

Point-of-care HIV viral load testing:

An essential tool for a sustainable global HIV/AIDS response

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Short Title: Point-of-care HIV viral load testing

Word Count: Summary – 199; Text – 6,500

Tables & Figures: 4 tables; 4 figures

References: 251

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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 towards achieving population targets for viral suppression. The capacity for laboratory-based 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 turn-around time of 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 healthcare workers, and the additional considerations for expanding point-of-care HIV viral load testing.

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 should 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 <1,000 copies/ml. People living with HIV 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 of HIV/AIDS (UNAIDS) launched the 90-90-90 project to achieve the following goals by the year 2020: (1) identify 90% of all PLHIV, (2) initiate 90% of all PLHIV who know their status on ART, and (3) 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 three 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 was 30 weeks [interquartile range (IQR) 17-53 weeks], and the median time from viremia to ART regimen switch was 68 weeks (IQR 35-124 weeks).^{10,11} While these problems may reflect broader weaknesses in the public health systems, POC VL testing could expedite detection of viremia, thereby increasing

viral re-suppression and reducing community viral loads.

Diagnostic point-of-care (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 healthcare services, and improve viral suppression. The development of POC HIV viral load assays are important to measure individual treatment success, as well as monitoring 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 healthcare workers within HIV programs, and evidence from modeling and cost-effectiveness studies.

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.^{12,14,15}

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 of 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 sub-types that represents global HIV sub-type 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, Figure 1](#)).¹³ 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 six companies that were previously described as being in the early to mid-development stages,¹³ 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 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 (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 800-1,000 copies/mL. The test cartridge contains all required reagents and has a capillary port to introduce 50 uL of plasma that must be separated from venous or capillary whole blood. Such a step requires a refrigerated centrifuge and adds further 15-20 mins to 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 minutes, 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 copies/ml, a Pearson coefficient of 0.59 (CI not provided) and a sensitivity and specificity to detect a viral load >1,000 copies/ml of 96.8% (95% CI 92.1-99.1%) and 47.8% (95% CI 42.2-53.4%) 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 (similar to m-Pima), and a 15-20 minutes 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.²⁹ On-cartridge sample processing and test analysis are automated with the total machine processing time, not including plasma separation, taking approximately 90 minutes. 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 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 pooled Pearson co-efficient was 0.94 (95% CI 0.89-0.97, n=8 studies) and pooled Spearman co-efficient was 0.96 (95% CI 0.86-0.99, n=3), demonstrating good correlation with laboratory reference results.⁴⁷ The Xpert HIV-1 had a mean bias of within 0.35 log copy/ml of the reference viral load assay. Variability in viral load thresholds meant that pooled results for sensitivity and specificity were not performed. However, for WHO prequalification, the Xpert[®] HIV-1 Viral Load assay had 94% sensitivity and 99% specificity for detecting HIV viral load >1,000 copies/mL.²⁷ In one study, the Xpert HIV-1 did not detect a viral load in patients 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.⁴⁷ 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 four ongoing trials of this assay being conducted in the United States and/or sub-Saharan Africa (NCT02461576, NCT03187964, NCT03533868, and NCT03066128).

SAMBA by Diagnostics for the Real World

Diagnostics for the Real World (DRW) have developed a simple amplification-based assay (SAMBA) for semi-quantitative HIV viral load measurement, called SAMBA semi-Q.⁴⁸ The SAMBA I system is a semi-automated 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 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 SAMBA assays use nucleic acid based-sequence amplification (NASBA),⁴⁹ an RNA-based isothermal amplification method to amplify HIV-1 RNA, detecting the single stranded NASBA amplicons via sequence-specific oligonucleotide capture followed with colorimetric detection on a nitrocellulose strip.⁵⁰ The time to process a specimen is approximately 90 minutes. The test result is visually scored on a lateral flow assay (LFA) format with a viral load threshold of 1,000 copies/mL. The SAMBA assays currently use plasma, adding 15-20 minutes to the test processing time and requiring a refrigerated centrifuge, although a whole blood testing format is in development.^{51,52} The SAMBA I semi-Q prototype assay had a reported 96.6% (CI not reported) concordance with the Roche COBAS AmpliPrep/COBAS TaqMan.⁵³ In a later study, the SAMBA HIV-1 Semi-Q on the SAMBA I demonstrated 98.1% (95% CI 96.5–99.1%) concordance with the Roche Taqman 2.0 assay.⁵⁴ However, in these two analyses, any result on the Roche Taqman 2.0 that was between 500-2000 copies was

262 automatically considered concordant with the SAMBA result, which may have biased
263 the concordance results. In a separate analysis, the SAMBA HIV-1 Semi-Q on the
264 SAMBA II was found to have 98.0% (95% CI 94.3–99.6%) concordance with the Abbott
265 RealTime assay.⁵⁴

267 *Molbio Diagnostics*

268 Molbio Diagnostics intends to launch a HIV viral load device in 2019 (Table 2).
269 According to the manufacturer, the technology uses real-time RT-PCR with a
270 TaqMan™ probe and can quantify HIV RNA from HIV-1 group M with a lower limit of
271 quantification of 500 copies/mL. The testing process is fully automated using tabletop-
272 based battery powered instruments, but sample preparation followed by amplification
273 and detection occur in two separate instruments.^{55,56} The total time to test results is
274 approximately 55 minutes, which included a 20-minutes sample preparation step to
275 process either whole blood or plasma, though a further 15-20 mins is required to first
276 separate the plasma. The amplification and detection of the RNA extracts is performed
277 on a test chip containing all necessary reagents. The current equipment is a single-,
278 two-, or four-module instrument that uses an android software platform for processing
279 test chips, storing data and communicating results and test location via mobile
280 telephone networks (Figure 1). Currently, there are no published evaluations of the
281 Molbio assay.

283 ***Technologies to advance next-generation tests***

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

POC viral load testing should be conducted on whole blood, either via venipuncture (0.2 – 2 mL), heel-prick, or finger-prick sampling (<200 uL).^{57,58} 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.^{59,60} Several equipment-free solutions for integrated plasma separation have emerged to eliminate additional user steps.⁶¹ Sedimentation techniques often require microchip fabrication and struggle to process volumes greater than 5 to 10 uL of undiluted blood.⁶²⁻⁶⁴ Other techniques using separation membranes, which can be sized to process large sample volumes, are easier to integrate in paper-based assays.⁶⁵⁻⁶⁹

A crucial step is thoroughly lysing 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.⁷⁰⁻⁷³ 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,⁷⁴ and have been translated into POC microfluidic or paper-based formats.⁷⁵⁻⁷⁷ Silica-based extraction requires exchanges of wash and elution buffers, a concept difficult to automate in simple POC devices. Several single-step nucleic acid purification strategies have emerged in paper-based devices, such as chitosan-coated membranes⁷⁸ and electrophoretic separation of nucleic acids from blood.⁶⁸ Despite these recent advancements in sample preparation techniques, automating HIV lysis and RNA extraction from blood samples remains a formidable challenge.⁷⁹⁻⁸²

Real-time PCR has long been the staple of nucleic acid amplification testing (NAAT), including most of the current gold standard viral load tests.⁷³ 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),^{83,84} helicase dependent amplification,⁸⁵ and recombinase polymerase amplification.⁸⁶ 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.⁸⁷⁻⁸⁹ For researchers developing HIV viral load isothermal amplification assays, the primary challenge remains demonstrating quantitative accuracy comparable to real-time PCR across wide ranging viral loads (10^3 – 10^6 copies/mL) and subtypes.

While not unique to POC testing, NAAT for HIV is also complicated by the virus' high rate of mutation, recombinant forms and different clades associated within regions of high prevalence.^{73,90} NAATs can account for sequence diversity with degenerate primers,⁹⁰ long primers capable of tolerating mismatches,⁸⁶ and targeting highly conserved regions of the HIV genome.^{91,92} Still, the HIV sequence diversity can impact the performance of an assay, especially when applied to a variety of subtypes.⁹³

When it comes to readout, quantitative NAATs most commonly use fluorescence-based methods to detect amplification,¹⁴ while LFA-based detection methods can provide semi-quantitative results.⁹⁴ Additional strategies have targeted reverse transcriptase activity⁹⁵ 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.^{68,77,97-100}

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 uL 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 clinic workflow,¹⁰⁷ which can result in loss of efficiency and 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 large 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.¹¹¹

Evidence and results from clinical studies

The implementation of RDTs for HIV¹¹⁸ 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 (90.3-91.1%), when compared to standard centralized laboratory testing (40.2-48.4%). 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 turn-around 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 USD 131 with conventional referral laboratory testing to USD 38 with POC testing. In a study for diagnosing acute HIV infection, 91% of the patients attending a community clinic in Spain received 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, with results expected from late 2018 to 2019 (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 Zimbabwe³² 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 multi-disease POC testing for sexually transmitted infections, tuberculosis and hepatitis C.^{128,129} The same study in rural Zimbabwe showed that multi-disease POC testing with GeneXpert at district and sub-district healthcare 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.¹⁵²⁻¹⁵⁴ 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 healthcare workers has been successfully implemented for both the diagnosis and management of HIV.¹⁵⁵⁻¹⁵⁷ Task shifting in LMICs has facilitated the creation of innovative 'differentiated care' services, which have increased healthcare coverage, improved monitoring, and reduced costs. However, the decentralization of POC HIV viral load testing poses a new set of opportunities and challenges both at facility and health system levels.¹¹³⁻¹¹⁷

The role of nurses and community healthcare workers for HIV care

Early ART programs in LMICs were provided through hospital-based, physician-led services, in a resource-intensive 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, WHO recommended decentralization and task shifting in public sector ART programs in 2004.^{158,159} 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,^{160,161} while nurse-led ART care is equivalent to physician led care when measured by clinical and immunological outcomes.¹⁶² In southern and eastern Africa, nurses now routinely manage ART initiation and HIV care, as well as screening for and treating TB, STIs and non-communicable diseases among PLHIV.

As ART programs have matured, decentralization and task-shifting have been integrated into differentiated care services.¹⁵⁷ These services aim to meet the varying needs of clients by adapting the location of care and ART delivery, the person providing care, and the time interval between clinical visits and ART collection.¹⁶³ 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.¹⁶⁴ Examples of differentiated care for ART delivery in LMICs include community-based ART clubs,¹⁶⁵ community ART delivery programs,¹⁶⁶ stream-lined ART pick-up and multi-month prescriptions.¹⁶⁷ Home-based ART provided by trained CHWs has also been found to be equivalent to physician-led care.¹⁶⁸ South Africa has been implementing fully automated kiosks for dispensing ART with support provided via tele-medicine interactions between clients and off-site pharmacists.¹⁶⁹ 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.¹⁷⁰⁻¹⁷²

Use of POC assays by nurses and healthcare 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 non-laboratory 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.^{173,174} 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.¹⁷⁵⁻¹⁷⁷ Despite the simplicity of

RDTs, quality assurance and supply chain management has remained challenging in programmatic settings.^{178,179}

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 minutes.^{180,181} The Pima™ CD4 (Abbott, Chicago, IL, US) can be operated by nurses in primary care clinics^{182,183} and had acceptable performance characteristics in two meta-analyses, with a sensitivity to detect a CD4 count of <350 cells/mm³ of 93% and 92% respectively, and specificity of 86 and 87% respectively.^{180,181} POC CD4 count testing has been accepted by patients and healthcare workers in many resource-limited settings,¹⁸¹ although failure rates ranging from 0-23.3% have been reported.¹⁸⁴ These may have been due to deficiencies in quality assurance procedures, such as inadequate sample collection or machine calibration.^{181,184}

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,^{185,186} particularly when performed by lay workers in home-based HIV testing services.¹⁸⁷ POC CD4 count assays have been used by nurses within healthcare facilities to allow same-day ART initiation, which was associated with increased overall ART initiation¹⁸⁸ and improved retention in care and subsequent viral suppression.¹⁸⁹ In addition, availability of POC creatinine, alanine aminotransferase and hemoglobin assays has similarly facilitated decentralized access to clinical monitoring. With universal test and treat, 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.¹⁹⁰ Four large trials of universal test and treat in southern and eastern Africa (ANRS TasP, SEARCH, BCPP and MaxART) have incorporated POC CD4 count testing by nurses or lay healthcare workers into community, home and facility-based HIV testing strategies.¹⁹¹ In Lesotho, a home-based, same-day ART initiation program in which nurses performed POC CD4 count, creatinine and hemoglobin testing improved ART initiation, retention in care and viral suppression.¹⁹²

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,⁴⁷ 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,¹⁹³ a strategy known as “viral-load informed differentiated care.”^{163,194} The International AIDS Society (IAS) provides a decision framework for designing differentiated care services, which encourages policy makers to focus on the clinical characteristics, sub-populations and contextual factors surrounding clients, and to adapt the location of services, the care provider and the services offered accordingly (Figure 3).^{163,195}

Clinical trials of POC viral load testing may facilitate task-shifting to nurses and referral into a differentiated care programs (Table 3).¹⁹⁶⁻²⁰⁰ In one study, integrated POC monitoring using POC CD4 count (PimaTM), 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 two months, and then be down-referred into a community ART delivery program, where they are seen by a nurse every six months (Figure 4).¹⁹⁶ 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 counselling, and time to switch 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 serves an important role in translating clinical trial findings into a broader set of population estimates.²⁰¹⁻²⁰⁵

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.²⁰⁶⁻²¹⁰ Models are typically individual-based and simulate a cohort of individuals with HIV or a population with births, deaths, and dynamic disease transmission.²¹¹⁻²¹⁵ 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.²¹¹⁻²¹⁵ The impact of POC HIV viral load testing on health outcomes can be estimated at multiple levels, including individuals 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,²¹⁶ Cameroon,²¹⁷ and Thailand²¹⁸ found CD4 count-based monitoring to be non-inferior to viral load monitoring and not substantially different from clinical monitoring over the first three 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.^{194,211,214,215,219} However, these studies were based on modelled estimates of the effectiveness of POC viral load testing, which were not informed by clinical trial results.

The estimated impact of laboratory-based²²⁰⁻²²⁷ 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.²²⁷ 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 of 0.15 QALYs per PLHIV receiving ART.²¹⁴

The largest effects of POC HIV viral load testing may come from expanding access to viral load-informed differentiated care. In clinical trials^{216-218,228,229} and modeling^{220-225,230-234} of laboratory-based HIV viral load monitoring, the ability to implement differentiated care was comparable or greater in impact to the direct health impact of viral load monitoring.²³⁵ Similar trends have emerged for models evaluating POC HIV viral load testing.^{194,215} However, centralized HIV viral load testing involves sample transportation and transfer of results,²³⁶ which has been challenging to forecast and adds uncertainty to model estimates.^{206-209,237,238}

Projections of Cost-Effectiveness Analysis for POC HIV viral load implementation

Modeling studies have estimated the cost-effectiveness of laboratory-based viral load monitoring,^{220-226,230-234} and more recently POC viral load monitoring.^{194,211,214,215,219} Models incorporating health systems effects of monitoring, such as differentiated care, finding increased evidence of cost-effectiveness.²³⁵ 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 lack of resources to provide viral load monitoring should not preclude further expansion of ART.^{219,239} In the era of universal test and treat, viral load monitoring is cost-effectiveness at the individual level, assuming similar costs for laboratory-based and POC viral load testing.^{194,211,214,215,219} Annual viral load testing was generally found to be more cost-effective than 6-monthly viral load testing.^{214,219} 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.²¹⁴ Enabling viral load-informed differentiated care may be critical to making viral load monitoring more cost-effective and potentially cost-saving.^{170-172,193,194} As the technology becomes more widely available, new synergies between POC HIV viral load testing and optimal health care delivery may emerge. However, the roll-out 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.^{240,241}

ADDITIONAL DIAGNOSTICS NEEDED FOR HIV MONITORING

In LMICs, the management of PLHIV who are identified as having an unsuppressed HIV viral load is complicated by the lack of objective measures of drug adherence and HIV drug resistance, which continues to emerge in LMICs.^{239,242} 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.²⁴³ 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 ARVs.²⁴⁴

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.¹⁵⁹ Fortunately, POC CD4 count, POC testing for TB using GeneXpert[®] or the TB-LAM assay, and screening for cryptococcal meningitis using a cryptococcal antigen LFA are available.^{190,245,246}

Integrated POC testing to include recommended clinical chemistry or hematology tests may be important to further improve HIV treatment services.²⁴⁷ 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 WHO to monitor for nephrotoxicity. Simple POC creatinine assays have been developed, but performance in the field requires further evaluation.²⁴⁸ Paper-based or LFA test for measurement of alanine transaminase could offer more reliable access to monitoring of liver function.^{249,250} As PLHIV are living longer due to better access to life-saving ART, management of non-communicable 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.²⁵¹

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 fingerprick 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 empiric 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 of 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

662 solutions to end the HIV/AIDS pandemic.

FUNDING

Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases (AI136648, AI124719, AI127200) and the National Institute of Biomedical Imaging and Bioengineering (EB022630) of the National Institutes of Health. A.T.B. was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award No. TL1TR000422 as well as a National Science Foundation Graduate Research Fellowship. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the National Science Foundation.”

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1338 **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 minutes total
Throughput	Minimum of 15 tests per 8-hour 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

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1341 **Table 2.** Point-of-care HIV viral load assays that are commercially available or in late development.

Manufacturer	Assay	HIV types	Amplification/ detection	Analytic sensitivity (copies/mL)	Testing time* (min)	Sample type & volume	Instrument dimensions	Test Instrument	WHO PQ, CE-IVD	Marketed
Abbott Inc. (formerly Alere)	m-PIMA™ (formerly Alere™ q HIV- 1/2 Detect)	HIV group- 1 M/N & O, HIV-2**	RT PCR/real time with competitive reporter hybridization	800-1,000	<70	Plasma, 50 µL	220 x 200, x 310 mm, weight 7.8kg	1 unit	Pending, Yes	Only in non- regulated markets
Cepheid	Xpert® HIV-1 Viral Load	HIV-1 Group M, N and O***	RT PCR/real time with molecular beacons	40	90	Plasma, 1 mL	102 x 305 x 298 mm weight 8.2kg	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 x 170 x 180 mm Assay module: 190 x 330 x 330 mm Display module: 2.1 kgs; Assay module: 9.9 kgs	2 units	No, Yes	Yes
Diagnostics for the Real World	Samba II WBSQ Blood Semi-	HIV-1	NASBA/ICS	1,000	90	Blood, 120 µL	Display module: 215 x 170 x 180 mm Assay module: 190 x 330	2 units	No, Yes	No

	Quantitative						x 330 mm Display module: 2.1 kgs; Assay module: 9.9 kgs			
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 X 300 X 120 mm Weight 3kg	2 units	No, No	No

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1343 Abbreviations: WHO, World Health Organization; PQ, prequalification; CE-IVD, Conformance European *in vitro* diagnostic; TAT, turnaround time; PSQ, Plasma
1344 Semi-Quantitative; WBSQ, whole blood Semi-Quantitative; DRW, Diagnostics for the Real World; RT PCR, reverse transcription polymerase chain reaction;
1345 NASBA, Nucleic acid sequence based amplification; ICS, immunochromatographic strip.

1346 * Testing time does not include time for plasma separation.

1347 ** Limits of Detection for m-PIMA: HIV-1 group M: 342 copies/mL [95% CI, 279 - 451] and 595 IU/mL [95% CI, 487 - 785]; HIV-1 group O: 228 copies/mL [95%
1348 CI, 187 - 295]; HIV-2 group A: 364 copies/mL [95% CI, 292 - 484] and 200 IU/mL [95% CI, 160 - 260].

1349 *** Diagnostic sensitivity at Limit of Detection with WHO 3rd International Standard: 18.3 copies/mL; Diagnostic specificity: 100% (95% CI= 96.7 – 100.0); Limit of
1350 Quantitation: 40 copies/mL.

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1352 **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 ¹⁹⁶ NCT03066128	Single site, South Africa	390 non-pregnant adults on ART who are due a viral load at 6 months after initiation	POC monitoring including Xpert [®] HIV-1 Viral Load testing, combined with task shifting to enrolled/auxiliary nurses, versus standard of care	Primary: <ul style="list-style-type: none"> Proportion of patients who are retained in care with viral suppression <200 copies/mL at 12 months after enrolment (18 months on ART). Secondary: <ul style="list-style-type: none"> Proportion of patients with viral load <1000 copies/ml 12 months from enrolment Costs per patient virologically suppressed and retained in care. Time to detection of virological failure, subsequent intensive adherence counselling and initiation of second-line regimen. Proportion of patients entered appropriately into differentiated ART delivery programs and time to appropriate entry into these programs. 	Q4 2018
NCT03288246 ¹⁹⁷	Single site, Haiti	150 adolescents aged 10-24 on ART for > 6 months	POC HIV viral load testing at enrolment, 3 and 6 months compared to standard laboratory testing at the same time points	Primary <ul style="list-style-type: none"> Number of steps in the HIV viral load cascade Secondary <ul style="list-style-type: none"> Comprehension of the relationship between ART adherence and HIV viral load assessed 1 month after receiving viral load result Viral suppression <1000 copies/ml at 6 months from enrolment 	Q4 2018
UltraHIV ¹⁹⁸ NCT03187964	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: <ul style="list-style-type: none"> Related to TB component of the study. Secondary: <ul style="list-style-type: none"> Proportion of patients diagnosed with viremia by 8 weeks. Of those with viremia, the proportion who: are identified to require adherence counselling and/or HIV resistance testing by 1 week are referred for adherence counselling and/or second-line ART by 8 weeks do not successfully start adherence counselling, HIV resistance testing or second-line ART by 12 weeks 	Q4 2019
NCT03533868 ¹⁹⁹	Two sites, Nigeria	794 adults being initiated on ART	POC Xpert [®] HIV-1 Viral Load monitoring at 6 and 12 months from enrolment versus standard laboratory viral load.	Primary: <ul style="list-style-type: none"> Proportion of patients with viral suppression <1000 copies per ml at 12 months on ART Secondary: <ul style="list-style-type: none"> Average adherence from pharmacy refill data Loss to follow up at 12 months Time to adherence counselling, confirmation of virological failure and switch to second line ART 	Q4 2019

				<ul style="list-style-type: none"> • Time from specimen collection to result availability and communication to patient • HIV drug resistance patterns • Patient and healthcare worker satisfaction 	
RAPID-Viral Load ²⁰⁰ NCT03553693	20 sites, Uganda	2,440 children, adolescents and adults on ART, including pregnant women and patients with unsuppressed HIV viral load.	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, forms to track viral load ordering and testing, with feedback and performance evaluations at regular intervals.	Primary: <ul style="list-style-type: none"> • Proportion of patients with HIV viral load ordered when indicated by country guidelines • Mean time to delivering HIV viral load result to patient Secondary: <ul style="list-style-type: none"> • HIV viral load suppression at 12 months from enrolment • HIV viral load suppression • Proportion switched to second line ART • Proportion of results present in Uganda's Central Public Health Laboratory system 	Q4 2019

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1355 **Table 4.** Priority research questions for point-of-care HIV viral load testing.

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Technology Development
Can a rapid test be valid and reliable when used on fingerprick capillary blood?
Can the test processing time be reduced to <30 minutes?
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?

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Figure 1. Point-of-care HIV viral load equipment and test cartridges currently marketed (A-G) or in development (H-I). Attendant key equipment for some devices such as modems, barcode scanners, or printers are not included. A, the Abbott q analyzer; B, the Abbott m-PIMA™ HIV-1/2 test cartridge; C, the Cepheid GX4 instruments; D, the Cepheid Xpert® HIV-1 Viral Load test cartridge; E, DRW, SAMBA II test module; F, DRW, SAMBA II controller; G, SAMBA II Plasma semi quantitative test; H Cepheid Omni instrument and controller; I, Molbio Diagnostics, Trueprep™ sample preparation device; J – L, Molbio Diagnostics, Truelab™ amplification instruments in Uno, Duo and Quattro modules formats.



Figure 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).

Figure 3. The building blocks of differentiated ART delivery with POC HIV viral load testing.

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