across wide ranging viral loads (10^3 to 10^6 copies/ml) and subtypes.

While not unique to POC testing, NAAT for HIV is also complicated by the virus's high rate of mutation, recombinant forms, and different clades associated within regions of high prevalence (74, 91). NAATs can account for sequence diversity with degenerate primers (91), long primers capable of tolerating mismatches (87) and targeting highly conserved regions of the HIV genome (92, 93). Still, the HIV sequence diversity can impact the performance of an assay, especially when applied to a variety of subtypes (94).

When it comes to readout, quantitative NAATs most commonly use fluorescence-based methods to detect amplification (14), while LFA-based detection methods can provide semiquantitative results (95). Additional strategies have targeted reverse transcriptase activity (58) or optically sense virus particles (96). While recent studies have reported innovative devices integrating NAAT operations, these platforms used assays for various infectious diseases, with no specific demonstration of HIV detection or quantification (69, 78, 97–100).

Moving forward, the central challenge facing POC HIV viral load tests is automating all diagnostic steps, including sample preparation and amplification, ideally in a manner that circumvents the high electrical power demands and instrumentation costs for robotics, optics, or pumps. Additionally, test developers face an obstacle in the target product profile, which proposes an optimal limit of detection of 200 copies/ml and sample specimen of less than 200 μl of finger capillary blood (Table 1). A low sample volume reduces the number of input of virions, elevating the limit of detection. HIV viral load tests will need to improve efficiency of sample preparation and sensitivity of amplification assays to achieve a low detection limit via capillary blood.

GENERATING THE EVIDENCE FOR IMPLEMENTATION OF DECENTRALIZED HIV VIRAL LOAD TESTING

Approaches to improve the delivery of HIV viral load testing that are effective, scalable, and sustainable are urgently needed, but under resource constraints, the allocation of resources for decentralizing HIV viral load testing should be based on evidence (101–104). If health facility factors are not properly taken into consideration, then implementation of decentralized HIV viral load testing will be jeopardized (105, 106). Introducing new diagnostic devices into clinics with heavy workloads may cause disruptions in the clinical workflow (107), which can result in a loss of efficiency and a decline in service quality (108, 109). Alternatively, the experience of staff in primary health facilities with routine use of rapid diagnostic tests (RDTs) for HIV diagnosis may facilitate the expansion of POC HIV viral load testing (110). An assessment of the barriers and facilitators is required to address challenges at both the facility and health system levels (111–117). In a systematic review of 132 studies, the most common barriers to POC implementation in HIV programs were related to integration into clinical practice, followed by concerns regarding diagnostic accuracy (29).

Evidence and Results from Clinical Studies

The implementation of RDTs for HIV (118) and CD4 count testing (119, 120) at the point of service has resulted in improvements of the HIV care cascade (121). A case in point is the use of qualitative POC technologies for early infant diagnosis (EID). A field evaluation in South Africa comparing POC Xpert HIV-1 Qual and lab-based molecular platforms showed that decentralized EID testing was accurate and increased the rate of result return when used in a maternity hospital (122). A recent cluster randomized clinical trial in Mozambique (123), and an observational study in Malawi (124), showed that the qualitative Alere q HIV-1/2 Detect accelerated the time to ART initiation, with an associated increase in the proportion of HIV-positive infants who were initiated on ART within 180 days of sample collection (90.3% and 91.1%, respectively), compared to standard centralized laboratory testing (40.2% and 48.4%, respectively). More recent evidence comes from a large POC EID program evaluation incorporating over 20,000 tests into routine clinical services as part of a "hub and spoke" design, which reduced sample turnaround time across 339 clinical sites in 8 African countries (125). The

proportion of HIV-positive infants who were initiated on ART by 60 days increased from 43.3% to 92.3%, with cost per result returned in 30 days decreasing from $131 (U.S. dollars) with conventional referral laboratory testing to $38 with POC testing. In a study for diagnosing acute HIV infection, 91% of the patients attending a community clinic in Spain were notified of their HIV-positive status the same day using the Xpert HIV-1 Qual assay (126). These studies demonstrate that POC platforms can be successfully implemented in a number of settings and have led to guidelines for the introduction of HIV POC diagnostics into national programs (127). The WHO recommended POC EID testing, and a programmatic update in 2016 confirmed that POC EID assays can be used for confirmatory testing (2).

Several randomized clinical trials in LMICs are investigating the clinical impact of POC HIV viral monitoring for PLHIV receiving ART (Table 3). Study populations vary but include children, adolescents, adults, and pregnant women, with interventions of POC viral load test alone or combined with new models of HIV care. Most studies include viral suppression as an outcome, alongside various process evaluation measures.

Results from an observational study in Zimbabwe (32) suggest that implementation of Xpert HIV-1 Viral Load for ART monitoring is feasible in this setting. In addition, use of the GeneXpert platform allows multidisease POC testing for sexually transmitted infections, tuberculosis, and hepatitis C (128, 129). The same study in rural Zimbabwe showed that multidisease POC testing with GeneXpert at district and subdistrict health care facilities was achievable but relied on supervision and quality management systems to ensure the accuracy of testing services (32). In some countries, large-scale, centralized HIV viral load testing is being performed using dried blood spot cards (130–132). The diversity of approaches that have shown promise implies that a combination of centralized and decentralized models should be considered for scale-up (133, 134).

Regulatory Issues, Quality Assurance, Supply Chain, and Data Connectivity

The lessons learned from establishing centralized models for HIV viral load testing could inform building networks for decentralized testing (135–137). Some challenges would be bypassed by POC testing, such as sample transportation. However, experience and planning for supply chain, reagent forecasting, human resources, maintenance of equipment, and laboratory-clinic interfaces would remain relevant for both centralized and decentralized HIV viral load testing (138–142).

Decentralizing HIV viral load requires that resources and processes are in place for training, monitoring, and quality assurance of test results at the clinic sites (143, 144). Unclear national regulatory pathways pose a challenge (145, 146), increasing the risk of delayed marketing of POC devices across neighboring countries in East Africa (147). Ensuring quality of POC testing through an external quality assessment (EQA) program poses numerous challenges, as the costs of setting up and maintaining such programs are often underestimated (148). The use of digital technologies can support strengthening EQA activities and supply chains within a network of peripheral testing centers using POC technologies (149, 150), but their full potential has not yet been realized due to issues around data ownership and confidentiality (151).

ROLE OF TASK SHIFTING FOR DIFFERENTIATED HIV CARE

Task shifting has been effectively implemented to facilitate HIV diagnostic screening and CD4 count testing activities and may be an effective strategy for POC HIV viral load testing in decentralized settings (18, 152, 153). A key consideration for decentralized HIV viral load testing is who will perform the test. Task shifting from physicians to nurses, and nurses to community health care workers has been successfully implemented for both the diagnosis and management of HIV (154–156). Task shifting in LMICs has facilitated the creation of innovative "differentiated care" services, which have increased health care coverage, improved monitoring, and reduced costs. However, the decentralization of POC HIV viral load testing poses a new set of opportunities and challenges at both facility and health system levels (113–117).

TABLE 3 Randomized controlled trials assessing clinical impacts of POC HIV viral load testing

Clinical trial	Location	Study population	Interventions	Outcomes	Estimated completion date
STREAM, NCT03066128 (49)	Single site, South Africa	390 nonpregnant adults on ART who are due a viral load test at 6 mo after initiation	POC monitoring including Xpert HIV-1 viral load testing, combined with task shifting to enrolled/auxiliary nurses, versus standard of care	Primary: (i) Proportion of patients who are retained in care with viral suppression at <200 copies/ml at 12 mo after enrollment (18 mo on ART) Secondary: (i) Proportion of patients with viral load of <1,000 copies/ml 12 mo from enrollment (ii) Costs per patient virologically suppressed and retained in care (iii) Time to detection of virological failure, subsequent intensive adherence counseling, and initiation of second-line regimen (iv) Proportion of patients entered appropriately into differentiated ART delivery programs and time to appropriate entry into these programs	Q4 2018
NCT03288246 (189)	Single site, Haiti	150 persons aged 10–24 yrs on ART for >6 mo	POC HIV viral load testing at enrollment, 3 and 6 mo compared to standard laboratory testing at the same time points	Primary: (i) Number of steps in the HIV viral load cascade Secondary: (i) Comprehension of the relationship between ART adherence and HIV viral load assessed 1 mo after receiving viral load result (ii) Viral suppression at <1,000 copies/ml at 6 mo from enrollment	Q4 2018
UltraHIV NCT03187964 (47)	Single site, South Africa	1,500 adults on ART who are due annual HIV viral load testing (another component of the study assesses Xpert Ultra for TB in a separate group of 1,500 adults)	POC Xpert HIV-1 viral load testing at site versus standard laboratory viral load testing	Primary: (i) Related to TB component of the study. Secondary: (i) Proportion of patients diagnosed with viremia by 8 wks (ii) Of those with viremia, the proportion who are identified to require adherence counselling and/or HIV resistance testing by 1 wk, are referred for adherence counselling and/or second-line ART by 8 wks, and do not successfully start adherence counseling, HIV resistance testing, or second-line ART by 12 wks	Q4 2019
NCT03533868 (48)	Two sites, Nigeria	794 adults being initiated on ART	POC Xpert HIV-1 Viral Load monitoring at 6 and 12 mo from enrollment versus standard laboratory viral load	Primary: (i) Proportion of patients with viral suppression at <1,000 copies/ml at 12 mo on ART Secondary: (i) Average adherence from pharmacy refill data (ii) Loss to follow-up at 12 mo (iii) Time to adherence counselling, confirmation of virological failure and switch to second-line ART (iv) Time from specimen collection to result availability and communication to patient (v) HIV drug resistance patterns (vi) Patient and health care worker satisfaction	Q4 2019
RAPID-Viral Load NCT03553693 (190)	20 sites, Uganda	2,440 children, adolescents, and adults on ART, including pregnant women and patients with unsuppressed HIV viral loads	RAPID-Viral Load study intervention testing and counselling package, which includes near-point-of-care HIV viral load testing at local testing hubs, structured viral load counseling, and forms to track viral load ordering and testing, with feedback and performance evaluations at regular intervals	Primary: (i) Proportion of patients with HIV viral load ordered when indicated by country guidelines (ii) Mean time to delivering HIV viral load result to patient Secondary: (i) HIV viral load suppression at 12 mo from enrollment (ii) HIV viral load suppression (iii) Proportion switched to second-line ART (iv) Proportion of results present in Uganda's Central Public Health Laboratory system	Q4 2019

The Role of Nurses and Community Health Care Workers for HIV Care

Early ART programs in LMICs were provided through hospital-based, physician-led services, in a resource-intense model of HIV care that was neither sustainable nor scalable. To provide ART to the large numbers of people living with HIV/AIDS in LMICs, the WHO recommended decentralization and task shifting in public sector ART programs in 2004 (157, 158). Since then, numerous observational cohorts and clinical trials have demonstrated that decentralizing ART care from hospitals to primary care clinics improved retention in care and reduced mortality (159, 160), while nurse-led ART care is equivalent to physician-led care when measured by clinical and immunological outcomes (161). In southern and eastern Africa, nurses now routinely manage ART initiation and HIV care, as well as screening for and treating TB, STIs, and noncommunicable diseases among PLHIV.

As ART programs have matured, decentralization and task shifting have been integrated into differentiated care services (156). These services aim to meet the various needs of clients by adapting the location of care and ART delivery, the person providing care, and the interval between clinical visits and ART collection (162). Differentiated care services may be based in clinical or community settings, may involve health care workers or lay community health workers (CHWs), and include services for HIV prevention, testing and treatment (142). Examples of differentiated care for ART delivery in LMICs include community-based ART clubs (163), community ART delivery programs (164), streamlined ART pick-up, and multimonth prescriptions (165). Home-based ART provided by trained CHWs has also been found to be equivalent to physician-led care (166). South Africa has been implementing fully automated kiosks for dispensing ART with support provided via telemedicine interactions between clients and off-site pharmacists (167). These strategies can make treatment less burdensome for stable, suppressed patients who can receive longer refills and care closer to home, increase availability of staff for patients in need for more intensive follow-up, and reduce health care costs through appointment spacing and task shifting (103, 166, 168).

Use of POC Assays by Nurses and Health Care Workers within HIV Programs

A key component of decentralized, differentiated care services has been the development of POC technologies that have enabled testing to be conducted by nonlaboratory staff in both clinic and community settings (12). The use of antibody-based POC HIV tests by trained lay workers has been successful and recommended by the WHO (117, 169). The ease of use and portability of RDTs has allowed them to be implemented in large community-based HIV testing campaigns to increase overall HIV testing coverage for achieving the first 90-90-90 target (170–172). Despite the simplicity of RDTs, quality assurance and supply chain management have remained challenging in programmatic settings (173, 174).

The WHO recommends CD4 count testing to stage disease at HIV diagnosis, and rapid, portable POC CD4 count assays have been developed to measure CD4 counts using venous or capillary whole blood in under 30 min (175, 176). The Pima CD4 (Abbott, Chicago, IL) can be operated by nurses in primary care clinics (177, 178) and had acceptable performance characteristics in two meta-analyses, with sensitivities to detect a CD4 count of $<$350 cells/mm^3 of 93% and 92% and specificities of 86% and 87% (175, 176). POC CD4 count testing has been accepted by patients and health care workers in many resource-limited settings (176), although failure rates ranging from 0% to 23.3% have been reported (179). These may have been due to deficiencies in quality assurance procedures, such as inadequate sample collection or machine calibration (176, 179).

When CD4 counts were used to determine ART eligibility, POC CD4 count testing was shown to increase retention in pre-ART care and increase ART initiation (104, 180), particularly when performed by lay workers in home-based HIV testing services (181). POC CD4 count assays have been used by nurses within health care facilities to allow same-day ART initiation, which was associated with increased overall ART initiation (182) and improved retention in care and subsequent viral suppression (183). In

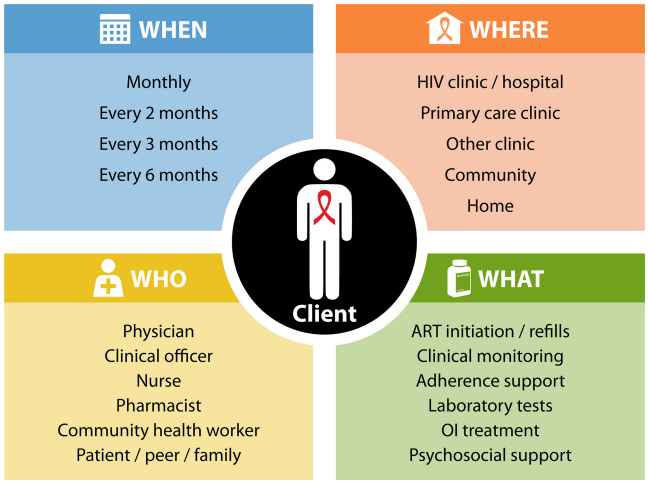

FIG 3 The building blocks of differentiated ART delivery with POC HIV viral load testing. OI, opportunistic infection. (Adapted from reference 187 with permission.)

addition, availability of POC creatinine, alanine aminotransferase, and hemoglobin assays has similarly facilitated decentralized access to clinical monitoring. With the universal test-and-treat strategy, whereby all people living with HIV are started on ART, CD4 count testing remains important for staging HIV disease and assessing eligibility for prophylactic treatment (184). Four large trials of the universal test-and-treat strategy in southern and eastern Africa (ANRS TasP, SEARCH, BCPP, and MaxART) have incorporated POC CD4 count testing by nurses or lay health care workers into community-, home-, and facility-based HIV testing strategies (185). In Lesotho, a home-based, same-day ART initiation program in which nurses performed POC CD4 count and creatinine and hemoglobin testing improved ART initiation, retention in care, and viral suppression (186).

Looking Ahead: The Role of POC HIV Viral Load Testing within Differentiated Care Services

While nurses and CHWs have used POC assays to improve HIV testing and ART initiation, there is less evidence for implementing POC diagnostics to monitor PLHIV receiving ART. Evidence for the feasibility of task shifting POC viral load testing is lacking (50), although some testing has occurred within primary care or mobile clinics (24, 38, 43). The development of more portable assays and use of finger prick whole-blood testing should make POC viral load testing easier for nurses and CHWs in a range of settings (30). POC viral load assays have the potential to streamline ART monitoring and quickly triage patients into more or less intense care pathways (187), a strategy known as "viral-load informed differentiated care" (133, 162). The International AIDS Society (IAS) provides a decision framework for designing differentiated care services, which encourages policy makers to focus on the clinical characteristics, subpopulations, and contextual factors surrounding clients and to adapt the location of services, the care provider, and the services offered accordingly (Fig. 3) (162, 187).

Clinical trials of POC viral load testing may facilitate task shifting to nurses and referral into differentiated care programs (Table 3) (47, 48, 188–190). In one study, integrated POC monitoring using POC CD4 count (Pima), POC creatinine, and POC HIV viral load (Xpert HIV-1) is being evaluated to rapidly identify stable patients who can be seen by an enrolled/auxiliary nurse every 2 months and then be down-referred to a community ART delivery program, in which they are seen by a nurse every 6 months (Fig. 4) (188). The primary outcome is viral suppression and retention in care after 12 months of POC monitoring, with secondary outcomes including costs of POC monitoring, time to receipt of results, time to adherence counseling, and time to switch

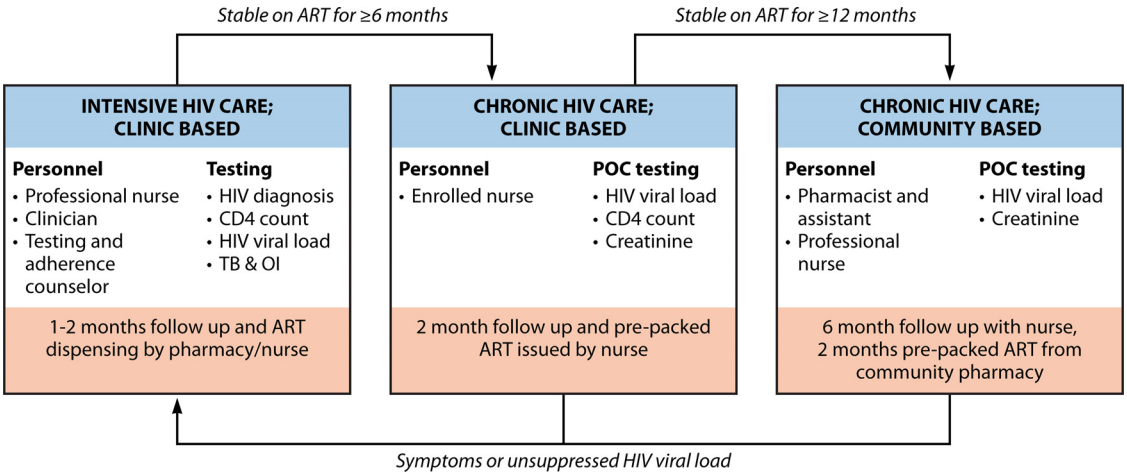

FIG 4 A conceptual model of integrated point-of-care testing within differentiated care.

to second-line ART. If found to be cost-effective, models of differentiated care with POC HIV viral load monitoring could be used to help achieve the 90-90-90 targets.

EVIDENCE FROM MODELING AND COST-EFFECTIVENESS

Role of Modeling in Evaluation of POC HIV Viral Load Testing

Modeling population-level impact and cost-effectiveness plays an important role in translating clinical trial findings into a broader set of population estimates (47–48, 188–191). Through modeling, trial results can be translated into standardized impact metrics such as disability-adjusted life years (DALYs) averted or quality-adjusted life years (QALYs) gained, as well as indirect benefits such as reduced HIV transmission (48, 136, 137, 192, 193). Models are typically individual based and simulate a cohort of individuals with HIV or a population with births, deaths, and dynamic disease transmission (194–198). Modeling can help to define the timing and detection threshold for POC viral load assays, based on cost-effectiveness analyses that account for the higher cost of second-line ART (194–198). The impact of POC HIV viral load testing on health outcomes can be estimated at multiple levels, including individual patients, the population, or national health systems.

Evidence from Modeling Studies for Benefit of POC HIV Viral Load Monitoring

The direct health gains from replacing clinical or laboratory-based CD4 count-based monitoring with laboratory-based viral load monitoring appear to be modest. Randomized trials in Zimbabwe and Uganda (199), Cameroon (200), and Thailand (201) found CD4 count-based monitoring to be noninferior to viral load monitoring and not substantially different from clinical monitoring over the first 3 years of ART. In contrast to centralized testing, POC HIV viral load testing provides results more rapidly, allowing for earlier adherence counseling and/or ART regimen switching to reduce the risk of HIV drug resistance, worsening immunosuppression, and onward HIV transmission. In multiple modeling studies, the benefits at the individual level of POC HIV viral load testing were estimated to be small relative to the impact of increasing coverage and retention on first-line ART (135, 194, 197, 198, 202). However, these studies were based on modeled estimates of the effectiveness of POC viral load testing, which were not informed by clinical trial results.

The estimated impact of laboratory-based (203–210) HIV viral load on transmission of HIV is beneficial but modest. In Malawi, 0.8% of HIV infections between 2017 and 2020 could have been averted through immediate scale-up of annual lab-based HIV viral load monitoring (210). A modeling analysis suggested that faster switching to second-line ART, more effective adherence counseling, and reduced transmission through viral suppression each contributed similar health gains, 0.15 QALY per PLHIV receiving ART (197).

The largest effects of POC HIV viral load testing may come from expanding access to viral load-informed differentiated care. In clinical trials (199–201, 211, 212) and modeling (139, 203–208, 213–216) of laboratory-based HIV viral load monitoring, the ability to implement differentiated care had an impact comparable to or greater than the direct health impact of viral load monitoring (217). Similar trends have emerged for models evaluating POC HIV viral load testing (135, 198). However, centralized HIV viral load testing involves sample transportation and transfer of results (218), which has been challenging to forecast and adds uncertainty to model estimates (48, 137, 192, 193, 219, 220).

Projections of Cost-Effectiveness Analysis for POC HIV Viral Load Implementation

Modeling studies have estimated the cost-effectiveness of laboratory-based viral load monitoring (139, 203–209, 213–216) and, more recently, POC viral load monitoring (135, 194, 197, 198, 202). Models incorporating health systems effects of monitoring, such as differentiated care, find increased evidence of cost-effectiveness (217). A comparison of three independently developed mathematical models estimated that implementing laboratory-based HIV viral load monitoring was not cost-effective prior to universal test-and-treat guidelines and concluded that a lack of resources to provide viral load monitoring should not preclude further expansion of ART (202, 221). In the era of the universal test-and-treat strategy, viral load monitoring is cost-effective at the individual level, assuming similar costs for laboratory-based and POC viral load testing (135, 194, 197, 198, 202). Annual viral load testing was generally found to be more cost-effective than 6-monthly viral load testing (197, 202). Patient monitoring contributes a small fraction of overall HIV care costs and thus can become cost-effective and even cost-saving when it enables other aspects of HIV care to become more efficient (197). Enabling viral load-informed differentiated care may be critical to making viral load monitoring more cost-effective and potentially cost-saving (103, 135, 166, 168, 187). As the technology becomes more widely available, new synergies between POC HIV viral load testing and optimal health care delivery may emerge. However, the rollout of dolutegravir-based first-line ART, which appears to have a lower risk of acquired drug resistance, may impact the role of HIV viral load monitoring (222, 223).

ADDITIONAL DIAGNOSTICS NEEDED FOR HIV MONITORING

In LMICs, the management of PLHIV who are identified as having unsuppressed HIV viral loads is complicated by the lack of objective measures of drug adherence and HIV drug resistance, which continues to emerge in LMICs (221, 224). The technological advances that have made POC NAAT available are also applicable to the development of POC HIV drug resistance assays that may allow for decentralized HIV resistance testing (225). Several assays are in development, while target mutations need to be fully characterized for specific drugs and drug regimens. In addition, being able to more accurately and objectively assess drug adherence may become more critical (137), and there are efforts to develop POC tests to measure drug concentrations of various antiretrovirals (ARVs) (226).

Additional tests could be considered for POC delivery to ensure more complete assessment of the health of PLHIV. Offering a package of services to identify patients with advanced HIV disease (defined as CD4 count less than 200 cells/ml) and test for common opportunistic infections is critical (158). Fortunately, POC CD4 count, POC testing for TB using GeneXpert or the lipoarabinomannan (LAM) assay, and screening for cryptococcal meningitis using a cryptococcal antigen RDT are available (184, 227, 228).

Integrated POC testing to include recommended clinical chemistry or hematology tests may be important to further improve HIV treatment services (229). Simple POC hemoglobin assays are becoming more widespread in primary care services and can be used for the monitoring PLHIV receiving zidovudine. For patients receiving tenofovir-based ART, annual creatinine measurement is recommended by the WHO to monitor for nephrotoxicity. Simple POC creatinine assays have been developed, but perfor-

TABLE 4 Priority research questions for point-of-care HIV viral load testing

Category	Questions
Technology development	Can a rapid test be valid and reliable when used on finger prick capillary blood? Can the test processing time be reduced to <30 min? Can the device be made portable and rugged enough for use in community settings? Can the technology assist in communicating the result to the patients more efficiently? Can proxy measures, such as virion markers, provide adequate measures of viral load?
Clinical testing	Are clinic personnel capable of running and interpreting rapid viral load tests? How accurate are current POC HIV viral load devices when used in clinical settings? Can POC HIV viral load assays be efficiently integrated with other required tests? Does clinic-based HIV viral load monitoring improve patient outcomes?
Implementation science	How do point-of-care viral load tests fit within models of differentiated HIV care? What is the optimal interval for clinic-based HIV viral load testing? Is it possible to conduct viral load testing in decentralized locations for ART refills? Is the implementation of POC viral load testing cost-effective?

mance in the field requires further evaluation (230). A paper-based test or RDT for measurement of alanine transaminase could offer more reliable access for monitoring of liver function (231, 232). As PLHIV are living longer due to better access to life-saving ART, management of noncommunicable diseases, such as diabetes and cardiovascular disease, may also benefit from an existing decentralized POC testing infrastructure, such as for lipids and hemoglobin A1c testing (233).

RESEARCH NEEDS AND PRIORITIES

POC HIV viral load testing may be an essential tool for accelerating declines in HIV/AIDS burden and incidence. However, since technologies and implementation are rapidly evolving, many clinical, translational, and basic science questions remain. In Table 4, we list some of the key research needs and priorities for each of the domains presented in this review. In general, these research questions fall into the domains of technology development, clinical testing, and implementation science.

Several technology development questions pertain to the future design of devices and potential use of easily obtainable finger prick capillary blood. Additional benefits could be achieved by reducing the processing time and developing a more durable system for use in community-based settings. Clinical research questions pertain to the accuracy of individual tests when used at the clinical point of care. Perhaps one of the most pressing research priorities is having a better understanding of the efficacy of clinic-based HIV viral load testing in terms of patient outcomes, and several clinical trials will provide results soon. Implementation science research questions pertain to how frequently HIV viral load testing should be performed and whether current or future devices may allow for further decentralization of testing. Finally, the cost-effectiveness of POC HIV viral load testing will need to be explored with empirical clinical trial data and mathematical modeling.

CONCLUSIONS

While the rapid expansion of access to ART remains the priority, access to HIV viral load testing will be critical for ensuring HIV treatment success, maintaining virological suppression, and ending the HIV/AIDS pandemic. Given the complexity and delays associated with laboratory-based HIV viral load testing, rapid clinic-based POC testing holds promise for facilitating HIV management and improving patient outcomes. In this review, we have highlighted the current knowledge of the technology for POC HIV viral load testing and offered opportunities and priorities for further exploration.

Through the development of better diagnostic tests and a greater understanding of the clinical role of POC HIV viral load testing, we may be able to devise more advanced and specific solutions to HIV/AIDS. By synthesizing the expanding knowledge and addressing existing research gaps of POC HIV viral load testing, the research and public

health communities may move forward together on developing sustainable solutions to end the HIV/AIDS pandemic.

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