Reaching the Third 90: Taking Routine Viral Load Monitoring to Scale

Guest Editors: Wafaa M El-Sadr, Miriam Rabkin, John Nkengasong and Deborah L Birx
Supplement Editors: Marlène Bras, Iryna Zablotska
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Realizing the potential of routine viral load testing in sub-Saharan Africa

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1 INTRODUCTION

The global HIV response has been remarkably successful. More than 19 million persons living with HIV (PLHIV) have accessed life-saving antiretroviral therapy (ART) [1] and the annual number of HIV-related deaths and new HIV infections have both plummeted [1]. As countries strive to reach the UNAIDS 90:90:90 targets (i.e. for 90% of PLHIV to be aware of their diagnosis, 90% of those who know their diagnosis to receive ART, and 90% of those on ART to have durable viral load suppression [2]), new guidelines, tools and implementation strategies are vitally important.

Viral load measurement is a critical tool to assess the impact of HIV treatment efforts, and is now endorsed by the World Health Organization (WHO) as the primary methodology for monitoring response to ART [3]. This recommendation is based on research demonstrating that viral suppression is associated with decreased HIV disease progression and mortality among PLHIV, and the prevention of HIV transmission to sexual partners [4,5]. Although stakeholders were initially slow to adopt this WHO recommendation, most funders and national programmes now strongly support scaling up access to routine viral load monitoring [6].

Because viral load measurement is a laboratory assay, it is unfortunately easy to misunderstand the challenge of viral load scale-up as one for laboratorians only. However, experience with other laboratory assays in resource-limited settings has shown that it takes far more than knowing their availability for a test to realize its potential. For example, even with the availability of testing for early infant HIV diagnosis, multiple challenges have been described in relation to coverage, quality and utilization of results. These include ensuring correct sampling methodologies for dried blood spot samples from HIV-exposed infants, obtaining specimens at the recommended timeframes, transporting specimens to the laboratory, ensuring tests are done in a timely fashion, enabling providers to promptly access test results and providing results to the infant’s caregiver to enable appropriate clinical decision-making [7]. These impediments delay the diagnosis of HIV infection among infants, thus delaying ART initiation in this vulnerable population [8–10].

The experience of early infant diagnosis (EID) scale-up highlights the importance of conceptualizing viral load testing as a continuum; a series of steps, each critical for achieving the ultimate goal – swift and appropriate clinical management to maximize the chance of sustained viral suppression (Figure 1). The first step in the viral load continuum is support for demand generation among both recipients of care and their health providers to motivate the former to request and the latter to order the test.

Once the sample is obtained, transportation systems are required to convey specimens, whether plasma or dried blood spot samples, to the appropriate laboratories. Laboratories need staff, equipment, laboratory information systems and quality assurance/improvement capacity to ensure that specimens are logged, tracked, tested and documented – and that results are transmitted back to the health facility, either electronically or physically. Point-of-care assays for viral load measurement offer the potential for overcoming the challenges encountered in transport of specimens and results [11]. Nonetheless, irrespective of laboratory method used, these results must then be readily available to the providers, whether in medical charts or via an electronic medical record.

Ultimately, the most critical step is for the providers to review the test results and to share them promptly with the recipients of services. Ensuring that clients are aware of the importance of viral load monitoring and viral suppression for both their own health as well as preventing onward transmission is critically important. Similarly, providers must be trained and supported to swiftly act upon viral load test results, reinforcing clients whose viral load is suppressed, and rapidly and accurately following national guidelines for patients with unsuppressed viral loads to increase adherence or adjust ART regimens if viral resistance is suspected.
In most countries, the first step after an unsuppressed viral load result is to provide enhanced adherence counselling (EAC) based on a careful assessment of all the factors that may be impeding clients’ ability to take ART regularly, followed by repeat viral load measurement [3]. In the absence of viral resistance testing – which is unavailable in many of the countries most severely affected by the HIV epidemic – failure to achieve viral suppression after EAC is assumed to reflect viral resistance, motivating change to a second line regimen [12]. With the recent expanding availability of integrase inhibitors, e.g. dolutegravir-containing regimens, simplification of both first and second line treatment is on the immediate horizon with the potential to enhance adherence due to decreased risk of side effects [13]. For children living with HIV, it is critically important to accelerate the development of similar regimens, particularly in formulations appropriate for young children [14].

Findings to date indicate that many clients who have unsuppressed viral load achieve viral suppression after EAC, demonstrating that in a significant proportion, the unsuppressed viral load is largely due to non-adherence [15–17]. This finding is in contrast to a recent report that raised concern regarding an increase in the prevalence of HIV resistance [18]. Of note, results from the four recently conducted nationally representative population-based HIV impact assessments (PHIAs) in Zimbabwe, Malawi, Zambia and Swaziland showed impressive viral load suppression (between 86.5% and 91.9%) among PLHIV who indicated that they were aware of their HIV-positive status and were on ART, suggesting the robustness of the commonly used current first-line regimen [19,20].

This supplement aims to summarize a workshop focused on viral load scale-up that took place from 27 to 30 June 2016 in Swaziland. The workshop, entitled “Reaching the Third 90: Implementing High Quality Viral Load Monitoring at Scale,” was attended by 150 participants from 16 sub-Saharan African countries, including individuals from diverse backgrounds reflecting key elements of the viral load continuum [21], such as clinical providers, civil society representatives, laboratori ans, programme managers, policy makers, researchers and funders. The workshop agenda was inspired by the concept of the viral load continuum and included cross-disciplinary panels and small group discussions to encourage attendees to think broadly beyond their own disciplines and areas of interest. The articles included in this supplement reflect this premise.

In their article, Killingo et al. describe the efforts of the International Treatment Preparedness Coalition to mobilize communities of PLHIV to demand access to viral load testing and to empower them to advocate for such access in the countries where they live [22]. Ensuring clients have immediate access to their results along with their health provider will increase client awareness of the importance of adherence. Peter et al. describe the lessons learned from scale-up of other laboratory tests, such as EID and CD4+ cell count assays, which can inform scale-up of viral load testing [23]. Ellman et al. discuss the optimal viral load threshold to use when defining virological failure [24], while Saito et al. describe the unique experience of providing viral load results to individuals participating in the PHIA Project [25]. Specific issues related to viral load testing among pregnant women, infants and children, adolescents and selected key populations are described in articles by Lesosky et al. [26], Arpadi et al. [27], Marcus et al. [28] and Schwartz et al. [29] respectively. Finally, the article by Barnabas et al. includes a systematic review of evidence related to the cost-effectiveness of routine viral load monitoring in low- and middle-income countries [30].

In summary, viral load measurement provides critical information for the management of individuals, as well as insight into the effectiveness of HIV programmes across the entire
HIV care continuum. This one test serves as a unique measure of the coverage, quality and impact of HIV programmes. As access to viral load testing expands, it is critical to learn from the lessons of the past, and to take a systems approach to strengthening every step of the viral load continuum [31]. All recipients of care deserve access to their viral load test results and all programmes need to move to utilize viral suppression as the indicator of programmatic effectiveness. Ultimately, viral load measurement is an asset that is too precious to waste.

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REFERENCES
**SHORT REPORT**

Community-driven demand creation for the use of routine viral load testing: a model to scale up routine viral load testing

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**Abstract**

**Introduction:** HIV treatment outcomes are dependent on the use of viral load measurement. Despite global and national guidelines recommending the use of routine viral load testing, these policies alone have not translated into widespread implementation or sufficiently increased access for people living with HIV (PLHIV). Civil society and communities of PLHIV recognize the need to close this gap and to enable the scale up of routine viral load testing.

**Methods:** The International Treatment Preparedness Coalition (ITPC) developed an approach to community-led demand creation for the use of routine viral load testing. Using this Community Demand Creation Model, implementers follow a step-wise process to capacitate and empower communities to address their most pressing needs. This includes utilizing a specific toolkit that includes conducting a baseline assessment, developing a treatment education toolkit, organizing mobilization workshops for knowledge building, provision of small grants to support advocacy work and conducting benchmark evaluations.

**Results and Discussion:** The Community Demand Creation Model to increase demand for routine viral load testing services by PLHIV has been delivered in diverse contexts including in the sub-Saharan African, Asian, Latin American and the Caribbean regions. Between December 2015 and December 2016, ITPC trained more than 240 PLHIV activists, and disbursed US $90,000 to network partners in support of their national advocacy work. The latter efforts informed a regional, community-driven campaign calling for domestic investment in the expeditious implementation of national viral load testing guidelines.

**Conclusions:** HIV treatment education and community mobilization are critical components of demand creation for access to optimal HIV treatment, especially for the use of routine viral load testing. ITPC’s Community Demand Creation Model offers a novel approach to achieving this goal.

**Keywords:** HIV treatment; routine viral load testing; community-led advocacy; demand creation

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1 | INTRODUCTION

HIV treatment outcomes among people living with HIV (PLHIV) are dependent on monitoring the response to antiretroviral therapy (ART). The use of routine viral load testing (RVLT) to monitor this response is the gold standard, and has been recommended by the World Health Organization (WHO) in its treatment guidelines since 2013 [1,2]. The UNAIDS 90-90-90 goals, of which the third 90 target aims for achieving viral suppression among 90% of PLHIV on ART, make the use of RVLT more relevant than ever. Many governments have adopted the WHO guidelines and updated their national HIV treatment guidelines to include RVLT for all PLHIV on ART. However, these policies alone have not translated into widespread implementation and consequently this has led to insufficient access for PLHIV [3–5]. Civil society groups and communities of PLHIV have recognized the need to close this critical gap between policy and implementation. This has motivated such groups to take responsibility for creating demand for RVLT, and to holding governments and donors accountable for providing RVLT at scale [6].

Creating demand for any service – including RVLT – is complex. It centers around the education and mobilization of recipients of care. It is only when affected communities are knowledgeable about their HIV treatment, including the value of viral load monitoring, that they become empowered to advocate for its availability. It is also through having such knowledge that they can confidently engage in policymaking and program implementation at national, regional, and global levels.

In this report, we present the model and methodology we developed for supporting the development of community-led demand creation for the use of RVLT and discuss key outcomes from work done using this model.
2 METHODS

The International Treatment Preparedness Coalition (ITPC) is a worldwide coalition of people living with HIV and community advocates working to achieve universal access to optimal HIV treatment of those in need. Formed in 2003 by a group of 125 HIV activists from 65 countries at a meeting in Cape Town, South Africa, ITPC actively advocates for treatment access in eight regions across the globe. ITPC’s work over the last decade has focused heavily on treatment education and community mobilization to fuel demand creation for services along the HIV Continuum of Prevention, Care, and Treatment (CoPCT) Cascade [7]. This model has been developed over the last 15 years through community consultative processes and lessons learned from best practices in community-led programming (Figure 1).

In this model, implementers follow a step-wise process to capacitate and empower communities to address their most pressing needs. Between December 2015 and December 2016, ITPC applied this model to focus specifically on increasing demand for RVLT services across the sub-Saharan African, Asian, and Latin American and the Caribbean regions.

2.1 Baseline assessment

As a first step, a baseline assessment is conducted to obtain a better contextual understanding of project needs (i.e. knowledge gaps to be addressed), to establish indicators and to serve as a baseline for project evaluation. This process usually entails a rapid or in-depth contextual analysis, which guides subsequent steps of the ITPC Community Demand Creation Model. In December 2015, ITPC undertook a survey to assess levels of awareness and knowledge among PLHIV on ART in nine East and Southern Africa countries: Democratic Republic of Congo (DRC), Kenya, Lesotho, Malawi, Mozambique, South Africa, Swaziland, Uganda and Zimbabwe. The survey demonstrated that the vast majority of PLHIV on ART surveyed had low levels of awareness and knowledge on the use of RVLT to monitor ART.

2.2 Development of a community toolkit

The baseline assessment identifies several key focus areas used to guide the development of a treatment education toolkit. The toolkit consolidates an in-depth literature review and contributions from technical experts in the field into a single resource utilized for training and knowledge building. In February 2016, ITPC launched its RVLT toolkit, guided by the outcomes of the baseline assessment conducted in East and Southern Africa. Entitled Activist Toolkit: Campaigning for Routine Viral Load Monitoring, the toolkit is a stand-alone resource that communities can use to improve and expand their understanding of HIV treatment and HIV treatment monitoring using routine viral load testing. The content includes an overview of the science of HIV, HIV treatment, use of viral load testing to monitor HIV treatment and defining what advocacy for access to RVLT means (Figure 2). The toolkit also discusses strategies for tackling the most common advocacy issues, providing various case studies on demand creation for RVLT. Based on community needs and preferences, the tool is available in both print and soft copy format and in four languages: English, French, Portuguese, and Spanish [8].

2.3 Education, skills building & mobilization

Following development and launch of the toolkit, in-person treatment education and mobilization workshops are held to facilitate uptake and utilization of the tool. The toolkit provides content for workshops and facilitates the exchange required to increase knowledge and awareness around key issues. The aim of the workshops is two-fold: (1) to provide community activists with the knowledge needed to demand RVLT scale-up; and (2) to capacitate activists to apply this information in their contexts.

Between March and November 2016, ITPC held four regional workshops and nine national workshops. At these 3-day workshops, participants included country representatives from various PLHIV networks, inclusive of representatives from key populations, women and youth groups.

The objectives of the workshops were: (1) to provide information about the importance of RVLT in the monitoring of HIV treatment; (2) to create national advocacy for addressing access to RVLT; and (3) to develop country awareness and advocacy plans regarding scale up of RVLT that feed into the Be Healthy – Know Your Viral Load campaign led by ITPC and its partners (described below).

ITPC facilitated the workshops alongside representatives from the relevant Ministry of Health and National Laboratory units. Pre- and post- tests, based on the content of the toolkit, helped assess changes in knowledge and awareness of participants – thereby helping to evaluate this component of the model.

Workshops culminated with the development of country-specific advocacy plans to be implemented in the next step of the model. Through guided discussions during the workshop, participants identified and prioritized issues for targeted advocacy.

2.4 Community-led advocacy

To support the execution of the country awareness and advocacy plans developed during the workshops, small grants of US$10,000 are provided to national network partners. This step in the process is critical to ensuring that ideas are translated into action. Given the constrained funding environments that many national networks operate in, small grants provide dedicated funds for addressing the specific issues partners prioritize in their content.

Figure 1. ITPC’s Community Demand Creation Model.
Upon completion of each workshop, ITPC provided the small grants to each of the nine national workshop partners. Where there were multiple partners working in a country, a closed call for proposals was used to solicit the strongest partner. In most cases, country partners work in consortium with an internally nominated lead organization and a designated principle recipient of funds. Advocacy plans are conducted over the course of six to 12 months. Activities range from peer-to-peer education on RVLT to media engagements and policy dialogue on inclusion of RVLT into national ART guidelines and strategy to support its implementation and scale-up.

In an effort to create synergy across national demand creation and advocacy work, ITPC and its partners have developed a community-driven campaign titled Be Healthy – Know Your Viral Load. The campaign serves as the overarching umbrella within which all national-level advocacy contribute, calling on governments to: (1) adopt the 2015 World Health Organization guidelines on the strategic use of routine viral load; (2) invest in the direct and strategic operationalization of guidelines that recommend the use of routine viral load testing; and (3) invest in the expeditious implementation of the RVLT guidelines at health facility level.

2.5 | Evaluation

The final stage of the ITPC Community Demand Creation Model is the conduct of an evaluation of the outcomes of the advocacy work to assess change achieved. Using the same methodology and indicators from the baseline assessment, a follow-up survey is conducted to evaluate the country project as well as the overarching campaign. This process helps to strengthen future efforts for the application of the model.

3 | RESULTS AND DISCUSSION

During 2016, ITPC conducted training for 242 PLHIV activists across Africa, Asia and Latin America and the Caribbean (Table 1). In all workshops, pre- and post-test scores showed an increase in knowledge among participants. A single lead conducted all 13 workshops, alongside various support staff. Baseline knowledge among activists in-country was extremely variable, with average pre-test scores ranging from 57.6% at a regional workshop in Ethiopia, to 89.5% at a regional workshop in Thailand. This highlighted the need for further skill and knowledge building in countries that are lagging with respect to advocacy for RVLT.

By the end of 2016, the nine country partners had engaged 1631 individuals, including adolescents, women, and key populations, in treatment education activities. This engagement included active attendance and participation in officially organized sensitizations, workshops, and trainings using varying formats. They also carried out 168 advocacy actions involving 2041 individuals and distributed 7219 materials such as booklets, flyers and posters. As a result of these advocacy activities, four of the partners succeeded in securing new commitments from national decision makers to scale up viral load testing. For example, in Malawi, partners conducted a baseline situational analysis to identify the barriers, best practices and opportunities to scale up RVLT. The results of the survey informed the development of a stakeholder consortium through which groups of PLHIV, non-governmental organizations (NGOs), and representatives from the Ministry of Health had regular meetings to discuss and plan for increased access to RVLT. As a result, the partner organizations were invited to join the Malawi Technical Working Group on ART organized by the Ministry of Health, to lead the group’s work on viral load testing issues. This was an important first step in increasing civil society’s voice and influence at the national policy level. In addition, the Malawi Community Health Services Unit committed to incorporating viral load testing information into their district-wide training for all health service providers, another important achievement.

In Uganda, partner organizations held meetings to advocate with policy makers and key implementers, including the AIDS Control Programme in the Ministry of Health and with the
National Coordinating Mechanism (CCM). As a result, partners secured the commitment for an increased number of viral load testing machines across the country, with support from the Ugandan Health System Strengthening Project, financed by the Global Fund. Furthermore, Ministry representatives committed to communicate in writing to all District Health Officers supporting the use of viral load testing for all PLHIV in Uganda. Such communications are critically important in disseminating information on national programmatic priorities. These initial powerful outcomes lay the groundwork for further advocacy.

National-level advocacy for RVLT is conceptualized to also inform the broader global movement related to RVLT through facilitation of South-to-South knowledge sharing, consequently amplifying impact at the regional and global levels. However, coordination of national level advocacy in this way remains a challenge, not surprisingly due to varying national priorities. Throughout the 13 workshops, several key issues arose consistently across all countries; however, not surprisingly, the prioritization of these often varied based on the national context. For example, in Swaziland, participants felt that the lack of information on RVLT available to PLHIV was the most critical barrier to uptake. Whereas in the DRC, challenges with sample transportation called for advocacy around the use of dry blood spots (rather than plasma specimens) and difficulty in accessing treatment led to advocacy for differentiated service delivery models of care that promote task shifting to trained PLHIV groups to expand access to treatment more generally. Cross-cutting initiatives, like the Be Healthy – Know Your Viral Load campaign, provide a meaningful approach to overcome these challenges and help in the harmonization of advocacy for RVLT across countries, allowing nationally specific advocacy plans to inform broader but regionally relevant overarching priorities.

ITPC’s Community Demand Creation Model has strengths as well as limitations. The results presented here also highlight the ability of the model to be adapted across national and regional contexts. It can be applied at scale and in various

<table>
<thead>
<tr>
<th>Type of workshop</th>
<th>Location</th>
<th>Number of participants</th>
<th>Countries represented</th>
<th>Average pre-test score (%)</th>
<th>Average post-test score (%)</th>
<th>Percent change in knowledge (based on pre- and post-test)</th>
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*Pre- and post-tests were piloted at the first regional workshop in Johannesburg, South Africa and therefore formal data is not reportable.
resource-limited settings based on both the needs of the community and the capability of the implementer partners within countries. However, all steps in the model (i.e. conducting an assessment, developing a tool, and conducting in-person mobilization workshops) require significant investments in time and resources. Alternative methods of delivery, such as digital applications or webinars, could provide means for overcoming these limitations, helping expedite the process when operating under short timeframes and limited resources. Additionally, the adaptability of the model presents challenges with respect to evaluation, as universal indicators to assess the model’s efficacy have yet to be developed. Civil society and community groups seeking to adopt this model should be encouraged to simultaneously establish monitoring and evaluation frameworks. As with any type of sub-granting, selection of national partners must be approached in a systematic manner to ensure the organizational capacity exists to implement the proposed advocacy plans. Furthermore, and of important note, the capacity built within organizations through knowledge sharing, technical assistance, and financial support enable the establishment of sustainable capacity for advocacy beyond the life of the project. Thus, it is important that capacity and commitment are assessed before this type of investment in specific partner organizations is made.

4 CONCLUSIONS

HIV treatment targets, including the UNAIDS 90-90-90 targets, will not be met without strengthening the capacity of PLHIV and activists to demand access to and use of RVLT. With expanded knowledge comes the ability to influence the entire viral load cascade. Thus, HIV treatment education and community mobilization are critical components of demand creation for access to optimal HIV treatment, including for the use of routine viral load testing. The work done using the ITPC Community Demand Creation Model serves as an example on how treatment education, coupled with small grants to civil society partner organizations, can create the desired outcomes for PLHIV and their communities.

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COMPETING INTERESTS
Authors have no competing interests to declare.

AUTHORS’ CONTRIBUTIONS
All authors contributed equally to this work. BK led the implementation of all aspects of the work on routine viral load testing presented here. WM provided technical oversight and implementation support. TT provided operational oversight and implementation support. TT wrote the main paper. All authors discussed the results and implications, and commented on the manuscript at all stages.

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COMMENTARY

Scaling up HIV viral load – lessons from the large-scale implementation of HIV early infant diagnosis and CD4 testing

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Abstract

Introduction: The scale-up of effective HIV viral load (VL) testing is an urgent public health priority. Implementation of testing is supported by the availability of accurate, nucleic acid based laboratory and point-of-care (POC) VL technologies and strong WHO guidance recommending routine testing to identify treatment failure. However, test implementation faces challenges related to the developing health systems in many low-resource countries. The purpose of this commentary is to review the challenges and solutions from the large-scale implementation of other diagnostic tests, namely nucleic-acid based early infant HIV diagnosis (EID) and CD4 testing, and identify key lessons to inform the scale-up of VL.

Discussion: Experience with EID and CD4 testing provides many key lessons to inform VL implementation and may enable more effective and rapid scale-up. The primary lessons from earlier implementation efforts are to strengthen linkage to clinical care after testing, and to improve the efficiency of testing. Opportunities to improve linkage include data systems to support the follow-up of patients through the cascade of care and test delivery, rapid sample referral networks, and POC tests. Opportunities to increase testing efficiency include improvements to procurement and supply chain practices, well connected tiered laboratory networks with rational deployment of test capacity across different levels of health services, routine resource mapping and mobilization to ensure adequate resources for testing programs, and improved operational and quality management of testing services. If applied to VL testing programs, these approaches could help improve the impact of VL on ART failure management and patient outcomes, reduce overall costs and help ensure the sustainable access to reduced pricing for test commodities, as well as improve supportive health systems such as efficient, and more rigorous quality assurance. These lessons draw from traditional laboratory practices as well as fields such as logistics, operations management and business.

Conclusions: The lessons and innovations from large-scale EID and CD4 programs described here can be adapted to inform more effective scale-up approaches for VL. They demonstrate that an integrated approach to health system strengthening focusing on key levers for test access such as data systems, supply efficiencies and network management. They also highlight the challenges with implementation and the need for more innovative approaches and effective partnerships to achieve equitable and cost-effective test access.

Keywords: HIV; viral load; early infant diagnosis; EID; CD4 implementation

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1 INTRODUCTION

Since 2013, when the World Health Organization strongly recommended the use of HIV viral load (VL) testing to monitor viral suppression in persons on antiretroviral therapy (ART) in low resource settings (LRS), the scale-up of this diagnostic test in low- and middle-income countries has been limited [1,2]. Of the estimated 19.5 million persons currently on ART in these countries, less then 40% have routine access to VL testing [3]. This is despite the utility of this test as a means to monitor viral suppression, enable early detection of treatment failure, and guide appropriate ART management. Based on current projections, access to VL testing will reach only 60% by 2020 [3].

Current VL technologies are complex nucleic acid assays that require sophisticated laboratory infrastructure, advanced technical skills, well-established sample logistics, and systems for results return [4]. Fostering the rapid and effective use of test results is also essential to achieve expected health outcomes, especially as the test is new, and unfamiliar to many clinicians and patients. Optimizing testing capacity, enabling health systems, and the appropriate use of test results to guide treatment is the focus of governments, implementing partners, donors, industry, and civil society [5,6]. Despite these efforts, scale up of routine VL testing has encountered delays and uneven success [2,7,8], which may impede the achievement of the global 2020 HIV 90-90-90 goals set by the Joint United Nations Programme on
HIV/AIDS (UNAIDS) and the aspiration of ending AIDS by 2030 [5].

The scale-up of VL testing is not the first large-scale implementation of an HIV-related diagnostic test in low and middle income countries. In particular, the experience of CD4 assays and early infant HIV diagnosis (EID) testing over the past 15 years provide important lessons for VL implementation [9–11]. This commentary reviews the use of EID and CD4 tests in RLS and identifies best practices, innovations and success factors to inform scale-up of VL services in these same settings. The primary lessons from past experience are to ensure linkage to care and the efficiency of testing.

2 | IMPROVING VL PROGRAMS

Over the past decade, public health programs in RLS have introduced and scaled up HIV early infant diagnosis and CD4 testing within many of the same laboratories and health facilities that are currently launching HIV VL testing. Testing coverage and volumes were initially modest – a few hundred thousand tests – but reached millions of tests within a few years [3]. By 2015, an estimated 60% of those eligible for CD4 testing had access to the service, and approximately 43% of infants had access to EID testing [12,13]. Unfortunately, there is also significant evidence that many test results are not delivered to patients and/or are not used to make the necessary clinical decisions. In other words, despite significant progress, there remains a long way to go before people living with HIV (PLHIV) in RLS have universal access to high-quality CD4 and EID testing services.

It is expected that over 20 million people will need access to VL testing by 2020 [3]. As VL services will be implemented at the same health facilities and laboratories as CD4 and EID, often utilizing the same staff, infrastructure, logistics, supply chains and data systems, applying lessons learned from CD4 and EID programs may accelerate scale-up of effective VL testing services (Table 1).

3 | ENSURE LINKAGE TO CARE

CD4 and EID implementation efforts have been heavily focused on building and equipping laboratories, training staff, and procuring test commodities. These activities were often highly successful, and both CD4 and EID laboratory capacity greatly exceeded test demand in many countries [9,10]. The same is true for VL testing; in 2014, VL test volumes in sub-Saharan Africa outside of South Africa were at 10% of the estimated 2 million test capacity of laboratories in this region [14]. The set-up of laboratories often occurs faster than health facilities can implement the clinical procedures needed to adopt and use the new tests. Because testing volumes, turn-around-time and costs have been the most common metrics for evaluating EID and CD4 programs, a striking fact is often overlooked – many test results are never delivered to patients and used to guide patient care. In sub-Saharan Africa, for example an estimated 50% of CD4 and EID test results were not used [15]. Common barriers to the effective utilization of test results include long test turn-around times leading to loss to follow up, the lack of health data systems, and facility-level operational challenges described elsewhere in this Supplement [16–20].

3.1 | Rapid sample referral and result delivery

Long test turnaround times (TAT) are particularly devastating in the case of EID, where median TAT remain long, from 20 to 60 days [24,25]. The EID cascade has been well described in a range of settings and geographies, including Africa and Asia, and highlights the challenges associated with a failure to effectively link patients to follow-on care after testing [16–20]. For infants tested at four to six weeks of age, EID test results are often returned after the early peak of infant HIV-related mortality [26]. TAT is also a barrier to utilization of CD4 results, and studies have shown that fewer than 50% of patients

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received their test results and initiated treatment promptly, when CD4 count thresholds were criteria for ART [22,23].

Several countries have implemented improved sample referral networks and electronic result delivery to reduce TAT. This has included the mapping of sample referral routes and establishing disease-integrated courier contracts to transport HIV, TB and other clinical specimens, e.g., with the Postal Service or Riders for Health. In Uganda, an extensive and robust sample referral network increased access to EID by 50% and reduced sample transport costs by 50% [24]. Similarly, mHealth initiatives have been implemented for rapid return of test results to clinics using short message system (SMS) printers and dashboards to consolidate and present geospatial testing data to track and follow-up on defaults to optimal TAT, for example in clinics using short message system (SMS) printers and dashboards to consolidate and present geospatial testing data to track and follow-up on defaults to optimal TAT, for example in South Africa where visual dashboards enabled data-driven interventions to improve health program performance against key indicators for the prevention of mother to child infection [27].

3.2 | POC diagnostics

The use of point-of-care (POC) diagnostic technologies significantly improves retention in the pre-ART care cascade. POC testing significantly reduced EID TAT and increased access to ART amongst HIV-infected infants in Mozambique [28]. Similarly, POC CD4 testing reduced TAT from ten days to less than one day on average [22]. In Mozambique, POC CD4 reduced loss-to-follow-up before ART initiation by 50% [23]. Access to POC VL testing may also help improve the management of treatment failure for patients on ART by dramatically reducing TAT and enabling faster clinical decisions, however studies on this are needed.

3.3 | Data systems to improve the cascade of care

Other critical enablers of effective test utilization include integrated data and clinical systems that improve the cascade of care from the identification of eligible patients, the provision of testing, and delivery of results back to the health facility and patient. This enables results to be used swiftly to make clinical decisions. It is therefore important to build diagnostic systems with patient care in mind, ensuring that delivery of results to health facilities is well integrated with clinical patient management and well synchronized with the patient pathway of care. Several interventions have been shown to improve the cascade of clinical care from testing through linkage to care, including clinical quality improvements such as the use of SMS result delivery to clinics or patients, and active patient follow-up by community health workers [29–35]. In Mozambique, SMS result delivery to clinics was associated with a 20% increase in receipt of test results by caregivers, and a three-fold decrease in testing errors [25,36]. Data systems that enable the follow-up of patients through the cascade of care have been shown to improve overall clinical outcomes, for example in South Africa where visual dashboards enabled data-driven interventions to improve health program performance against key indicators for the prevention of mother to child infection [27].

3.4 | Application to VL programs

It will be useful to draw from the above interventions that have proven to be successful with CD4 and EID programs so that steps can be taken early in VL implementation to establish effective practices. In particular, testing programs need to ensure that VL testing is well integrated with ART failure management processes, for example that test TAT do not introduce long delays in detecting and confirming failure, and that results are delivered to clinicians and patients in order for timely follow-on care, such as enhanced adherence support and/or a drug regimen switch. VL monitoring and evaluation programs should also include metrics such as testing coverage, test TAT, test delivery to clinics and patients, and test utilization to guide ART management. In many settings, VL programs can leverage existing EID and CD4 sample referral and electronic result delivery networks. The utility of POC VL still needs further investigation, but it is possible that the availability of rapid VL results may improve patient adherence, differentiated care, and reduce program costs (Table 1).

4 | IMPROVE TESTING EFFICIENCY

The establishment of large scale CD4 and EID testing programs in low-resource settings over the past 15 years faced many challenges [9,11]. As a result the focus of these programs was often on ensuring test access. As access has improved, attention is turning to testing efficiency in order to ensure the clinical impact of testing and to reduce costs. Key interventions to improve efficiency are described below (Table 1).

4.1 | Procurement and supply chain

Large-scale VL testing programs will consume significant quantities of diagnostic commodities run on networks of instruments. Ensuring the reliable and efficient supply of testing products and preventing breakdowns of instruments requires some of the innovative approaches that have been developed within EID and CD4 testing programs. At the outset of these programs, test kit and instrument costs were high, test procurement was highly disaggregated across government, donors and implementing partners, and stock outs and instrument breakdowns were frequent. Many of these challenges have not yet been resolved; a recent WHO survey found approximately 10% of instruments were not in use due to stock-outs, breakdowns or non-installation [37]. Two supply chain innovations – global access price deals and bundled agreements – have been implemented for the CD4 and EID markets, and are highly relevant to VL.

Global access price deals are negotiated centrally and provide equitable access to low pricing for all public sector buyers irrespective of procurement volume. This allows smaller countries with limited purchasing power to access the same pricing as high volume countries. Price reductions of 30% to 50% for CD4 and EID tests have resulted in substantial commodity budget savings for countries and donors around the world, and have helped expand access to these tests [38,39]. Access pricing is also available for certain VL test suppliers and this has helped make VL more accessible [40].

Supply chain initiatives can have significant impact, reducing costs and increasing health product availability [41]. For diagnostics, supply terms such as all-in or price-per-result (incorporating instruments, reagents, training, quality assurance,
distribution and test failures), reagent rental agreements that remove up-front instrument capital cost, and bundled reagent-maintenance agreements that eliminate separate maintenance contracts, have been designed and implemented for EID and CD4 testing networks. These are designed to reduce costs and financial barriers, improve procurement flexibility, efficiency and supplier accountability, and reduce instrument down-time and stock-outs. They also establish partnerships between suppliers and procurers and encourage more co-ordinated procurement. Coordinated procurement, whereby testing volumes and ordering schedules across procurers and over time are consolidated to negotiate improved supplier terms, has been effectively used to improve CD4 and EID supply chains.

The Global Fund has established framework agreements with major VL suppliers that provide mechanisms for standardized access to bundled supply terms [42]. In addition, several national testing programs, for example Brazil, South Africa, Kenya and Uganda, have implemented bundled agreements for VL testing. These build on procurement principles and mechanisms developed with large-scale CD4 and EID programs. Instead of procuring instruments, testing kits, and annual instrument service and maintenance separately, national testing volumes have been consolidated (by the government or through a procurement consortium of government, donors and implementing partners), and a single contract for supply of instruments, reagents and service and other test components at prices lower than disaggregated procurement. Bundled procurement helps ensure service and maintenance is always accessible; a critical need in many countries. The recent WHO survey found that most CD4 instruments in public laboratories were not covered by service and maintenance contracts, were not serviced regularly and breakdowns were frequent [37]. Bundled procurement requires well-established forecasts and regular ordering cycles, which help ensure reliable test manufacture and supply. Bundled agreements also provide the flexibility to switch, if needed, to more competitive suppliers at the end of each contract because the instruments were not purchased. For example, bundled agreements have been used in South Africa and Brazil for over ten years and have enabled easier switches in testing technologies without having to formally retire instruments and the financial hurdle of paying for new equipment up front [14].

Although they are valuable tools for optimizing supply chain, bundled agreements have been infrequently used for VL testing programs, partly due to unconsolidated procurement or difficulty with undertaking multi-year procurement commitments. As VL testing programs scale-up to meet growing demand, the need for more effective procurement mechanisms and better coordinated procurement across buyers will also grow. Given the relatively high reagent and capital costs, and the technical complexity of VL instruments, and hence need for routine service by an engineer, carefully negotiated bundled agreements and access pricing will likely be useful measures to increase the sustainability and reliability of large-scale testing programs.

### 4.2 Laboratory networks

Health systems in many LRS often have limited ability to support large testing networks [43,44]. In particular, instrument technology-based testing programs require substantial supportive systems. To ensure widespread access, test networks are required, comprising a tiered network of laboratory services a wider network of health facilities. The functioning of such networks relies heavily on testing systems such as sample referral to ensure access to laboratory capacity over wide geographic areas, health data systems to ensure rapid dissemination of test results for clinical, programmatic and surveillance uses, and quality assurance to ensure reliable results irrespective of testing location [45,46]. Laboratory networks have been strengthened in numerous countries, establishing active sample referral and results delivery connections between central and decentralized levels of the health care system. For example, Mali, Burkina Faso and Senegal through the Resalab program have improved surveillance and outbreak detection readiness, in line with the eight WHO laboratory requirements of the International Health Regulations and laboratory readiness requirements of the Global Health Security Agenda [47].

The rational deployment of testing technologies within the networks is a key factor for efficiency. A common feature of CD4 and EID testing networks to date has been over-capacity and under-utilization of the instrument base. A 2013 WHO survey in 127 countries identified a surplus of global CD4 capacity, sufficient instrumentation to conduct 4.6 tests per year for every person living with HIV, and 12.8 tests/year for every person on ART, as opposed to the 1 to 2 tests per year required at that time [37]. Capacity utilization across instruments was only 13.7%. At the start of scale-up programs it was likely common to deploy excess instruments to ensure no capacity limitations. As testing programs mature, there are opportunities to build more efficient networks and to increase instrument utilization. The lessons for VL deployment are to start testing programs by placing devices with appropriate capacity at each testing location. For example, placing high throughput instruments at central test demand locations and lower throughput devices at smaller sites with robust sample referral linkages that maximize instrument utilization and therefore, the return on the investment made for each instrument [48]. This requires data on testing current and projected needs across the network of health facilities, the mapping of sample referral routes, and coordinated national instrument procurement and deployment plans [24,49]. Several tools now exist to help optimize testing networks, including the USAID-developed LabEQIP tool [50].

### 4.3 Resource mobilization

One of the key lessons from the scale-up of CD4 and EID programs is while significant donor funding has gone into laboratory services over the past decade, long-term national investment in laboratory testing is needed. Effective national laboratory systems such as logistic and health data systems are often under-funded and not fully part of routine service. This is partly because the full costs of testing services, especially when new diagnostics are being rapidly scaled up, and the financial resources needed to ensure access to essential diagnostic tests at national scale are difficult to estimate and track. As a result, large-scale public testing programs such as VL face risks and may be unstable and unsustainable unless appropriate investments are made in testing and necessary supportive systems. For example, in Zimbabwe despite a goal
of 21% VL coverage in 2015, only 5.6% test coverage was achieved due to challenges in resource mobilization and related factors [49]. For fast growing testing programs such as VL, test projections need to routinely inform national laboratory budgets to reduce the risk of funding shortfalls. Data systems such as test dashboards, that are connected to laboratory and POC instruments, can track test volumes and utilization in real time and produce consumption data to better inform national HIV diagnostics quantification exercises, for example using the USAID-developed ForLab tool [50].

In addition, the investment case for laboratory systems strengthening needs to be more clearly articulated so that sustainable funding for these systems can be established. Investments in scaling up CD4 and EID in many countries have often included laboratory system strengthening programs for logistics, data and quality, providing an opportunity to build on these investments to support VL testing programs [9]. Guidelines of the Global Fund clearly elaborate a comprehensive range of critical laboratory strengthening investments that countries can make using Global Fund resources, including human resource capacity development, procurement and equipment management systems, quality improvement, development of tiered laboratory networks, and data systems [51].

### 4.4 Management

The unprecedented scale of CD4 and EID testing programs has highlighted the need for stronger management within public laboratory programs, both operational and quality management. Laboratory quality improvement programs such as the Strengthening Laboratory Management Towards Accreditation (SLMTA), developed by the United States Centers for Disease Control and Prevention, and the WHO Strengthening Laboratory Improvement Towards Accreditation (SLIPTA) program supported by the African Society for Laboratory Medicine have increased quality management skills and have established a growing trend towards accreditation in public laboratories [52]. Countries such as India, Ethiopia, Ghana, Nigeria, and the Caribbean region have made significant steps towards strengthening quality management skills and laboratory accreditation [53–55]. Although quality improvement systems are still to fully establish across a wider range of countries, these quality initiatives provide a foundation that VL programs will be able to leverage to ensure reliable testing.

Tiered networks of laboratories have significant operational management needs to ensure efficiency; however most leaders of public health laboratory networks are not trained in operations [56]. This includes the infrastructure management, i.e. ensuring adequate physical space and equipment within laboratories, financial management including budgeting, supply chain and distribution systems, logistics and data systems, and monitoring and evaluation. Improved operations management within laboratory networks may improve adherence to performance standards and ensure a service-oriented relationship with health facilities and other stakeholders in testing services. Many of the systems weaknesses observed with CD4 and EID scale-up and described above, such as gaps in supply chain, slow sample referral and test turn around times, and limited use of data systems may be related to inadequate operations management capacity and skills. The strengthening of this capacity within public departments responsible for laboratory services may help ensure more effective delivery of diagnostic tests within the parameters needed for clinical management and improved patient outcomes.

### 5 Conclusions

The global scale-up of EID and CD4 testing services has established important systems and experience with large-scale public health testing programs. It has also identified weaknesses in diagnostic access that may ultimately limit the success of these programs, as well as new tests such as VL. There are many innovations and best practices from these initial large-scale testing programs to learn from, as well as persistent challenges to overcome. There are critical needs and opportunities in linkage to care and testing efficiency, including improved data and sample referral systems, POC tests, improved supply terms, and more effective laboratory network management that are important to address during the scale-up of HIV VL testing programs in resource limited settings (Table 1). Learning from prior experiences with CD4 and EID test scale-up will help ensure accessible and reliable VL services and help overcome major test implementation barriers.

### Authors' Affiliations


### Competing Interests

The authors have no conflicts of interest.

### Authors' Contributions

TP, CZ, ZK, AE, BA, LV, AC, ND and IJ developed and finalized the manuscript.

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Selecting a viral load threshold for routine monitoring in resource-limited settings: optimizing individual health and population impact

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Keywords: viral load; HIV monitoring; resource limited setting; threshold; antiretroviral therapy; scale-up

The routine use of HIV viral load tests for monitoring patients on antiretroviral therapy (ART) in resource-limited settings has the potential to greatly benefit those with HIV infection as well as public health in general. Declines in viral load after ART initiation result in improved clinical outcomes [1,2] and viral load testing has therefore been considered the gold standard for measuring ART response in high-resource settings for many years [3]. Reductions in viral load also reduce the risk of perinatal [4] and sexual transmission of HIV [5]. However, availability of viral load testing has been limited in resource-limited settings where less sensitive and specific clinical and immunologic measures have largely been used to determine response to therapy; as of 2013 it was estimated that less than 20% of ART patients in Africa receive routine viral load testing [6,7]. In the past few years, enormous efforts have been made to scale-up availability of viral load testing for routine monitoring, however, some countries remain with little access, others are testing low proportions of patients on ART, and only a few are testing the majority of their ART patients [8,9]. Further, the impact of this recent viral load scale-up on clinical and public health outcomes are yet to be determined.

While initial studies in resource-limited settings found no mortality benefit when comparing viral load to CD4 count for monitoring [10,11], the rationale for monitoring viral load in patients on ART is based on several factors that pertain to both individual patient management as well as optimizing population health. Viral load testing can find individuals who might benefit from additional adherence support and leads to earlier and more accurate identification of treatment failure than clinical and immunologic indicators [10,12,13]. This allows for appropriate antiretroviral regimen selection and improved outcomes for individual patients, and provides a public health benefit through more appropriate allocation of second-line medications. Prompt detection of treatment failure through viral load monitoring may also prevent emergence of drug resistance mutations, providing benefit to the individual in settings where antiretroviral drug options are limited, and also at the population level by limiting transmission of drug-resistant virus [14].

The World Health Organization (WHO) guidelines recommend the use of viral load as the preferred method for monitoring treatment response over clinical and immunological approaches, and define virologic failure with a threshold of 1000 copies/ml [7,15]. The selection of this threshold has generated debate as to whether the desired goals of routine viral load monitoring, on individual and public health levels, will be achieved by using the 1000 copies/ml threshold and whether it will prove optimal across patient populations such as infants, children, adolescents, and pregnant and breastfeeding women.

In most resource-rich contexts, the goal of ART is to achieve viral suppression, usually defined as below the level of detection of the assay (e.g. <20, <25, <37, <40 copies/ml) [16]. While studies show that transient episodes of viremia that subsequently return to below the limit of detection, often called “blips,” do not predict subsequent virologic failure [17,18], persistent low-level viremia carries some increase in risk of emergence of drug resistance and subsequent virologic failure [18,19]. Data show that persistent low-level viremia between 50 and 999 copies/ml, especially at the higher end of that range, is associated with an increased risk of resistance mutations, particularly M184I/V and K103N [19], which may impact effectiveness of first-line regimens most commonly used in resource-limited settings. Persistent viremia below 1000 copies/ml has also been noted to be associated with an increased risk of virologic failure [18], including with viral load levels as low as 50 to 199 copies/ml that persist for at least six months [20].

At the same time, there is also evidence to support the selection of a viral load threshold of 1000 copies/ml, particularly in resource-limited settings. Though the optimal value is not known, a viral load below 1000 copies/ml is associated...
with a low risk of disease progression [21] and with a decrease in HIV transmission. Available data demonstrate that sexual transmission is very unlikely with a viral load <1700 copies/ml and even less likely with a viral load <400 copies/ml [22–24], and mother-to-child transmission is around one percent in women on antiretroviral drugs with a viral load <1000 copies/ml [4]. As a result, using a threshold of 1000 copies/ml appears to provide both individual and public health benefits while also simplifying the approach to routine viral load monitoring.

The choice of threshold for viral load among patients on ART in resource-limited settings is also influenced by available technology for viral load measurement. Use of dried blood spots (DBS) for viral load testing is a promising approach which offers advantages related to ease of specimen collection and handling, and allows for specimen transport without a cold chain, however, its use also impacts the choice of viral load threshold. Adapting laboratory viral load assays to accommodate DBS specimens poses specific technical challenges, such as lower sensitivity due to the lower specimen volume, differences in efficiency of nucleic acid extraction, and presence of amplification inhibitors such as hemoglobin [25]. As a result, lower limits of detection using DBS are much higher than those of plasma even for the same assay. In addition, amplification of cell-associated DNA or RNA in DBS reduces the specificity of DBS viral load testing [25].

The specific issues related to DBS measurement led to an initial reluctance to use the 1000 copies/ml threshold for DBS. Thus, the WHO 2013 guidelines suggest considering a threshold of 3000 to 5000 copies/ml for such specimens [15]. However, advances in technology such as the introduction of RNA-specific extraction and amplification procedures to commercial kits have improved the specificity of DBS-based viral load testing [26]. Furthermore, a systematic review demonstrated acceptable performance characteristics for DBS compared to plasma for most technologies at the 1000 copies/ml threshold [7]. Therefore, the recent WHO guidelines recommend the threshold of 1000 copies/ml for viral load testing through DBS on most laboratory-based platforms [7,26], when there are operational barriers to using plasma. This threshold was recommended for all viral load methodologies, whether plasma or DBS-based, in order to simplify the training of diverse clinical providers and to enable the consistent and accurate implementation of viral load monitoring. However, there is an urgent need for additional data on the performance of DBS specimens using a viral load threshold of 1000 copies/ml in routine program settings, as well as data on the outcomes of patients with the use of this threshold for viral load monitoring.

Implementation of viral load testing for routine monitoring of ART response in resource-limited settings has the potential to lead to improved individual patient outcomes as well as to decreased risk of HIV transmission, potentially changing the trajectory of the HIV epidemic. While treatment experts advocate for the use of the lowest possible viral load threshold as the goal of HIV treatment, those with interest in the public health impact of viral load monitoring support the use of the 1000 copies/ml threshold as a pragmatic choice. The latter is offered as a compromise between the ideal for the individual and the need for a focus on achieving the greater good.

Moving forward, it will be particularly important to carefully evaluate the effect of use of the 1000 copies/ml threshold in terms of individual and population impacts. Such data will be critically important in informing future recommendations and guidelines. Most importantly, while viral load scale-up is an important priority, it is critical that it be coupled with ensuring access to such testing for all HIV-positive patients on treatment and effective utilization of results, irrespective of the viral load threshold selected, in order to achieve the promise of HIV treatment.

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**COMPETING INTERESTS**

Authors have no competing interests to declare.

**AUTHOR’S CONTRIBUTIONS**

TME, WMES, and EJA conceptualized the paper. TME drafted the manuscript with key contributions from BA, SA, AAH, WMES, and EJA. All authors have read and approved the final manuscript.

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Abstract

Introduction: Logistical complexities of returning laboratory test results to participants have precluded most population-based HIV surveys conducted in sub-Saharan Africa from doing so. For HIV positive participants, this presents a missed opportunity for engagement into clinical care and improvement in health outcomes. The Population-based HIV Impact Assessment (PHIA) surveys, which measure HIV incidence and the prevalence of viral load (VL) suppression in selected African countries, are returning VL results to health facilities specified by each HIV positive participant within eight weeks of collection. We describe the performance of the specimen and data management systems used to return VL results to PHIA participants in Zimbabwe, Malawi and Zambia.

Methods: Consenting participants underwent home-based counseling and HIV rapid testing as per national testing guidelines; all confirmed HIV positive participants had VL measured at a central laboratory on either the Roche CAP/CTM or Abbott m2000 platform. On a bi-weekly basis, a dedicated data management team produced logs linking the VL test result with the participants’ contact information and preferred health facility; project staff sent test results confidentially via project drivers, national courier systems, or electronically through an adapted short message service (SMS). Participants who provided cell phone numbers received SMS or phone call alerts regarding availability of VL results.

Results and discussion: From 29,634 households across the three countries, 78,090 total participants 0 to 64 years in Zimbabwe and Malawi and 0 to 59 years in Zambia underwent blood draw and HIV testing. Of the 8391 total HIV positive participants identified, 8313 (99%) had VL tests performed and 8245 (99%) of these were returned to the selected health facilities. Of the 5979 VL results returned in Zimbabwe and Zambia, 85% were returned within the eight-week goal with a median turnaround time of 48 days (IQR: 33 to 61). In Malawi, where exact return dates were unavailable all 2266 returnable results reached the health facilities by 11 weeks.

Conclusions: The first three PHIA surveys returned the vast majority of VL results to each HIV positive participant’s preferred health facility within the eight-week target. Even in the absence of national VL monitoring systems, a system to return VL results from a population-based survey is feasible, but it requires developing laboratory and data management systems and dedicated staff. These are likely important requirements to strengthen return of results systems in routine clinical care.

Keywords: HIV viral load monitoring; turnaround time; TAT; return of results; population-based surveys; PHIA
minutes of blood collection but it remains difficult to return VL results as testing is still mainly done at central reference laboratories.

Operationalizing the return of VL test results as part of a national population-based survey relies on the existing infrastructure for VL testing in routine HIV clinical care. Since the release of the 2013 WHO guidelines on the use of antiretrovirals, 47 out of 52 low and middle income countries have adopted routine VL monitoring for early detection of treatment failure in their national HIV policies [7,8]. However, on-site VL testing remains limited as documented in a recent study of 262 HIV care and treatment sites in 45 countries [9]. The study found only 14% of 87 majority urban facilities in southern Africa had on-site VL testing capabilities in 2014 [9].

In this context of limited and concentrated capacity of VL testing in urban centers, ensuring that VL test results are returned in a timely manner to survey participants in a large, national population-based survey requires development of survey-specific specimen and data management systems. In order to obtain quality VL results, specimens must be well collected, transported under proper conditions, and monitored for arm-to-freezer time from participants’ homes to specialized laboratories for processing and testing. Adding to the complexity, a mechanism to interface with existing VL testing instruments and laboratory information systems (LIS) at the laboratories must be established to handle survey specimens apart from clinical specimens. Return of VL results in the clinical setting has been described in past studies [10–13]. To date, there is a dearth of data on process and system adaptations needed to return VL results with acceptable turnaround time (TAT) in the context of population based surveys identifying ~2500 HIV positive individuals spread nationwide [14]. In a small population-based household survey in two rural sub-districts in South Africa, Lippman, et al. used a study phone number for 158 HIV positive participants to call to obtain VL results but did not report TAT [14].

The Population-based HIV Impact Assessment (PHIA) Project, implemented by ICAP at Columbia University in collaboration with the Ministries of Health, US Centers for Disease Control and Prevention (CDC) and other partners, is assessing the status of the HIV epidemic in 13 countries in sub-Saharan Africa (SSA) and Haiti by measuring nationally representative, population-level HIV prevalence, incidence and VL suppression. In the context of national household surveys, the PHIA project established a system to measure VL among HIV+ individuals and return results to their preferred health facility within eight weeks of the sample collection. Herein, the processes and systems established to return VL results and the TAT achieved in the first three surveys in Zimbabwe (ZIMPHIA), Malawi (MPHIA), and Zambia (ZAMPHIA) are described.

2 | METHODS

Consenting participants aged 0 to 64 years in ZIMPHIA and MPHIA and 0 to 59 years in ZAMPHIA underwent in-home counseling and HIV rapid testing according to each country’s HIV national testing guidelines [15–17]. The consent forms specifically referred to blood draw, home-based HIV rapid testing and, depending on the country, other point of care tests, such as syphilis, hepatitis B surface antigen (HBsAg), and CD4. The consent forms also referred to receiving at a nearby healthcare facility VL test results that came from assays conducted at central laboratories. Depending on age, whole blood was collected from participants either by venous blood draw, finger prick or heel stick for household-based testing and additional biomarker testing at the laboratory. At the end of each collection day, all field specimens were shipped to pre-selected Ministry of Health (MOH) district laboratories with project-specific lab capacity enhancements near the area of field work for processing into plasma and/or dried blood spot (DBS) specimens, quality assurance (QA) testing and -20°C freezer storage. Approximately weekly, the plasma and DBS specimens were then shipped to a central reference laboratory to conduct specialized tests, including VL testing on HIV+ specimens and long-term storage at -70°C or below.

2.1 | Viral load testing

Samples from all HIV positive participants were tested for VL levels using an automated platform at a central reference laboratory in each country. For ZIMPHIA and ZAMPHIA, the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0 was performed on the Roche (Pleasanton, CA) platform while the Abbott m2000rt System (Chicago, IL, USA) using the Abbott Real Time HIV-1 Assay was performed in MPHIA, both according to the manufacturers’ instructions. The primary specimen type for VL testing was plasma, but in 4 to 5% of all cases and <1.1% of positive cases only DBS samples were available; DBS were tested using a modified Abbott assay for DBS elution in MPHIA and ZAMPHIA, while the NucliSENS easyQ (bioMérieux, Marcy-l’Étoile, France) platform was used for DBS VL testing in ZIMPHIA. On a weekly basis, trained laboratory scientists on the PHIA Project reviewed viral load results for quality control and quality assurance.

2.2 | Data management

For the entire PHIA Project, a centralized data management system was established to process and monitor return of results (RoR) across each country (Figure 1). Extensive preventative steps were taken to ensure that all personally identifiable data were securely stored with limited access to a few select individuals to ensure participant confidentiality. In the home, along with blood collection, the participant’s age, unique participant identification number (PTID), HIV rapid test results and preferred health facility to collect the VL results were captured in an Open Data Kit (ODK) software application configured and implemented on Google Nexus 9 Android tablets. Blood tubes collected in the household were affixed with PTID labels, and received and logged according to date and time at the MOH district laboratories using a laboratory data management system (LDMS, Frontier Science, Boston, MA). LDMS generated labels with unique specimen IDs for each plasma and DBS aliquot derived from an individual participant blood sample. Plasma and DBS storage time and location in individual freezers were also recorded in LDMS. LDMS data files and shipment reports were generated each week and sent with plasma and DBS specimens to the central reference laboratory where the specimen data were imported into the LDMS.
A data sharing architecture was developed to securely transmit the data at least weekly from the field teams and central reference laboratories to a data warehouse hosted on a central PHIA server (Figure 1). Twice weekly, participant data from ODK and specimen data from LDMS were merged using the PTIDs in the central data warehouse. For records that successfully merged, laboratory orders for VL testing, containing PTID, unique specimen ID, and specimen location were generated using a program written in SAS for Windows version 9.3 (SAS Institute Inc., Cary, NC, USA). For MPHIA and ZAMPHIA, orders were posted to a secure file transfer protocol (FTP) server for lab technicians to download; for ZIMPHIA orders were submitted via an XML (extensible markup language) interface directly into the laboratory information system (LIS) at the central reference laboratory. Based on the VL testing orders, technicians retrieved the specimens and performed the VL testing. For records that were not successfully merged, reconciliation efforts were made by contacting field teams and MOH district lab teams to retrieve paper documentation to verify and correct erroneous entries into ODK or LDMS.

For ZIMPHIA and MPHIA, the VL test instruments were connected to the existing local LIS and individual participant results were generated and printed in report form from the LIS in the same manner as routine clinical testing. For ZAMPHIA, a laboratory data manager exported instrument files in CSV (comma separated values) format and uploaded on a bi-weekly basis to the central data warehouse, where a SAS program was run to generate participant result reports as PDF (portable document file) files fashioned after laboratory results reports used for clinical patients. The PDF files were then downloaded and printed at the central reference laboratory and mailed out using the national courier system. For participants who had chosen a facility with an active Project Mwana account, an SMS system managed by the Zambia Ministry of Health to deliver HIV-related test results to health facilities, a CSV file containing results, facility, and location information was created and fed into the system to send results to the health facility and reminders to participants (https://www.rapidms.org/projects/project-mwana/) [18].

### 2.3 Reporting VL results to health facilities

In addition to laboratory orders, twice a week a contact list of HIV+ participants identified by PHIA surveys was generated using a SAS script running off the central data warehouse. It contained each participant’s PTID, unique specimen ID, data collection date, field HIV test result, sample type (plasma/DBS), first name, last name, address, phone number (optional), and preferred health facility name. The project staff based in the ICAP office (ZIMPHIA/MPHIA) or the central reference laboratory (ZAMPHIA) downloaded this list to track the status of the VL result report for each HIV+ participant. For ZIMPHIA and MPHIA, the administrative officer and the information, communication and technology (ICT) officer worked to coordinate the RoR process. In ZAMPHIA, a dedicated RoR coordinator was recruited and worked directly with the laboratory team performing the VL testing. In ZIMPHIA and MPHIA, the participant VL result reports were sent via the national courier system or project driver. In ZAMPHIA, in addition to the national courier system, results were sent through a new module created in Project Mwana to transmit viral load results. During the household visit, all participants were told to visit the health facility to collect the test results.
after eight weeks. Participants who provided cell phone numbers received text messages regarding availability of test results from the project staff or Project Mwana. Project staff verified identification of the recipient using security questions provided during the interview prior to sending the messages. For a small minority of results with missing or invalid health facility information, VL results were sent to health facilities selected by the other participating household members or all health facilities in the catchment area of the participant’s home.

2.4 | Monitoring and analysis

Monthly summary statistics were generated to track each stage of the RoR process from specimen processing and merging of participant interview, specimen, and VL results data, to generation and couriering of participant results reports to health facilities. Median time from blood draw to results received at the health facility was also tracked, disaggregated by month, residence (urban vs. rural), and RoR stages. The ROR stages were divided into 3 stages: stage 1 was time from blood draw to receipt at central reference laboratory; stage 2 was from receipt at central reference laboratory to the availability of approved VL test result; and stage 3 was time from availability of approved VL test result to results delivered to the health facility. We used Wilcoxon Rank Sum tests to compare median TAT by facility characteristics.

2.5 | Ethics statement

Survey protocols for the Zimbabwe, Malawi and Zambia PHIAs were approved by the Centers for Disease Control and Prevention Institutional Review Board (IRB), the Columbia University Medical Center IRB, and relevant local regulatory bodies, including the Medical Research Council of Zimbabwe, National Health Science Research Committee of Malawi, and the Tropical Disease Research Center in Zambia.

3 | RESULTS AND DISCUSSION

3.1 | Returning VL results

In ZIMPHIA, MPHIA, and ZAMPHIA, a total of 78,090 participants provided a blood sample from 29,634 households located in 196 districts combined (Table 1; Figure 2). The three surveys identified 8391 HIV+ participants, of which, 8313 (99.1%) were tested for VL levels. Of the VL tests successfully run, 8245 (99.2%) were returned to the health facility. There were 68 results that were unable to be delivered to the specific health facilities selected by participants due to missing participant contact or health facility information (n = 43), unresolved PTID entry errors (n = 11), discrepant serology results that required household revisits after survey completion (n = 13), and instrument failure (n = 1). Per protocol, these results were sent to health facilities selected by other consenting household members or health facilities in the catchment area of the participant’s home.

3.2 | TAT for sending VL results to health facilities

In ZIMPHIA and ZAMPHIA where return dates were systematically recorded, 5082 of 5979 (85.0%) VL results were returned within eight weeks of blood draw (Table 2). Return dates were unavailable in approximately 5% (ZIMPHIA) to 10% (ZAMPHIA) of cases and, in those instances, dates sent by project staff were used. The exact timing of return of results in MPHIA is unavailable as dates VL results were delivered to health facilities were not systematically captured; however based on dates when RoR logs were shared from project staff in country with the central data management team, all results were returned within 75 days. Median time from blood draw to results being sent back to the health facility in ZIMPHIA and ZAMPHIA was 48 days (IQR range: 33 to 61 days) (Table 3) with similar results for participants living in urban and rural areas (46 days vs. 49 days, respectively; p = 0.35) (Table 3). TAT was significantly longer for specimens collected in the first month of survey implementation and shortened after the second month of each study (55 days vs. 44 days, respectively; p < 0.01). Overall, stage 3 of the RoR process (time from approved VL test results to delivery of results to the health facility) took the longest, with a median of 26 days (IQR range: 16 to 43 days). In Zimbabwe, stage 3 required a median of 36 days, while in Zambia, only 21 days was needed to complete this stage. Stage 1 (time from blood draw to receipt of specimens at the central reference laboratory) was the shortest interval at 7 to 8 days in all countries. There was substantial variation by country in time required for stage 2: while in Zimbabwe and Zambia it took medians of 9 and 11 days respectively, in Malawi, it took 20 days to provide VL results after receiving specimens at the laboratory.

Table 1. Participants interviewed and tested for HIV in ZIMPHIA, MPHIA, and ZAMPHIA, 2015 to 2016

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>ZIMPHIA</th>
<th>MPHIA</th>
<th>ZAMPHIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total participants</td>
<td>78,090</td>
<td>27,609</td>
<td>23,353</td>
<td>27,128</td>
</tr>
<tr>
<td>Adults</td>
<td>56,877</td>
<td>20,577a</td>
<td>17,187a</td>
<td>19,113b</td>
</tr>
<tr>
<td>Children (0 to 14)</td>
<td>21,213</td>
<td>7032</td>
<td>6166</td>
<td>8015</td>
</tr>
<tr>
<td>Households with participants</td>
<td>29,634</td>
<td>10,897</td>
<td>9359</td>
<td>9378</td>
</tr>
<tr>
<td>Number of districts</td>
<td>196</td>
<td>91</td>
<td>31</td>
<td>74</td>
</tr>
</tbody>
</table>

15 to 64 year.
15 to 59 year.
results being returned to the health facility of 48 days was on par with the return of clinical VL results documented in past studies [10–13]. For example, a recent assessment of national VL monitoring scale up in seven sub-Saharan African (SSA) countries found that TAT ranged from three and four days in South Africa and Namibia to 42 and 50 days in Malawi and Cote d’Ivoire [10]. Careful planning and intensive training of field and laboratory staff to ensure timely transportation and management of specimens as well as on-going monitoring of each positive specimen from blood draw to VL results being sent to health facilities were critical in achieving the TAT goals in the PHIA project.

The first set of PHIA surveys provided a critical lesson on the importance of recruiting dedicated RoR staff that can work directly with laboratory staff at the central reference laboratory to implement RoR processes. The median TAT decreased from the second month onward in ZAMPHIA which coincided with the recruitment of a dedicated RoR coordinator. In ZIMPHIA and MPHIA where the RoR activities were managed by staff with other core responsibilities, TAT either did not significantly improve (ZIMPHIA) or adequate documentation on return dates was not maintained (MPHIA). The RoR coordinator served a critical role of tracking, for each HIV+ participant identified in ZAMPHIA, the specimen location, contact information and VL test result originating from different data sources. In addition, the RoR coordinator kept track of elapsed time since the date of blood collection to ensure processes and systems ran smoothly to meet the eight week goal.

In all three countries, we found that the existing RoR systems for clinical care were only partially adaptable for use for the PHIA surveys. To be able to track and confirm the status of each VL result from test order to receipt at health facility in a timely manner required the creation of a robust data system that allowed staff on a weekly basis to monitor the progress and identify bottlenecks. The development of the system required highly skilled programmers and data managers. However, the system has proven to be replicable within the context of the PHIA Project and is being implemented with minimal adaptations in subsequent PHIA

Figure 2. PHIA enumeration areas across the 196 districts in ZIMPHIA, MPHIA, and ZAMPHIA, 2015 to 2016.

Table 2. Summary Statistics for return of VL results in ZIMPHIA, MPHIA, and ZAMPHIA, 2015 to 2016

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>ZIMPHIA</th>
<th>MPHIA</th>
<th>ZAMPHIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td>8391</td>
<td>3505</td>
<td>2326</td>
<td>2560</td>
</tr>
<tr>
<td>HIV+ participants identified</td>
<td>8313 (99.1)</td>
<td>3499 (99.8)</td>
<td>2315 (99.5)</td>
<td>2499 (97.6)</td>
</tr>
<tr>
<td>VL test performed</td>
<td>8245 (99.2)</td>
<td>3481 (99.5)</td>
<td>2266 (97.9)</td>
<td>2498 (99.96)</td>
</tr>
<tr>
<td>Returned</td>
<td>5082 (85.0)*</td>
<td>3104 (89.2)</td>
<td>N/A</td>
<td>1978 (79.2)</td>
</tr>
<tr>
<td>Within eight weeks</td>
<td>773 (13.1)*</td>
<td>360 (10.3)</td>
<td>N/A</td>
<td>413 (16.5)</td>
</tr>
<tr>
<td>After eight weeks</td>
<td>124 (2.0)*</td>
<td>17 (0.5)</td>
<td>N/A</td>
<td>107 (4.3)</td>
</tr>
<tr>
<td>Not returned</td>
<td>68 (0.8)</td>
<td>18 (0.5)</td>
<td>49 (2.1)</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>VL test not performed</td>
<td>78 (0.9)</td>
<td>6 (0.2)</td>
<td>11 (0.5)</td>
<td>61 (2.4)</td>
</tr>
</tbody>
</table>

*Includes only ZIMPHIA and ZAMPHIA results. Denominator is 5979 VL test returned in ZIMPHIA and ZAMPHIA.
The high level of RoR in the first three PHIA surveys is particularly encouraging as return of clinically relevant laboratory test results, such as VL levels for HIV+ individuals, could serve as a useful strategy to incentivize participation by those who already know their HIV+ status and are engaged in clinical care. With expanded access to HIV testing and treatment services in the past decade in SSA, some population-based surveys have found decreased participation by this group, resulting in underestimation of HIV prevalence [20, 21].

Given the importance of population-based HIV surveys to monitor the population-level progress toward the global “90-90-90” HIV treatment targets, employing strategies to incentivize participation by such groups is critical [6].

Our RoR had several limitations. In Malawi, because we did not recruit an RoR coordinator, it was challenging for project staff with competing priorities to keep track of delivery dates on a consistent basis. Additionally, the long distance between the project office and central reference laboratory added complexity to communications and coordination of RoR, evidenced by the longer interval experienced from approved VL results to delivery of results to health facility (stage 3), compared to Zimbabwe and Zambia. A small minority of delivery dates to the facility recorded for ZIMPHIA and ZAMPHIA were dates project staff sent out the results, such as when the national courier systems were used, while when project vehicles or Project Mwana were used delivery dates were tracked by the driver or the Project Mwana system. The TAT summarized here may therefore be a slight underestimate.

The first three surveys did not collect any data on whether potential participants decided to take part in the survey because of the offer to learn about their VL results. There are no data on what happened after the VL results arrived at the health care facility, therefore there are no data on how many participants learned their VL results or whether the VL results were used by clinicians to evaluate treatment progress. Future PHIA surveys will track these additional data at a minimum in a sample of health facilities to better understand how survey participants use the PHIA results to improve their health. However, confirming receipt of VL results for all participants requires visiting hundreds of health facilities nationwide and retrieving participant records from existing clinic data systems after the conclusion of the survey. Substantial human and logistical resources are needed that may not be feasible for many HIV surveillance projects.

## 5 CONCLUSIONS

The PHIA Project surveys in Zimbabwe, Malawi and Zambia have demonstrated that returning VL results in the context of a national population-based survey is feasible, but requires establishing specimen and data management systems to allow for tracking each participant result to ensure timely return as specified in the survey protocols. Having dedicated data management staff and RoR coordinators facilitated timely return of VL results. These are likely important requirements to strengthen RoR systems in routine clinical care.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS’ CONTRIBUTIONS

SS, YTD, MM, JEJ, and ACV conceptualized and drafted the manuscript. SS, MM, and KL conducted the data analysis. HP, KS, JM, FMO, WK, RM, OM, FC, CM, VM, HM, TN, NSV, GC, CN, BP, JEJ, and ACV provided critical inputs in the draft manuscript.

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Optimal timing of viral load monitoring during pregnancy to predict viraemia at delivery in HIV-infected women initiating ART in South Africa: a simulation study

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Abstract
Introduction: HIV viral load (VL) monitoring is a central tool to evaluate ART effectiveness and transmission risk. There is a global movement to expand VL monitoring following recent recommendations from the World Health Organization (WHO), but there has been little research into VL monitoring in pregnant women. We investigated one important question in this area: when and how frequently VL should be monitored in women initiating ART during pregnancy to predict VL at the time of delivery in a simulated South African population.

Methods: We developed a mathematical model simulating VL from conception through delivery using VL data from the Maternal and Child Health – Antiretroviral Therapy (MCH-ART) cohort. VL was modelled based on three major compartments: pre-ART VL, viral decay immediately after ART initiation and viral maintenance (including viral suppression and viremic episodes). Using this simulation, we examined the performance of various VL monitoring schema in predicting elevated VL at delivery.

Results and discussion: If WHO guidelines for non-pregnant adults were used, the majority of HIV-infected pregnant women (69%) would not receive a VL test during pregnancy. Most models that based VL monitoring in pregnancy on the time elapsed since ART initiation (regardless of gestation) performed poorly (sensitivity <50%); models that based VL measures in pregnancy on the woman's gestation (regardless of time on ART) appeared to perform better overall (sensitivity >60%). Across all permutations, inclusion of pre-ART VL values had a negligible impact on predictive performance (improving test sensitivity and specificity <6%). Performance of VL monitoring in predicting VL at delivery generally improved at later gestations, with the best performing option a single VL measure at 36 weeks' gestation.

Conclusions: Development and evaluation of a novel simulation model suggests that strategies to measure VL relative to gestational age may be more useful than strategies relative to duration on ART, in women initiating ART during pregnancy, supporting better integration of maternal and HIV health services. Testing turnaround times require careful consideration, and point-of-care VL testing may be the best approach for measuring VL at delivery. Broadening the scope of this simulation model in the light of current scale up of VL monitoring in high burden countries is important.

Keywords: HIV; antiretroviral therapy; viral load monitoring; pregnancy; mathematical model; simulation

1 | INTRODUCTION

There are more than 18 million HIV-infected women of childbearing age globally and an estimated 1.4 million pregnancies annually in HIV-infected women [1]. Viral suppression through the use of lifelong antiretroviral therapy (ART) is the critical intervention to support the long-term health of HIV-infected women and mothers and the prevention of both sexual and mother-to-child transmission (MTCT). While there have been global advances in programmes that promote universal initiation of lifelong ART for PMTCT [2], major concerns have emerged related to postpartum ART adherence [3], and up to one-third of women initiating ART in pregnancy experience a loss of viral control during the postpartum period [4].

HIV viral load (VL) monitoring is the central tool to evaluate ART effectiveness and transmission risk, and there is a global movement to expand use of VL monitoring following on recent recommendations from the World Health Organisation (WHO) [5,6]. While there are well-developed guidelines for VL monitoring in non-pregnant adults on ART, there has been little consideration given to implementation of VL monitoring in pregnant and postpartum women. Despite the importance of effective ART services during this period, current guidelines for adult VL monitoring in most countries do not address pregnant...
and postpartum women specifically. Although South African guidelines [7] have recommendations specific to pregnant and postpartum women, there is little empirical evidence to support this approach and the generalisability to other settings is unclear. In turn, there is a clear and urgent need for research to guide evidence-based recommendations into optimal VL monitoring strategies during pregnancy and breastfeeding.

Mathematical simulations are ideally suited to explore diverse scenarios for monitoring disease progression and/or response to treatment. In many contexts, designing empirical studies that examine different monitoring strategies can be impossible due to prohibitive study duration, logistics, ethical considerations and/or research costs [8–11]. While limited aspects of VL monitoring strategies have been investigated in recent modelling work [12], these have not included the key population of pregnant and breastfeeding women.

There are basic questions facing country programmes and international guidelines around when and how frequently VL should be monitored in HIV-infected women initiating ART during pregnancy. Recent WHO guidance notes that an enhanced regimen of antiretroviral prophylaxis may be given to newborns of women with a raised VL at delivery, and the period of labour and delivery is well-recognised as a high-risk window for MTCT [1]. However, the best approach to predict VL at delivery among women initiating ART in pregnancy has not been explored. To help address this issue, we used a simulation based on South African data to examine the ability of VL monitoring at different time points in pregnancy to predict VL at the time of delivery.

## METHODS

Working in R (R Foundation, Vienna, Austria), we developed a simulation of VL from conception through delivery, and then examined the performance of various VL monitoring schema in predicting VL at delivery. This simulation approach models VL at regular intervals before, during and after ART initiation in pregnancy, providing insights that would not be possible through direct observation of patients. For this, a cohort of HIV-infected women not using ART at the time of conception was simulated on a weekly time step from conception through delivery. The model tracked VL (including VL pre-ART and after ART initiation), timing of ART initiation in pregnancy, the presence and timing of (i) initial viral suppression and (ii) elevated VL after ART initiation, and the date and gestation of delivery.

### 2.1 Simulation model

Using this model structure, we simulated continuous VL measures in 10,000 South African women initiating ART in pregnancy. Figure 1A shows a schematic for the model structure. The model was parameterised using data from the Maternal and Child Health – Antiretroviral Therapy (MCH-ART) study (ClinicalTrials.gov register number NCT01933477) [13]. This study followed a cohort of HIV-infected women from the start of antenatal care, including 620 women initiating ART during pregnancy who underwent regular viral load testing, as described previously [5,14,15]. Parameters drawn on from MCH-ART were gestational age at ART initiation (weeks), gestational age at delivery (weeks), viral suppression trajectories (estimated in copies/mL with fractional polynomials), rate of viraemic episodes after initial viral suppression (as a proportion with VL ≥1000 copies/mL over N eligible) and outcomes after initial viral rebound (ongoing viraemia or viral resuppression as a proportion). Of the individuals that experienced viraemic episodes after initial suppression, a fraction experienced complete loss of viral control, with their subsequent VL sampled from the woman’s pre-ART VL distribution. Those that lost viral control only temporarily (‘viral blips’) regained viral suppression and remained virally suppressed for the remainder of the observation period. The duration of viral blips varied, depending on the magnitude of the response and the modelled VL trajectory. Fractional polynomial models were used to estimate trajectories on both sides of the maximum magnitude of the viral blip. Median and interquartile range (IQR) are calculated from the source data for continuous measures and frequency (percent) for counts.

### 2.2 VL trajectory modelling

Continuous valued VL was simulated for each woman at each week of pregnancy. VL was modelled based on three major compartments: pre-ART VL, viral decay immediately after ART initiation and viral maintenance (including viral suppression and viraemic episodes). Each compartment had a different generation model and each simulated woman transitioned independently of other individuals through all conditions. VL measures were sampled from different distributions per compartment, and have dependencies on that woman’s pre-ART VL value. Figure 1B shows sample VL distributions generated by the simulation. The slopes for suppression and rebound trajectories were based on fractional polynomial models, the parameters of which were dependent on pre-ART VL values. Throughout, VL was simulated as a continuous measure and additive non-Gaussian noise was included in all simulations.

### 2.3 Viral load monitoring strategies

Using this simulation, we evaluated the predictability of different approaches to VL monitoring at different time points during the antenatal period to predict VL at the time of delivery. Given the costs of VL testing, we focused on strategies which minimized the number of VL tests required for a woman. Three broad approaches to monitoring were examined: (i) a single VL test conducted based on duration of ART use (regardless of gestation), (ii) a single VL test based on gestation (regardless of duration of ART use) and (iii) the addition of a pre-ART VL test to assist in either (i) or (ii). For approach (i), we investigated the results of VL testing at 4, 8, 12, 16, 20 and 24 weeks after ART initiation, and for (ii) we examined testing at 12, 20, 24, 32 and 36 weeks gestational age. For all analyses, women in the simulated cohort were eligible if they had initiated ART by the time of the proposed test (the input distribution based on the distribution of gestations at ART initiation in the MCH-ART data) and had not delivered by that time (based on the distributions of gestations at delivery in the MCH-ART data [15]). In all cases, we describe the proportion of women who would not be tested under each strategy due to either of these factors (e.g. late ART initiation or premature delivery).
Different classes of predictive models were applied to simulated data to predict continuous VL at delivery. Predicted VL at delivery was made discrete and utilised for evaluation of model performance as a binary construct of \(<1000\) versus \(\geq1000\) copies/mL in keeping with WHO guidelines and based on the finding that MTCT transmission risks are greatly increased above 1000 copies/mL [16,17]. Models were applied to the full cohort of 10,000 and to a subset of individuals initiating ART before 20 weeks gestational age (early ART initiation). Simple linear models were examined; here, we present estimates based on a last observation carried forward (LOCF) model as it represents the most common approach in real-world clinical care; this model assumes the VL at delivery will be equal to the VL measures during gestation (i.e. the VL measure is "carried forward" to delivery). Linear regression models were used to incorporate pre-ART VL into the LOCF model.

### 2.4 Model performance outputs

Model parameters are summarised with median (IQR) for continuous measures and percent (standard deviation) for binary measures. For each of the specified VL monitoring time points, the sensitivity (SE), specificity (SP), negative likelihood ratio (LR –), positive likelihood ratio (LR+), likelihood ratio (LR+/LR–), positive (PPV) and negative predictive value (NPV) were calculated evaluating the ability of the categorised VL measured at that point in pregnancy to predict VL at the time of delivery, and reported with estimated 95% confidence intervals. Predictive models were run independently on the “training” simulation run of 10,000 individuals; performance was evaluated on a “test” simulation run, again of 10,000 individuals; initiated with a different random seed.

### 3 RESULTS

#### 3.1 Model calibration

Table 1 shows key features of the simulated cohort. Averaged across runs, the median (IQR) gestational age at ART initiation in the simulated cohort was 18 weeks (14, 23) and pre-ART VL was 3.99 log10 copies/mL (3.28, 4.66). The mean percent of women with VL \(<1000\) copies/mL at the time of delivery was 89% (sd, 0.3%) and median (IQR) time on ART at
The median (IQR) gestation at delivery was 39 weeks (38, 40).

### 3.2 Statistical predictive models

On each analysis set, statistical models were applied using the VL measure, time on ART and pre-ART VL to develop a model for VL at delivery (training data). The details of the models can be found in Table 2. Each model was applied to a new simulation run (holdout data), and the model performance statistics were calculated based on correct model predicted viraemia at delivery or not (based on ≥1000 copies/mL).

Most models that based VL monitoring in pregnancy on the time elapsed since ART initiation (regardless of gestation) demonstrated poor sensitivity (SE <50%) and good specificity (>85%) (Table 2). When monitoring in pregnancy was based on time since ART initiation, the optimal timing for a single VL appeared to be a VL measured at 20 weeks after ART initiation (SE: 42%, SP: 99%); however, only 50% of women would be eligible for this measure (the remainder having delivered by this time point). Generally, these models incorrectly specified a relatively small proportion of individuals as suppressed when they were truly viraemic at delivery, but misclassified a much higher proportion of women as being viraemic at delivery when they were truly suppressed; this was due in large part to the inclusion of women who initiated ART late in pregnancy and had not yet achieved initial viral suppression by the time of testing. If VL monitoring was based on guidelines for non-pregnant adults, with a first VL conducted 6 months after ART initiation, only 31% of the cohort would be eligible to be tested before delivery.

In contrast, most models that based VL measures in pregnancy on the woman’s gestation (regardless of time on ART) appeared to perform better overall (Table 2). VL tests conducted late in pregnancy appeared able to test higher proportions of women in the simulated cohort. Model performance generally improved at later gestations, with perfect sensitivity and specificity achieved by VL testing at the time of delivery, by definition. In addition, the proportion of the cohort eligible to be tested decreased late in the third trimester as premature deliveries pre-empted VL testing in pregnancy. Overall, the optimal time point appeared to be testing at 36 weeks’ gestation with approximately 90% of women eligible to be tested and relatively high sensitivity (72%) and specificity (95%) observed in detecting VL ≥1000 copies/mL at delivery (Figure 2).

Across all permutations, inclusion of pre-ART VL values had a negligible impact on predictive performance when evaluating VL monitoring based on either gestational age or duration on ART, using linear models. Models which included pre-ART VL in addition to a VL after ART initiation increased modelled specificities and sensitivities by <6%, compared to the corresponding models without pre-ART VL, however, were hampered by a tendency to make out of range predictions due to the linear structure.

### 4 DISCUSSION

This simulation study provides several important new insights into routine VL monitoring strategies for women who initiate ART during pregnancy. First, if monitoring in pregnancy is based on current guidelines for non-pregnant adults, with a
first VL after 6 months on ART, only 31% of women in this simulation would be tested in pregnancy. Second, VL monitoring strategies based on time on ART may not be ideal for VL monitoring in pregnancy, while the best-performing monitoring schedule in pregnancy appears to be a single test at 36 weeks gestation. Third, the addition of pre-ART VL measures improves prediction only by a small proportion of those with elevated VL at delivery, and may not be a cost-effective approach to VL monitoring in pregnancy.

Monitoring strategies based on gestational age versus time on ART may be easier to implement in many settings, as they could coincide with routine antenatal visits. We found that a single VL test at 36 weeks gestation can predict 73% of the 9% of women with VL $\geq 1000$ copies/mL at delivery. This is reassuring as this approach is implied by recent WHO guidelines [5], however, we found that only 91% of all HIV-infected women would be tested at this time due to preterm deliveries, and in turn testing at later gestations (such as 37 or 38 weeks gestation) would increase the proportion of women who could be tested towards 100%. By definition, the optimal approach to predicting VL at delivery would be to test VL at the time of delivery. However, testing turnaround times for existing VL monitoring systems (which are routinely $>1$ week and often $>4$ weeks in many parts of sub-Saharan Africa) would preclude VL testing at or just prior to delivery from informing infant management immediately postpartum, including the initiation of enhanced antiretroviral prophylaxis [18]. To help address this issue, rapid point-of-care VL tests could be conducted at delivery [19,20], and would theoretically have perfect sensitivity and specificity in predicting VL at delivery, thereby allowing for timely and effective infant management. The simulation was conducted in a single South African cohort, and validation with other datasets from other settings is required, noting that data on VL trajectories in HIV-infected women initiating ART in pregnancy in low-resource settings are limited. We did not include in our model the turnaround times associated with VL monitoring, and thus this work assumes that all VL specimens collected would have results available; given the complexities of the VL "cascade" in many LMIC settings [21], the implications of different turnaround times for interpreting these findings should be considered carefully. Finally, we did not consider the costs of VL testing in this model-based analysis.

Table 2. Predictive model performance statistics resulting from last observation carried forward model of viral load monitoring at specified time points. Women were eligible for testing if they had initiated ART in pregnancy and had not delivered at the time point of evaluation.

<table>
<thead>
<tr>
<th>Timing of test</th>
<th>n</th>
<th>% of women eligible for testing</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR test (LR+/-LR-)</th>
<th>LR positive (95% CI)</th>
<th>LR negative (95% CI)</th>
<th>Negative predictive value (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing based on duration of ART use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Four weeks on ART</td>
<td>9724</td>
<td>1</td>
<td>0.74 (0.71, 0.77)</td>
<td>0.64 (0.63, 0.65)</td>
<td>5.05</td>
<td>2.05 (1.96, 2.15)</td>
<td>0.41 (0.36, 0.45)</td>
<td>0.96 (0.96, 0.97)</td>
<td>0.17 (0.16, 0.18)</td>
</tr>
<tr>
<td>Eight weeks on ART</td>
<td>9112</td>
<td>0.9</td>
<td>0.5 (0.46, 0.54)</td>
<td>0.86 (0.85, 0.87)</td>
<td>6.19</td>
<td>3.6 (3.27, 3.96)</td>
<td>0.58 (0.54, 0.63)</td>
<td>0.96 (0.95, 0.96)</td>
<td>0.21 (0.19, 0.23)</td>
</tr>
<tr>
<td>12 weeks on ART</td>
<td>8104</td>
<td>0.8</td>
<td>0.36 (0.31, 0.41)</td>
<td>0.95 (0.94, 0.95)</td>
<td>100</td>
<td>6.75 (5.74, 7.93)</td>
<td>0.67 (0.63, 0.73)</td>
<td>0.97 (0.96, 0.97)</td>
<td>0.26 (0.22, 0.29)</td>
</tr>
<tr>
<td>16 weeks on ART</td>
<td>6906</td>
<td>0.7</td>
<td>0.38 (0.32, 0.44)</td>
<td>0.97 (0.97, 0.98)</td>
<td>23.59</td>
<td>15.06 (12.19, 18.6)</td>
<td>0.64 (0.58, 0.7)</td>
<td>0.97 (0.97, 0.98)</td>
<td>0.39 (0.34, 0.45)</td>
</tr>
<tr>
<td>20 weeks on ART</td>
<td>5106</td>
<td>0.5</td>
<td>0.42 (0.35, 0.5)</td>
<td>0.99 (0.99, 0.99)</td>
<td>72.27</td>
<td>42.3 (30.47, 58.74)</td>
<td>0.59 (0.52, 0.66)</td>
<td>0.98 (0.98, 0.98)</td>
<td>0.60 (0.51, 0.69)</td>
</tr>
<tr>
<td>24 weeks on ART</td>
<td>3082</td>
<td>0.4</td>
<td>0.62 (0.52, 0.72)</td>
<td>0.99 (0.99, 1.0)</td>
<td>290.29</td>
<td>109.5 (66.6, 179.9)</td>
<td>0.38 (0.29, 0.48)</td>
<td>0.99 (0.98, 0.99)</td>
<td>0.79 (0.69, 0.87)</td>
</tr>
<tr>
<td>Testing based on gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks’ gestation</td>
<td>1406</td>
<td>0.1</td>
<td>0.77 (0.61, 0.88)</td>
<td>0.43 (0.4, 0.46)</td>
<td>2.48</td>
<td>1.34 (1.13, 1.6)</td>
<td>0.54 (0.51, 0.58)</td>
<td>0.98 (0.97, 0.99)</td>
<td>0.04 (0.03, 0.06)</td>
</tr>
<tr>
<td>20 weeks’ gestation</td>
<td>5047</td>
<td>0.5</td>
<td>0.56 (0.48, 0.63)</td>
<td>0.57 (0.56, 0.59)</td>
<td>1.67</td>
<td>1.3 (1.13, 1.34)</td>
<td>0.78 (0.66, 0.82)</td>
<td>0.97 (0.96, 0.97)</td>
<td>0.04 (0.03, 0.05)</td>
</tr>
<tr>
<td>24 weeks’ gestation</td>
<td>6980</td>
<td>0.7</td>
<td>0.58 (0.53, 0.64)</td>
<td>0.69 (0.68, 0.7)</td>
<td>3.13</td>
<td>1.89 (1.7, 2.08)</td>
<td>0.6 (0.53, 0.69)</td>
<td>0.97 (0.97, 0.98)</td>
<td>0.08 (0.07, 0.09)</td>
</tr>
<tr>
<td>32 weeks’ gestation</td>
<td>8946</td>
<td>0.9</td>
<td>0.58 (0.54, 0.61)</td>
<td>0.88 (0.87, 0.89)</td>
<td>9.98</td>
<td>4.81 (4.45, 5.25)</td>
<td>0.48 (0.44, 0.53)</td>
<td>0.96 (0.96, 0.97)</td>
<td>0.27 (0.24, 0.29)</td>
</tr>
<tr>
<td>36 weeks’ gestation</td>
<td>9118</td>
<td>0.9</td>
<td>0.72 (0.69, 0.75)</td>
<td>0.96 (0.95, 0.96)</td>
<td>56.9</td>
<td>16.67 (14.94, 18.6)</td>
<td>0.29 (0.26, 0.33)</td>
<td>0.97 (0.97, 0.97)</td>
<td>0.63 (0.60, 0.66)</td>
</tr>
</tbody>
</table>

Figure 2. Sensitivity and specificity of viral load monitoring conducted at selected gestations during pregnancy to detect viral load $\geq 1000$ copies/mL at the time of delivery.
testing, or the subsequent cost-effectiveness of different VL monitoring approaches, noting that these are critical considerations for policymaking. Broadening the consideration of VL monitoring to include the possible role of VL monitoring in supporting ART adherence may enhance the cost-effectiveness of monitoring, but data to support this are limited [22].

More broadly, this work demonstrates the value of simulation studies for investigating complex questions related to the implementation of VL monitoring in LMIC settings. While we focused on women initiating ART in pregnancy, there is also a growing population of women who enter antenatal care already on ART (having initiated before pregnancy), and the optimal VL monitoring strategies for this population require further attention in similar modelling approaches [15]. These methods can also be applied to address a wider range of issues, including VL monitoring during breastfeeding, a time of growing concern for MTCT risk [1], or in other patient populations. With expanding insights into the implementation and findings of routine VL monitoring in countries where HIV is prevalent, there is a growing body of data to help inform the design and parameterization of such simulations, and this is an important area for future investigation.

In summary, this simulation suggests that pregnant women warrant VL monitoring approaches different from non-pregnant adults. A single VL test conducted late in gestation may be used to predict approximately three-quarters of all elevated VL at delivery, but effective implementation would require rapid turnaround times. Furthermore, POC VL testing may be important to detect larger proportions of viraemic women on ART for intervention.

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COMPETING INTERESTS
None of the authors have any competing interests to declare.

AUTHORS’ CONTRIBUTIONS
ML, LM and EA developed the initial concept and idea. ML developed and wrote the first version of the simulation models. NYH assisted in study conceptualization provided expertise regarding viral load monitoring. ML, TG and EM carried out the simulations, calibration and statistical analysis. ML drafted the first version of the manuscript. All authors contributed to writing and reviewing the science. All authors have read and approved the final manuscript.

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REFERENCES
Routine viral load monitoring in HIV-infected infants and children in low- and middle-income countries: challenges and opportunities

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Abstract

Introduction: The objective of this commentary is to review considerations for implementing routine viral load (VL) monitoring programmes for HIV-infected infants and children living in low- and middle-income countries (LMIC). Since 2013, the World Health Organization (WHO) guidelines recommend VL testing as the preferred monitoring approach for all individuals treated with ART in order to assess treatment response, detect treatment failure and determine the need to switch to a second-line regimen in a timely manner. More recently, WHO guidelines from 2016 identify HIV-infected infants and children as a priority group for routine VL monitoring.

Discussion: There are a number of reasons why HIV-infected infants and children should be prioritized for routine VL monitoring. Data from national VL monitoring programmes as well as systematic reviews and meta-analyses from LMIC indicate rates of viral suppression are lower for infants and children compared to adults. The number of antiretroviral drugs and palatable formulations suitable for young children are limited. In addition, emotional and developmental issues particular to children can make daily medication administration difficult and pose a challenge to adherence and achievement of sustained viral suppression. VL monitoring can be instrumental for identifying those in need of additional adherence support, reducing regimen switches and preserving treatment options. The needs of infants and children warrant consideration in all aspects of VL monitoring services. If capacity for paediatric venipuncture is not assured, platforms that accept dried blood spot specimens are necessary in order for infants and children to have equitable access. Healthcare systems also need to prepare to manage the substantial number of infants and children identified with elevated VL, including adherence interventions that are appropriate for children. Establishing robust systems to evaluate processes and outcomes of routine VL monitoring services and to support drug forecasting and supply management is essential to determine best practices for infants and children in LMIC.

Conclusions: The particular concerns of HIV-infected infants and children warrant attention during all phases of planning and implementation of VL monitoring services. There are a number of key areas, including frequency of monitoring, blood specimen type and adherence challenges, where specific approaches tailored for infants and children may be required.

Keywords: viral load; HIV/AIDS; implementation; paediatrics; children; monitoring

1 | INTRODUCTION

Access to antiretroviral therapy (ART) in children <15 years has greatly expanded, with an estimated 920,000 children <15 years reportedly receiving ART in 2016 compared to 18,000 children in 2000 [1]. The new treatment paradigm recommends initiating ART at earlier ages in all children independent of CD4 T-cell counts or clinical stage. This approach could expedite access to treatment for an additional 1,180,000 HIV-infected children in need of ART. Developing and implementing monitoring strategies to optimize outcomes in children on ART in low- and middle-income countries (LMIC), where over 90% of children with HIV live, is a critical clinical and public health challenge.

Since 2013, the World Health Organization (WHO) guidelines recommend viral load (VL) testing as the preferred monitoring approach for all individuals treated with ART in order to assess treatment response, detect treatment failure and determine the need to switch to a second-line regimen in a timely manner [2]. More recently, WHO guidelines from 2016 identify HIV-infected infants and children as a priority group for preferential routine VL monitoring [2]. The objective of this commentary is to review considerations for implementing routine VL monitoring for HIV-infected infants and children in LMIC.
1.1 | Reasons for prioritizing HIV-infected infants and children for VL monitoring services

HIV-infected infants and children are considered a priority group for routine VL monitoring for a number of reasons. The efficacy of early ART for achieving viral suppression, promoting immune reconstitution, and reducing morbidity and mortality in children is well-established [3,4]. However, until recently, data on rates of VL suppression among children undergoing routine monitoring in LMICs in contrast to more targeted VL testing of children suspected of treatment failure were unavailable. Initial results from national routine VL monitoring programmes in Kenya and Uganda that include large representative samples with age-disaggregated reporting indicate that rates of viral suppression are low for infants, children and adolescents compared to adults [5,6]. The overall rate of viral suppression among children in five eastern–southern African countries with nationally representative data from routine viral load monitoring was 62% [7]. Similar low rates of viral suppression are reported from earlier studies from single or multiple facilities in LMIC [8,9]. Lower rates of viral suppression among paediatric and adolescent patients compared to adults have also been reported in several systematic reviews and meta-analyses. A meta-analysis by Ciaranello et al. [10] in 2009 using data from nine studies in resource-limited settings collected from 1997 to 2008 found the pooled estimate for 12-month viral suppression (HIV RNA <400 copies/mL) in children <15 years to be 70% (95% confidence interval [CI]: 67–73). A large meta-analysis conducted in 2016 of both observational studies and randomized controlled trials evaluating viral suppression identified 72 studies reporting on 51,374 children <18 years. After 12 months on first-line ART, viral suppression was achieved by 64.7% (95% CI: 57.5–71.8) in studies conducted from 2000 to 2005, 74.2% (95% CI: 70.2–78.2) in studies conducted from 2006 to 2009 and 72.7% (95% CI: 62.6–82.8) in studies conducted after 2010 [11]. These rates are considerably lower than those typically observed in adults, including in a meta-analysis of virologic outcomes in adults, which found viral suppression rates >80% in the first five years on ART [12].

The number of antiretroviral drugs and palatable formulations suitable for young children are limited [2], making avoidance of unnecessary changes in ART particularly important. For example, nevirapine and efavirenz, first-generation non-nucleoside reverse transcriptase inhibitors (NNRTI), are not recommended for children less than three years of age [2]. This is due to findings from clinical trials that demonstrated elevated rates of failure among children on NNRTI-based regimens compared to protease inhibitor (PI)-based regimens regardless of prior exposure to NNRTI for prevention of mother-to-child transmission (PMTCT) [13,14]. Thus, these agents, which for many years have been the cornerstone of first-line ART for adults living in LMIC, are not the preferred option for children under three years for whom ritonavir-boosted lopinavir (LPV/r)-based regimens are used as first-line ART. In addition, for a number of reasons including cold chain limitations, LPV/r may not be consistently available in all settings. Newer agents, such as darunavir, etravirine and raltegravir, used in second-line regimens are difficult to acquire for children failing first-line PI-regimens in many LMIC, and are often only available through donation programmes if at all.

Routine regularly scheduled VL monitoring has the potential to preserve treatment options through early identification of those with non-suppression who might benefit from timely intensified adherence support to prevent treatment failure and the need for regimen changes.

Finally, there are issues particular to children that may undermine ART adherence and contribute to poorer virologic outcomes. Due to a number of emotional and developmental factors, daily medication administration to infants and young children can be extremely difficult, especially with bad tasting preparations, and child-caregiver conflicts over medication are not uncommon [15,16]. Swallowing of tablets, when available in paediatric formulations can also be difficult for many children. A child’s adherence is also vulnerable to changes in social environments. As children are reliant on adult caretakers for monitoring home supply and administration of ART and clinic visits, caretaker changes or alterations in household routines are a frequent cause of disruptions in adherence [17]. In addition, dose-adjusting is required to account for growth and failure to do so may result in under-dosing of one or more antiretroviral agents in a regimen.

2 | DISCUSSION

The particular needs of infants and young children should be considered at each phase of planning and implementation of VL monitoring at all levels of the healthcare system, ranging from national programmes to individual health facilities. In this section, we discuss key aspects in implementing VL monitoring programmes, where attention to the needs of infants and children is warranted. An overview of these aspects is provided in Figure 1.

Planning and implementation of routine VL monitoring services would benefit from considering lessons learned from national early infant diagnosis (EID) programmes or evaluating existing programmes that monitor VL testing for children suspected of treatment failure. A number of countries report shortcomings, including inadequate specimen collection and transport systems, inefficient (e.g. duplicative) lab information systems, test kit stock outs, insufficient technical personnel, long turnaround times, inefficient reporting of results and suboptimal clinical decision-making once results are returned to clinical care sites [18–21]. In some environments, less than half of EID results were ever available for patient care decisions [22].

National decision-making and planning bodies (e.g. technical working groups) should include individuals with technical expertise relevant to paediatrics. Updated national guidelines should include VL monitoring recommendations specific to infants and children. If a phase-in approach for implementation is planned, priority populations for early access should include infants and children.

The optimal timing and frequency for routine VL monitoring in infants and children on ART has not been established, and currently, there is little evidence to inform this question. Nonetheless, it is essential that clear guidance be provided even if considered provisional until additional studies are available. The WHO advises VL monitoring at 6, 12 months and then every 12 months for patients that are stable on first-line ART and grades the supportive evidence for this recommendation as
very low quality [24]. A number of countries with national VL monitoring programmes currently endorse the WHO recommendation of a single schedule for VL monitoring for non-pregnant and breastfeeding ART-treated adults, as well as for infants and children [23–25], while others have adopted paediatric specific schedules. For example, the Botswana National Guidelines recommend VL testing for infants and children on ART every three months [26]. Evaluating whether more frequent monitoring together with support for adherence leads to lower rates of first-line treatment failure is an important area of future research.

It is also important to consider infants and children when selecting specimen type and platform or assay for VL testing. Apart from specialized paediatric care settings, reliance on plasma-based specimens poses a major obstacle to implementation of VL monitoring for infants and children [27]. Unless or until capacity for paediatric venipuncture is assured, the only practical way for young children and infants on ART to access VL monitoring is by means of assay platforms that accept dried blood spot (DBS) specimens, a number of which have been validated against plasma [28,29]. Introduction of point-of-care (POC) VL platforms may also provide advantages, particularly for children in situations where turnaround times for results from central labs may undermine the value of monitoring schedules that call for shorter testing intervals.

There are also specific training issues for healthcare workers relevant to VL monitoring for infants and children. The currently recommended criteria for viral failure (i.e. persistent VL above 1000 copies/mL after at least six months of taking ART) by WHO is the same for all ages [2]. Here, again the recommendation for the optimal threshold to define viral failure and criteria for switching ART is provisional and may require adjustments as additional evidence becomes available. The threshold of 1000 copies/mL is based on evidence mainly from studies conducted in adults suggesting that risk of HIV disease progression is very low below this threshold [30], as well as evidence that intermittent low-level viraemia (50–1000 copies/mL) is not associated with short term treatment failure [31]. Results from a randomized clinical trial conducted among children ages 0.1–17.8 years (median 6.5 years) starting first-line therapy found no difference in four-year VL outcomes when ≥1000 copies/mL was used as the switching threshold compared to ≥30,000 copies/mL [32]. However, the higher switching threshold, affects drug-related resistance, among those on an NNRTI-based regimen; more nucleoside reverse transcriptase inhibitor (NRTI) mutations were detected in those switching at 30,000 copies compared to those switching at 1000 copies/mL. No differences in clinically important PI or NRTI mutations were detected between the two switching thresholds. The long-term clinical and virologic outcomes in children when using a threshold of 1000 copies/mL has not yet been evaluated and is an important research question.

In addition, due to high levels of viral replication during the first few months of life, some infants may require more than six months to achieve initial suppression to below 1000 copies/mL [33]. Further research is required to determine if obtaining pre-treatment baseline VL for young infants is warranted in order to assist with the interpretation of VL results on ART. These considerations may become more important with greater emphasis on early ART initiation [3,4]. Healthcare workers will require ongoing training on these issues.

Widespread availability of VL monitoring provides the opportunity for earlier detection of treatment failure and allows for timely switching of ART regimens, as well as avoids unnecessary changes in medications when compared to reliance on CD4 and clinical status alone [34,35]. In addition, detection of elevated VL identifies individuals who might benefit from targeted adherence interventions in order to achieve (re)-suppression and preserve future treatment options. Healthcare workers and healthcare systems need to prepare and develop capacity to manage the potentially substantial number of infants and children with elevated VL. This entails provision of intensified adherence assessments and interventions that are appropriate for children at various stages of development, as well as for household members and individuals involved in the care of the child [36]. Disclosure to the child of their HIV status can also be an important aspect of adherence counselling. There remains a great need to determine the best practices for improving adherence among HIV-infected children.
in LMIC, as much of limited prior research was conducted in high income countries [37,38]. Support for effectiveness of a number of adherence interventions in children on viral suppression is available including use of peer-support, adherence counsellors, educational session and home visits. A review by Bonner et al. [39] reported a pooled estimate of 70.5% (95% CI: 56.6–84.4) of repeat VL below 1000 copies/mL found by routine VL testing with prior VL >1000 copies/mL. A smaller study of children by Jobanputra et al. conducted in Swaziland reported that 61% of those with elevated VL who had undergone enhanced adherence counselling had a VL <1000 copies/mL when repeated at least 60 days later [40]. Healthcare workers must be knowledgeable about common adherence barriers experienced by infants and children and their caregivers and potential remedies.

Routine VL monitoring can be also anticipated to bring a new urgency to securing or establishing the capacity for timely switches in ART regimens for children with viral failure as demonstrated by persistently elevated VL despite good adherence. As shown in prior studies, VL monitoring is associated with higher rates of second-line ART [41,42]. Standardized procedures suitable to the context for establishing processes, roles and responsibilities of key persons for switching infants and children to second-line and third-line ART regimens are required. An assessment of the human resources and specialized skills of the key cadre(s) for these tasks may be required. In some LMIC, nurses are among the most important prescribers of first-line ART [43]. Future options may include expanding their scope of practice to include switching children to second or third-line regimens, or establishing other centralised processes as available resources allow.

Finally, monitoring systems that support accurate and timely evaluation of all facets of routine VL monitoring for infants and children are required, including supporting a dynamic drug forecasting, procurement and distribution system that can rapidly respond to changes in demand for therapeutic agents required for second- and third-line paediatric ART regimens. Monitoring systems to support the integration of VL data between health facilities and laboratories and between healthcare workers and patients will need to be adapted for paediatric purposes. Quality assessment and improvement activities will depend on the timely availability of age-disaggregated reports.

3 | CONCLUSIONS

In order for national VL monitoring programmes in LMIC to have a maximal impact on outcomes for all patient groups, the particular concerns of HIV-infected infants and children warrant attention during all phases of planning and implementation. There are a number of key areas, including frequency of monitoring, type of blood specimen and adherence challenges, where specific approaches tailored for infants and children may differ from those for adult patients. There are a number of key policy and practice areas for which supportive evidence is limited at this time. Rapid evaluation of initial efforts and experiences scaling up routine VL monitoring for infants and children in LMIC is essential to determine best practices.

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COMPETING INTERESTS

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The case for viral load testing in adolescents in resource-limited settings

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Abstract

Introduction: The success of HIV treatment programmes globally has resulted in children with perinatally acquired HIV reaching adolescence in large numbers. The number of adolescents living with HIV is growing further due to persisting high HIV incidence rates among adolescents in low- and middle-income settings, particularly in sub-Saharan Africa. Although expanding access to HIV viral load monitoring is necessary to achieve the 90-90-90 targets across the HIV care continuum, implementation is incomplete. We discuss the rationale for prioritizing viral load monitoring among adolescents and the associated challenges.

Discussion: Adolescents with HIV are a complex group to treat successfully due to extensive exposure to antiretroviral therapy for those with perinatally acquired HIV and the challenges in sustained medication adherence in this age group. Given the high risk of treatment failure among adolescents and the limited drug regimens available in limited resource settings, HIV viral load monitoring in adolescents could prevent unnecessary and costly switches to second-line therapy in virologically suppressed adolescents. Because adolescents living with HIV may be heavily treatment experienced, have suboptimal treatment adherence, or may be on second or even third-line therapy, viral load testing would allow clinicians to make informed decisions about increased counselling and support for adolescents together with the need to maintain or switch therapeutic regimens.

Conclusions: Given scarce resources, prioritization of viral load testing among groups with a high risk of virological failure may be required. Adolescents have disproportionately high rates of virological failure, and targeting this age group for viral load monitoring may provide valuable lessons to inform broader scale-up.

Keywords: adolescent; viral load; HIV; resource-limited

1 | INTRODUCTION

The numbers of adolescents living with HIV has increased globally by 30% since 2005 [1]. The paediatric HIV epidemic is maturing, with increasing numbers of children living into adolescence and young adulthood due to the scale-up of antiretroviral therapy (ART), and HIV-infected children with slow disease progression presenting to health services for the first time in adolescence [2,3]. The persisting high incidence of HIV among adolescents in low and middle-income settings (LMICs), particularly among young women and girls, is also a significant contributor to the increase in numbers of adolescents living with HIV over the past decade. HIV is the second biggest cause of death among adolescents globally, and accounts for a substantial proportion of deaths in sub-Saharan Africa [4]. Notably, HIV-related deaths among adolescents have risen during a period in which there has been a significant decline in HIV-related mortality among other age groups [5].

HIV viral load (VL) testing allows accurate monitoring of antiretroviral treatment and detection of virological failure. Expanding access to VL monitoring is necessary to achieve the ambitious UNAIDS treatment target that stipulates that 90% that those on ART should have durable viral suppression. Universal access to HIV VL testing has yet to be achieved however. We discuss the rationale for prioritizing VL monitoring among adolescents.

2 | THE STATE OF THE ADOLESCENT HIV EPIDEMIC

An estimated 1.8 million adolescents between 10 and 19 years old were living with HIV in 2015, an increase of 28 per cent since 2005 [6]. The majority of these adolescents live in resource-limited settings, 82% in sub-Saharan Africa, and nearly half of the estimated numbers of adolescents living with HIV are in five countries, India, Kenya, Nigeria, South Africa and Tanzania [4,7]. This growing cohort of adolescents comprises of two groups; those with perinatally acquired infection born before widely available prevention of mother-to-child transmission (PMTCT) who are surviving into...
adolescence and young adulthood, and those with largely sexually acquired new infections [8]. The numbers of children infected with HIV is declining due to the concerted global effort of PMTCT. The use of antiretroviral therapy as part of PMTCT programmes has averted 350,000 new perinatally infected newborns, with a remarkable reduction in the annual number of new infections amongst children by 70% since 2001 [9].

Children with perinatally acquired HIV who otherwise have died in infancy and early childhood are now reaching adolescence in large numbers due to earlier diagnosis, treatment initiation and the global scale-up of antiretroviral therapy (ART) [10]. At least a third of HIV-infected infants have slow progressing disease, with a median survival of at least 16 years [11,12]. Many children infected a decade or so ago before PMTCT programmes were available therefore present to health services for the first time in adolescence [1].

While the rate of new infections among adults has stabilized in many countries, the decline in the incidence of infection among adolescents and young people has been slower. A third of new infections occur in the 15–24 year age group, with an estimated 670,000 young people in this age group newly infected with HIV in 2015, representing over 40% of new HIV infections globally [13]; of these, 250,000 were adolescents aged 15–19 years old [8].

This growing cohort of adolescents presents a challenge to resource-limited health services not used to effectively managing adolescents, a subset of whom have complex treatment histories and chronic illness [10].

### 3 | ADOLESCENTS AND TREATMENT OUTCOMES

Adolescence is a period of physiological and psychological growth characterized by biological, sexual and identity development and increasing social autonomy [14,15]. This stage of development is a high-risk period in terms of engagement with healthcare services, as adolescents often experience destabilizing socio-cultural change coupled with increased risk-taking behaviour and decreased parental support [16]. Poor adherence to treatment during adolescence has been reported for many chronic conditions, including diabetes, asthma and epilepsy [16]. HIV is no exception, and adolescents living with HIV are not only less likely to initiate ART than adults, but those who do start ART are less likely to remain in care and adhere to treatment [17]. Intermittent medication adherence increases the risk of treatment failure and subsequent development of drug resistance [18,19]. Studies in high- and low-resource settings have shown that adolescents have worse virological outcomes than other age groups [20–22]. Those with chronic conditions may be more impacted by the risk-taking behaviours that characterize adolescence than their peers without chronic medical problems in terms of impact on their health and ability to manage their illness [23,24]. Living with chronic disease can result in considerable psychological burden, involving social and educational disruption, real or perceived stigma, and the difficulties of adjusting to adult healthcare services as they transition from paediatric care [25]. In addition, particularly those adolescents with perinatally acquired infection may have lost one or both parents to HIV, with significant economic, social and psychological consequences and adverse impacts on treatment access and health outcomes [26].

Both adolescents with perinatally acquired and non-perinatally acquired HIV have varied and overlapping risk factors for treatment failure and subsequent development of drug resistance. Adolescents in both groups face the complexities of living with an oft-stigmatized condition throughout adolescence and into adulthood with the attendant risks on adherence and retention in care.

Adolescents with perinatally acquired HIV are at high risk for treatment failure and multiclass drug resistance for several reasons. Those who have reached adolescence are likely to have had exposure to ART to prevent perinatal HIV infection or started ART early in life, and may be heavily treatment experienced [27,28]. Subtherapeutic drug concentrations caused by limited paediatric drug formulations, variable pharmacokinetics and physiological changes may increase the risk of drug-resistant virus with subsequent virologic failure [29–31]. Many perinatally infected adolescents today would have started ART early in life in a time when triple ART regimens were unavailable [1]. Mono- or dual therapy regimens may have resulted in incomplete viral suppression and the emergence of drug-resistant virus [32–34]. In a European multicentre paediatric HIV cohort, 25% had triple-class failure after 8 years on ART [34], and in LMICs, multiclass drug resistance of up to 90% has been demonstrated in perinatally infected children and adolescents [20,27,35]. In the absence of VL testing, detection of treatment failure may be delayed and patients may be maintained on inadequate and subtherapeutic treatment, with subsequent increased risk of development of drug resistance [36]. The consequences of drug-resistant virus and treatment failure may have life-limiting consequences in children and adolescents who will require treatment for many years longer than adults.

Adolescents with recently acquired HIV infection are also at substantial risk of treatment failure and drug resistance [37,38]. HIV acquisition in adolescence is often associated with high-risk sexual behaviour including low rates of condom use, multiple concurrent partners, transgenerational and transactional sex [39]. In sub-Saharan Africa, adolescent girls have a four times higher prevalence of HIV than their male counterparts [4]. Adolescents from key populations, including men who have sex with men (MSM), transgender people, injecting drug users and commercial sex workers have a particularly high HIV prevalence [4]. Available data suggest that young MSM often have a higher risk of acquiring HIV than heterosexual young men or older MSM, with prevalence rates of between 3% and 24% reported across a diverse range of settings in 10–24 year olds [40]. The risk factors and social conditions that lead to HIV acquisition in adolescence may subsequently impact on their ability to engage in care, with the attendant risks of treatment failure [41]. Sexual risk behaviours and subsequent HIV risk in adolescents are also subject to stigmatization [39,42]. HIV-related stigma in youth correlates with factors that threaten ART adherence with an increased potential for developing drug-resistant virus [43–45]. Data from the USA reports a high prevalence of genotypic and phenotypic drug resistance in newly infected youth [37,38] and more data is emerging from LMICs on the rising
prevalence of transmitted drug resistance in newly infected adolescents and adults [46,47].

4 | THE CASE FOR VIRAL LOAD MONITORING FOR ADOLESCENTS

Viral load testing is recommended by the WHO as the gold standard for monitoring HIV treatment and failure in all patients [48]. In high-income countries, HIV VL testing is routinely used for monitoring patients on ART, whereas in resource-limited settings, clinical and immunologic (CD4 count) monitoring is largely used to diagnose treatment failure [49]. It is recognized that this approach is inadequate for treatment monitoring as clinical or immunological monitoring delays recognition of virological failure with potential accumulation of drug resistance mutations and a subsequent reduction in future treatment options [50]. It may also lead to unnecessary switching to second-line therapy in those with suspected poor adherence, for example in those whose CD4 counts have not fully reconstituted since ART initiation or in those who develop an opportunistic infection but are in fact virologically suppressed [51,52].

VL monitoring is not available in most resource-limited settings [1,27,50]. While all populations living with HIV would benefit from the scale-up of VL testing, VL roll-out could initially be targeted at certain high-risk populations especially vulnerable to virological failure such as during adolescence, a period when maintaining sustained adherence to treatment and engagement with care is particularly challenging [13,53]. Although universal VL monitoring in LMIC may not be cost-effective while costs of VL testing remain high, selecting key populations at risk of poor adherence might allow for more efficient use of resources by identifying those with an undetectable VL for whom less intensive differentiated care options are more appropriate, and highlighting those individuals who need more intensive support [54].

Adolescence is also a period of increased sexual risk taking with subsequent risk of both HIV acquisition and transmission and of unplanned pregnancy [55,56]. VL monitoring will allow those who are not virologically suppressed to be identified, thereby allowing targeted adherence interventions to reduce onward sexual and vertical transmission. Young people begin to assert more autonomous control over their decisions during adolescence [14]. Chronic illness can engender a feeling of powerlessness amongst adolescents, who may then choose to exercise control by not taking medication, or attending appointments for example [57]. Using VL testing as a definitive marker of treatment outcomes may allow for active adolescent participation in tracking self-progress.

As adolescents with perinatally acquired HIV may be heavily treatment experienced and on second or even third-line therapy, and both those with perinatally acquired HIV and newly infected adolescents may have suboptimal treatment adherence, VL testing in this age group would allow clinicians to make informed decisions about increased counselling and support for adolescents together with the need to maintain or switch therapeutic regimens. VL monitoring accompanied by appropriate regimen change will reduce the time spent on a failing regimen avoiding the selection of resistant viral mutations [58]. This is of particular importance in adolescents with perinatally acquired HIV, who often have a history of inadequate viral suppression. Even without widespread availability of genotypic resistance testing, VL monitoring would give clinicians an important decision-making tool that will impact an adolescent’s treatment options for many years.

In low- and middle-income countries where limited VL testing is available, measuring VL six months after treatment initiation gives healthcare professionals the opportunity to intervene with targeted adherence and support interventions [52,59]. Risk factors such as poor adherence, female gender, high baseline VL, and non-nucleoside reverse transcriptase inhibitor (NNRTI) based-regimes have been associated with virological failure among adolescents [27,34]. Preservation of ART regimens is important in an adolescent population who will require ART for longer than adults. Given that adolescents are at higher risk of treatment failure when compared with adults, targeting VL testing at certain adolescent subgroups at high risk of failure may increase the yield of detecting treatment failure and make regime choices more efficient.

5 | OPPORTUNITIES FOR DEVELOPING VL MONITORING FOR ADOLESCENTS

Adolescents are a mobile group, with migration linked to key transitions into adulthood, for example from rural to urban areas for employment or educational opportunities [60]. Engaging and retaining these populations in care using traditional healthcare facilities is challenging, and innovative and adolescent-responsive differentiated models of HIV care may improve outcomes across the HIV care continuum [61]. Point-of-care (POC) technology may be particularly beneficial in targeting adolescents as part of a hard-to-reach group [62]. Although cost of POC technology is currently prohibitive for widespread roll-out in low-resource settings, research and development for a semiquantitative POC VL assay is in progress [63]. Near-patient VL testing technology could be incorporated into mobile health clinics for example, which use rapid and near-patient technologies for HIV testing and CD4 count monitoring to engage hard-to-reach adolescent populations in care [62]. Flexible methods of VL testing including decentralized and near-patient VL testing with rapid availability of results will allow clinicians to make prompt decisions about treatment failure or the need for regime change, and may obviate need for repeated clinic visits thereby reducing educational, employment and social disruption. Blood obtained from a finger prick with results read from a test strip, much like a POC HIV test, would remove the need for phlebotomists or centrifugation and may be more acceptable to adolescents than venesecion [64]. One such POC VL system has received regulatory approval in Malawi, and product approval in Uganda and Kenya, but has not been validated for paediatric or adolescent use [63].

Phased implementation of VL testing would allow logistical and technical capacity-building for universal access in a context where introduction of routine VL monitoring for the general population living with HIV is not feasible. Initial implementation of VL assays in LMICs could prioritize groups such as adolescents who are at higher risk of treatment failure and constitute a smaller group compared to adults with HIV. Initiating VL testing in adolescents as a sub-section of
the population living with HIV could provide a platform for investigating the feasibility, cost-effectiveness, and acceptability of VL testing in these settings, with the potential to inform wider scale implementation.

6 | CONCLUSIONS

The impact of global ART programme scale-up has produced astounding gains in mortality, turning an inevitably fatal condition into a chronic disease requiring lifelong treatment with sustained adherence. The Global Plan for the eradication of vertical transmission of HIV has significantly reduced the number of children born with HIV. Early diagnosis and treatment has resulted in most of these children reaching adolescence. The global community set the goal of ending the HIV epidemic by 2030, with ambitious targets to get 90% of people with HIV tested, 90% of those tested on treatment and 90% of those on treatment virally suppressed. Yet in 2016, we saw almost 2 million new HIV infections, most of those in adolescents and young people. As universal ‘test-and-treat’ becomes reality, the numbers initiating ART will rise. One group who will continue to pose significant treatment challenges are adolescents either graduating from paediatric care or newly established on ART treatment who may encounter treatment fatigue with an associated risk of failure. Unlike in the early days of ART where saving lives was the primary objective, we are entering a phase where VL testing is essential in order to successfully maintain people on long-term ART to ensure the promise of universal treatment scale-up. VL testing scale-up is critical in all groups, yet, focusing on adolescents for initial operational research and scale-up will allow targeted investigation into optimum ways of integrating VL monitoring into differentiated models of care, cost-effectiveness and evaluating how this cost can be weighed against other HIV prevention and care programme priorities for this vulnerable group.

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AUTHORS’ CONTRIBUTIONS

All authors contributed to writing and review, and all approved the final version.

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COMMENTARY

HIV viral load monitoring among key populations in low- and middle-income countries: challenges and opportunities

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Abstract

Introduction: Key populations bear a disproportionate HIV burden and have substantial unmet treatment needs. Routine viral load monitoring represents the gold standard for assessing treatment response at the individual and programme levels; at the population-level, community viral load is a metric of HIV programme effectiveness and can identify “hotspots” of HIV transmission. Nevertheless, there are specific implementation and ethical challenges to effectively operationalize and meaningfully interpret viral load data at the community level among these often marginalized populations.

Discussion: Viral load monitoring enhances HIV treatment, and programme evaluation, and offers a better understanding of HIV surveillance and epidemic trends. Programmatically, viral load monitoring can provide data related to HIV service delivery coverage and quality, as well as inequities in treatment access and uptake. From a population perspective, community viral load data provides information on HIV transmission risk. Furthermore, viral load data can be used as an advocacy tool to demonstrate differences in service delivery and to promote allocation of resources to disproportionately affected key populations and communities with suboptimal health outcomes. However, in order to perform viral load monitoring for individual and programme benefit, health surveillance and advocacy purposes, careful consideration must be given to how such key population programmes are designed and implemented. For example, HIV risk factors, such as particular sex practices, sex work and drug use, are stigmatized or even criminalized in many contexts. Consequently, efforts must be taken so that routine viral load monitoring among marginalized populations does not cause inadvertent harm. Furthermore, given the challenges of reaching representative samples of key populations, significant attention to meaningful recruitment, decentralization of care and interpretation of results is needed. Finally, improving the interoperability of health systems through judicious use of biometrics or identifiers when confidentiality can be maintained is important to generate more valuable data to inform monitoring programmes.

Conclusions: Opportunities for expanded viral load monitoring could and should benefit all those affected by HIV, including key populations. The promise of the increasing routinization of viral load monitoring as a tool to advance HIV treatment equity is great and should be prioritized and appropriately implemented within key population programmatic and research agendas.

Keywords: HIV; viral load; key populations; sub-Saharan Africa; Asia; implementation; epidemiology; surveillance

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1 | INTRODUCTION

Despite a global plateauing in HIV disease burden, the decline in HIV incidence and expanded coverage of antiretroviral therapy (ART), HIV is not equally distributed across populations [1]. Given the biology of HIV and individual, network-level and structural risk determinants for infection, key populations (KP) are disproportionately at risk for HIV infection [2–5]. KP include gay men and other men who have sex with men (MSM), transgender women, sex workers, people who inject drugs (PWID) and incarcerated populations [6]. Furthermore, KP remain generally underrepresented in HIV treatment programmes [7]. There has been an increased focus on the content and implementation of HIV prevention strategies to serve KP, with the goal of achieving individual- and population-level benefits [6]. Condom provision, tailored HIV testing and counselling, and needle and syringe exchange programmes are examples of programmes that have been implemented for KP [8]. While such interventions are critical, it is increasingly clear that greater attention to the HIV treatment needs of KP living with HIV is necessary to promote equitable access to healthcare and to change the course of the epidemic [9].

Access to viral load monitoring represents one strategy that can inform the implementation of programmes to address the specific treatment needs of KP. Specifically, routine viral load monitoring can serve as a metric of optimal adherence to ART and an indicator of potential ART resistance, thereby serving as a means of gauging treatment response. From an individual perspective, knowledge of viral load is a powerful tool for focusing on personal health since attaining and maintaining an
undetectable viral load can motivate ART adherence by indic-
ing to individuals that their regimen is working. As such, viral load monitoring is among the most powerful HIV preven-
tion tools available [10].

Apart from individual-level benefits, viral load monitoring can also be a population-level HIV surveillance tool and a measure of programmatic success [11]. These opportunities warrant further exploration as they can facilitate the evaluation of the global response to HIV.

Despite these potential benefits, the path to increased viral load monitoring among KP faces challenges, including the usual barriers of cost and limited laboratory capacity in low-
resource settings, as well as logistical and ethical hurdles unique to KP which are explored below [12]. It is important to consider operational challenges and potential solutions, so that the benefits of this individual and public health intervention might be realized by those most affected by HIV.

In this paper, we explore opportunities along with associ-
ated cautions related to data interpretation and ethical imple-
mentation of viral load monitoring among marginalized KP in low- and middle-income settings. We consider the potential benefits and challenges from programmatic, population and public health advocacy perspectives. Case studies selected from our collective work in West Africa, Southern Africa and South Asia provide illustrative examples (Table 1).

2 | DISCUSSION

2.1 | Viral load monitoring as a health surveillance tool for KP

At the programmatic level, viral load monitoring can provide data regarding HIV treatment access, uptake and effectiveness. Low rates of viral suppression within geographic areas, hotspots, specific age or other subgroups may indicate a need for enhanced programmatic efforts or structural interventions [13]. For example, HIV cascade analyses can highlight where individuals fall out of the HIV treatment cascade [14–16]. Furthermore, identifying sub-
groups of individuals who are at increased risk of not achieving viral suppression and offering more intensive services or differenti-
ated care to them may help to improve health outcomes, thereby targeting resources at those who most need them.

Given the significant risks of HIV transmission among members of KP with unsuppressed viral replication, programmatic efforts should be directed at implementing services tailored to the specific needs of diverse populations of KP who generally share structural determinants of risk including marginalization, and at times, mobility [17,18]. Culturally and clinically compet-
tent services, which foster improved treatment coverage and sustained adherence are necessary to improve health out-
comes for KP [19,20]. Failure to do so can result in individuals at high risk of onward HIV transmission not accessing health-
care due to perceived or experienced stigma from non-sensi-
tized health providers [7,21]. To this point, however, most programmes have measured success based on services deliv-
ered to KP rather than on the impact or effectiveness of those services. As demonstrated through South African data, viral load offers a metric for programme effectiveness (Table 1).

From a population perspective, viral load data collected through integrated HIV biobehavioral surveys can help describe local epidemics and trends, as well as the population attributable fraction of HIV that could potentially be addressed through more effective KP programming [11,22]. Data from MSM and PWID in India suggest that the prevalence of detectable viraemia is a strong surrogate of HIV inci-
dence, and thus may be an important programme evaluation as well as HIV surveillance tool (Table 1) [23]. Similarly, assessment of community viral load may provide insights of epidemic trends in the population [23–25].

Caution must be taken, however, when using viral load data for HIV surveillance. Unsuppressed viral load can be used as a reason to blame KP for the epidemic [26], That is, there is the risk for unsuppressed viral loads to exacerbate stigma already associated with particular sexual and/or drug use practices if KP are seen as “bridge” populations potentiating transmission to the “general population”. Notably, these same HIV-related determinants are generally not only stigmatized but often criminalized, both of which undermines treatment retention and adherence and thus reinforce poor outcomes [27–30].

Additionally, selection biases, who is overrepresented and underrepresented in viral load data and how this relates to exposure to treatment, may affect understanding of epidemic trends within KP. There are multiple opportunities to reach KP with viral load monitoring, however, each approach has its own advantages and disadvantages (Table 2). For example, program-
matic data tend to oversample people engaged in the pro-
grame, which may in turn overestimate overall engagement in care and treatment compared to sampling methodologies that achieve greater sampling depth and breadth across networks [31,32]. Thus, as noted in the South African case study (Table 1), high rates of viral suppression from non-representa-
tive programme data may mask inequities amongst KP by over-
looking those who are unengaged in care and treatment.

Furthermore, longitudinal KP programme or surveillance data from low- and middle-income countries remain scarce. As observed in the Nigerian example (Table 1), those retained in services are likely very different in terms of viral suppression outcomes to those who are lost to follow-up. Although this is true in any programme, consistent marginalization and exten-
sive mobility of KP may contribute to poorer retention in care among KP, thus resulting in greater biases in viral load sup-
pression rates due to differential loss to follow-up among KP [33]. Attempts to ascertain clinical outcomes of individuals lost to follow-up from national registries or laboratory data may be limited by the inability of health monitoring and information systems to link patient data across clinics or geographic areas, particularly if, for confidentiality purposes, those initially accessing care in KP-specific programmes were tracked through unique identifiers, which are deliberately not linked to a government-issued ID nor national health records. Serial cross-sectional viral load monitoring through repeat network-based sampling methods studies, such as respondent driven sampling, or time-space sampling may be used for population-
level HIV surveillance purposes and can circumvent some of the aforementioned problems [34].

2.2 | Considerations around implementation models for KP viral load monitoring in low-resource settings

Despite the potential promise of viral load monitoring among KP in resource-limited settings, implementation
<table>
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<th>Population</th>
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<th>Methods &amp; illustration of viral load utility</th>
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<tbody>
<tr>
<td>PWID, MSM</td>
<td>India</td>
<td>• Serial cross-sectional respondent driven sampling</td>
<td>• Prevalence of viraemia is the closest correlate of HIV incidence in the community</td>
<td>• Viral suppression data is from research studies, which suggest that treatment and viral load monitoring must be provided alongside other CBO services due to gaps in linkages to referral centres</td>
<td>• Solomon et al. [23]. • Mehta et al. [14]. • McFall et al. [53].</td>
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<tr>
<td>FSW</td>
<td>South Africa</td>
<td>• Programmatic data and cross-sectional respondent driven sampling</td>
<td>• Programmatic data from the urban centre of Hillbrow demonstrate higher rates of viral suppression among FSW participating in the programme than corresponding clinic data from the broader population</td>
<td>• Programme data may mask population-level disparities in treatment initiation and viral suppression among FSW not engaged in care</td>
<td>• Program data Wits Reproductive Health Institute (Direct Correspondence, F. Venter) • University of California in San Francisco, Anova Health Institute, and WRHI [54]</td>
</tr>
<tr>
<td>MSM, FSW</td>
<td>Cameroon</td>
<td>• Implementation science and programmatic data • Community-based specimen collection</td>
<td>• Viral load monitoring can be performed through integrated, community-based programmes which collect specimens within the community</td>
<td>• Lack of point-of-care diagnostics are a challenge; blood work for viral load monitoring is sent to reference laboratory, where results often take 45–60 days to be returned</td>
<td>• CHAMP program data (Direct correspondence I. Mfochive Njindam)</td>
</tr>
<tr>
<td>Transgender FSW</td>
<td>South Africa</td>
<td>• Programmatic data • Impact of community-based programmes on viral load</td>
<td>• Clinician has taken HIV treatment and viral load monitoring services to a local NGO space in Cape Town • Laboratory results are provided individually before support meetings • No patients were previously linked to HIV treatment, many now virally suppressed</td>
<td>• Absence of point-of-care diagnostics due to small scale of services • Data sent to reference laboratory which requires patient names and sex which may not match patients’ identity</td>
<td>• Anova Health Institute’s Health4Men program data (Direct correspondence K. Rebe)</td>
</tr>
<tr>
<td>MSM</td>
<td>Nigeria</td>
<td>• Cohort study • Advocacy</td>
<td>• Viral load can be an objective marker of the impact of stigma and discriminatory policies</td>
<td>• Loss to follow-up higher among men not engaged in care, potentially leading to overestimation of viral suppression</td>
<td>• Schwartz et al. [52]. • Chauraut et al. [33].</td>
</tr>
</tbody>
</table>

PWID, people who inject drugs; MSM, men who have sex with men; CBO, community-based organisation; FSW, female sex worker; ART, antiretroviral therapy; LTFU, loss to follow-up. Case studies present work from authors or collaborators.
involves critical logistical and ethical concerns. These include where and how to reach KP in order to obtain specimens, how to return laboratory results to individuals, how to ensure treatment support, whether the frequency of viral load monitoring for populations at high risk of onward HIV transmission should follow or exceed national guidelines, how to protect anonymity and confidentiality of those engaged in activities prohibited by law, and how to safely integrate laboratory and clinical data between service delivery programmes and national health registries.

Implementation experience of viral load monitoring for KP living with HIV in Cameroon highlights some of these challenges (Table 1).

KP may be easiest to reach in community settings; however, viral loads are typically done within clinical facilities. Furthermore, KP programmes typically refer those living with HIV to standard ART clinics that may not be sensitized to providing KP-competent services, thereby resulting in substantial drops in linkage to care following HIV diagnosis [35–38]. Decentralized models which offer HIV testing, ART provision and management including viral load monitoring, STI screening and treatment, and TB treatment in a stigma-free venue would likely have better HIV service outcomes for KP [8]. These decentralized models providing care at community-based organisations (CBOs) or mobile clinics can harness the potential of point-of-care viral load diagnostics as they become available or employ dried blood spots sent to reference laboratories [39].

Increasing focus on differentiated service delivery models which adapt care to patient needs and preferences present particular opportunities for KP. For example, adherence clubs, CBO-based HIV services and mobile services could all become venues for viral load monitoring [40]. Moreover, the nature of KP-dedicated programmes could support increased focus on quality, potentially resulting in greater clinical utilization of viral load results in patient management. For instance, KP who use drugs or alcohol often experience suboptimal adherence and consequently higher treatment failure, prompting the need for more frequent viral load monitoring among these groups in order to identify treatment failure early, further preventing the development and onward transmission of resistant strains [21]. In cases where KP-specific training and services exist, the quality is often high and the potential for these programmes to effectively provide ART care is great [41].

### 2.3 Biometrics to support individual viral load monitoring among KP

Viral load monitoring implementation challenges further include those related to data sharing and individual follow-up. Given the mobile nature of KP, as individuals transition between research, KP-specific service delivery and national treatment programmes, there is a need to consider how to streamline viral load monitoring rather than reinforcing parallel, duplicate systems. In order to protect the rights of individuals who do not attend venues are not represented and may be substantively different from those that do.

### Table 2. Methods for sampling key populations (KP) for viral load monitoring

<table>
<thead>
<tr>
<th>Sampling methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key population programme service delivery</td>
<td>• KP-identifiable and viral loads returnable using programmatic resources</td>
<td>• Sample includes those engaged in services and underrepresents those not engaged in care</td>
</tr>
<tr>
<td></td>
<td>• Blood draws can be collected in the community where KP are more easily reached</td>
<td>• Data may include duplicates if biometrics are not utilized</td>
</tr>
<tr>
<td>Clinic data and national registries</td>
<td>• Data longitudinal, assuming individuals are retained in care</td>
<td>• Difficult and often impossible to identify KP through clinic data or national registries</td>
</tr>
<tr>
<td>Social network-based recruiting, such as respondent driven sampling or snowball sampling</td>
<td>• Methods can reach those not engaged in care</td>
<td>• Sample includes those engaged in services and under-represents those not engaged in care</td>
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<td></td>
<td>• Results may be generalizable to underlying population of interest</td>
<td>• Difficult to verify that individuals truly belong to KP</td>
</tr>
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<td></td>
<td>• If serial cross-sectional studies are conducted, can ascertain insight into changes over time in terms of KP viral suppression</td>
<td>• Need to account for recruitment methods, which may not be possible for subanalyses such as viral suppression due to breaks in chains since not all individuals enrolled will be living with HIV</td>
</tr>
<tr>
<td>Venue based sampling</td>
<td>• Efficient recruitment method</td>
<td>• May be difficult at certain venues to verify that individuals truly belong to KP</td>
</tr>
<tr>
<td></td>
<td>• Community-based viral load monitoring may reach those not engaged in care</td>
<td>• Individuals who do not attend venues are not represented and may be substantively different from those that do</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In the absence of point-of-care diagnostics, returning results to individuals may be challenging</td>
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<tr>
<td></td>
<td></td>
<td>• Individuals may be recruited at multiple sites, potentiating duplicate enrolments if biometrics are not utilized</td>
</tr>
</tbody>
</table>

- **Advantages**: Sampling methods Advantages
- **Disadvantages**: Sampling methods Disadvantages
particpants engaging in activities that may be illegal and for whom the use of names or national IDs may increase risks. KP programmes often use unique identifiers, such as aliases or identification numbers. These unique identifiers may be generated by the client and provider based on a set of questions only the client can answer. Furthermore, in transgender populations, sex and legal names on official identification documents may not match the patient’s gender or used name (Table 1). However, unique identifiers can complicate patient-level tracing both within programmes and between different parts of the health system.

Biometric identifiers hold the potential to overcome some of these challenges by providing a technological solution that is easy to implement and able to be secured and encrypted. However, a biometric identifier is typically indelible, which can present significant human rights concerns for KP in some contexts [42]. Ethical and human rights considerations suggest a need for close attention to security and identifying settings where biometrics may pose more risk than reward. Somewhat different considerations apply depending upon context.

First, in the healthcare delivery setting, medical records that track viral load can help ensure patients are retained in care and that both clinicians and individuals can act on viral load information – results that do not reach the patient or are not used to optimize treatment decisions provide no benefit. A unique identity signifies a unique person who warrants care and protection [43]. Here, development of a biometric identified health record used by KP and non-KP alike in the health system, integrated with KP-service delivery, provides clear benefit to individuals. However, identifying specific individuals as engaged in criminalized activities creates data that can be exploited by governments and ill-intentioned individuals to threaten the wellbeing of KP. Examples include police raids on a LGBT-friendly clinic in Uganda and the recent government mandated closing of community-based HIV organisations serving MSM in Tanzania, data breaches of electronic KP patient records, and evidence that some health workers share confidential information [44–47]. To enhance privacy, the data linked to biometrics should be limited to the minimal extent necessary for the intended purposes. In such records, there is rarely a need to identify individuals as KP. In addition, measures such as identifying clinics by numbers rather than names may help to improve confidentiality and privacy. Measures to add encryption, record biometric data like fingerprints as codes rather than as images, and boost data security are also essential [48]. Guidelines on data access should be developed that make unauthorized use legally punishable. Taking these steps and consulting with KP communities before introduction of technology is critical.

Second, research and surveillance on viral suppression among KP ideally includes measures to avoid duplicate participants, for which some have suggested biometric identifiers or KP-identifiable medical records. Sound data about a population subgroup is a first step in identifying a group-level need for care [43]. HIV surveillance alone, however, does not provide individual-level benefit and potentially exposing individuals to harm in the process is ethically unjustifiable. Constructing databases of identifiable KP presents significant human rights concerns, heightened further by the insecurity of many databases and the potential for rights violators to use them to identify members of stigmatized KP. In addition, the very act of collecting biometrics, particularly fingerprints, can instill fear in criminalized groups, which is likely to bias participation. Therefore, while in less hostile settings biometrics may be appropriate, in environments where there is significant criminalization and stigma related to particular sexual and drug use behaviours, it is advisable to continue the use of anonymizing unique identifiers for research and surveillance. This may require duplicate sample collection for personal health records that are not KP identified, but the benefits are worth the added costs.

2.4 | Viral load monitoring as an advocacy tool

Viral load data can play a pivotal role in advocacy for human rights [49]. The burden of unsuppressed viral load, coupled with the population attributable fraction estimates, can be used to demonstrate the need for services, support equitable allocation of resources, and evaluate progress toward realization of the right to health for KP [50]. Comparing viral suppression between KP and the broader population in different countries should help to identify inequities and identify focus areas for programming. This has been done on a broader scale to advocate for specific geographic areas or age groups and can similarly be applied among KP [51].

Furthermore, viral load monitoring data can be used to demonstrate the impact of policies or to advocate for an intervention. For example, in Nigeria, viral load data served as an objective metric to demonstrate the negative impact of healthcare-related stigma on HIV treatment outcomes [52]. These data were also used as an indirect measure of the effect of a discriminatory legal policy on health outcomes and thus served as an important public health advocacy tool [52].

3 | CONCLUSIONS

As routine viral load monitoring becomes the standard of care for patients living with HIV, it offers important benefits for individuals, programmes and communities. There are many opportunities for expanded use, and new technologies have the potential to be “leapfrog” advances addressing operational, structural and programmatic challenges in HIV service provision. It is essential that KP are not forgotten in innovative methods for scale-up of ART programmes nor the rollout of routine viral load monitoring. These advances must result in benefit for KP individuals and the communities most affected by HIV. An AIDS-free generation is simply impossible without the achievement of equity for KP and the communities in which they live and work. The promise of viral load monitoring as a tool to advance HIV treatment equity is great, and should be realized with all due urgency and careful implementation.

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COMPETING INTERESTS
The authors have no competing interests to declare.

AUTHORS’ CONTRIBUTIONS
All of the authors (SRS, MMK, JS, SSS, IMN, KR, TCQ, CTK, CB and SDB) contributed to the conceptualization and writing of the manuscript.

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Cost-effectiveness of routine viral load monitoring in low- and middle-income countries: a systematic review

Ruanne V Barnabas1, Paul Revill2, Nicholas Tan1 and Andrew Phillips3

Abstract

Introduction: Routine viral load monitoring for HIV-1 management of persons on antiretroviral therapy (ART) has been recommended by the World Health Organization (WHO) to identify treatment failure. However, viral load testing represents a substantial cost in resource constrained health care systems. The central challenge is whether and how viral load monitoring may be delivered such that it maximizes health gains across the population for the costs incurred. We hypothesized that key features of program design and delivery costs drive the cost-effectiveness of viral load monitoring within programs.

Methods: We conducted a systematic review of studies on the cost-effectiveness of viral load monitoring in low- and middle-income countries (LMICs). We followed the Cochrane Collaboration guidelines and the PRISMA reporting guidelines.

Results and Discussion: We identified 18 studies that evaluated the cost-effectiveness of viral load monitoring in HIV treatment programs. Overall, we identified three key factors that make it more likely for viral load monitoring to be cost-effective: 1) Use of effective, lower cost approaches to viral load monitoring (e.g. use of dried blood spots); 2) Ensuring the pathway to health improvement is established and that viral load results are acted upon; and 3) Viral load results are used to implement HIV care in patients with viral suppression (i.e. differentiated care, with fewer clinic visits and longer prescriptions). Within the context of differentiated care, viral load monitoring has the potential to double the health gains and be cost saving compared to the current standard (CD4 monitoring).

Conclusions: The cost-effectiveness of viral load monitoring critically depends on how it is delivered and the program context. Viral load monitoring as part of differentiated HIV care is likely to be cost-effective. Viral load monitoring in differentiated care programs provides evidence that reduced clinical engagement, where appropriate, is not impacting health outcomes. Introducing viral load monitoring without differentiated care is unlikely to be cost-effective in most settings and results in lost opportunity for health gains through alternative uses of limited resources. As countries scale up differentiated care programs, data on viral suppression outcomes and costs should be collected to evaluate the on-going cost-effectiveness of viral load monitoring as utilized in practice.

Keywords: HIV viral load; cost; cost-effectiveness

1  |  INTRODUCTION

Routine viral load monitoring for HIV-1 management of persons on antiretroviral therapy (ART) has been recommended by the World Health Organization (WHO) since 2013 as the preferred method to identify treatment failure [1]. In the initial WHO global HIV treatment guidelines (2003), viral load monitoring was not recommended in low- and middle-income countries (LMICs) due to the requirements for transportation of plasma specimens under controlled conditions, limited laboratory infrastructure and availability of the assay, and relatively high cost of viral load monitoring. Instead, clinical monitoring and/or CD4 count measurement were used to detect treatment failure [2]. Over the next ten years the availability of viral load testing increased, the cost of viral load assays decreased, concerns over resistance accumulation at an individual and population level grew, methods for viral load testing on dried blood spot (DBS) specimens were developed, ART guidelines changed to recommend ART for all HIV-positive persons, and the cost of first- and second-line ART decreased [3]. These changes challenged the initial recommendation not to use viral load to monitor the outcome of HIV treatment. However, viral load testing represents a substantial cost in resource constrained health care systems in LMICs.

HIV policymakers and program managers are concerned with affordability and costs because the implications of costs affect the health care they can provide from their limited available resources (i.e. costs imply lost opportunities for generating health) [4]. Cost-effectiveness analysis is a widely-applied approach to guide whether the health benefits of an intervention are large enough compared to its costs, such that its provision from within limited health care resources would
represent “value for money.” This essentially requires determining a cost-per-unit of health gained (e.g. per quality-adjusted life year (QALY)-gained; or disability-adjusted life year (DALY)-verted) from alternative ways of providing viral load monitoring in comparison to other approaches (i.e. clinical, routine CD4 monitoring) and, critically, assessing whether the estimated cost per unit of health gain represents value against a benchmark.

Several published studies have concluded that routine viral load monitoring is cost-effective in LMICs by referencing the cost per DALY to a benchmark of one to three times gross domestic product (GDP) per capita of a country [5–7]. However, given the level of resource constraints in countries, such benchmarks are now widely recognized as being inappropriate to inform value for money assessments and risk lowering population health through diverting investments away from greater priorities [8,9].

Suitable benchmarks are context-specific and can be difficult to ascertain. An emerging stream of research has shown that, for general health care, values are much lower than previously acknowledged – for example $60 to 100 in Malawi – due to high levels of unmet health needs [10,11]. However, HIV interventions remain overwhelmingly reliant on overseas aid which is specifically earmarked for this condition, and the overall level of such aid means in practice that HIV-related interventions may be cost-effective at higher values than this (e.g. $300 to $500) [12–14]. A number of papers sought to specifically assess whether viral load monitoring would improve population health compared to committing the required resources to continued scale-up of ART and have often found that it would not [15,16]. The central challenge then is whether and how viral load monitoring may be delivered such that it would justifiably constitute a component of HIV care, even in the context of the higher cost effectiveness threshold operating for HIV interventions, and does not divert resources away from other priority health care activities that could generate greater health benefits.

We conducted a review of recent studies on the cost-effectiveness of viral load monitoring in LMICs. Our hypothesis was that key assumptions about program design and costs of monitoring drive the cost-effectiveness of programs that incorporate viral load monitoring. The primary review objective was to identify characteristics of programs that make viral load testing more or less likely to be cost-effective and contribute to improvements in population health, recognizing there are other calls on limited HIV program resources.

2 | METHODS

We reviewed cost and cost-effectiveness studies of viral load testing in HIV treatment programs in LMICs and summarized the key factors that determine cost-effectiveness. We followed Cochrane Collaboration guidelines in conducting our review [17], and PRISMA guidelines in reporting results [18].

2.1 | Search strategy, selection of data, synthesis

We conducted an electronic search of the PubMed database on 14 February 2017 for studies published from 1 January 2000, onwards, using the following MeSH terms: (“viral load” MeSH Terms) OR “viral” (All Fields) AND “load” (All Fields) OR “viral load” (All Fields) AND (“economics” Subheading) OR “economics” (All Fields) OR “cost” (All Fields) OR “costs and cost analysis” (MeSH Terms) OR “costs” (All Fields) AND “cost” (All Fields) AND “analysis” (All Fields) OR “costs and cost analysis” (All Fields)). The EMBASE data base was searched using the equivalent search terms. Reference lists of papers meeting criteria were hand searched for additional articles. To ensure that we included unpublished data, abstracts were reviewed from the past meetings of the Conference on Retroviruses and Opportunistic Infections (CROI).

Abstracts and full-text articles of potentially relevant studies were reviewed independently by two authors (N.T. and R.V.B.) against pre-defined criteria. Papers were eligible for inclusion if the analysis was conducted in a LMIC setting and a cost-effectiveness result for viral load monitoring was included. Data were extracted using a standardized data extraction form. Discrepancies regarding eligibility of papers were discussed and consensus reached. The methodological quality of included studies was reviewed by N.T. and R.V.B. Discrepancies in quality rating were discussed and consensus reached. Studies were rated as low, moderate, or high risk of bias, dependent on whether they met standard guidelines for health economic evaluation reporting [19]. The study results were summarized and synthesized for discussion; a quantitative summary statistic was not estimated for the cost-effectiveness of viral load monitoring. To assess factors that increased the cost-effectiveness of viral load monitoring, we reviewed the model and program parameters that determined cost-effectiveness relative to the base case and qualitatively summarized and grouped the factors into three main themes.

3 | RESULTS

The electronic search yielded 1248 results of which 1165 were unique abstracts. We identified 23 manuscripts and four conference abstracts for review of which 18 met the search criteria and addressed the cost-effectiveness of viral load monitoring (Table 1).

The studies were conducted in a range of LMIC settings (sub-Saharan Africa, Cameroon, Uganda, South Africa, Zambia, Zimbabwe, Cote d’Ivoire, Vietnam and Thailand). Two health economic analyses were based on clinical trials conducted in Uganda and Cameroon [20,21]. The remaining analyses collated surveillance data, worked closely with programs, and reviewed the literature to obtain parameters for health economic modeling. Study outcomes were reported as the cost per DALY averted, cost per QALY gained, cost per life year gained (LYG), and/or year of life saved (LYS).

Cost-effectiveness analyses were conducted from 2004 [22] and projected out to 2035 [23]. Twelve [5,22–32] of the 18 studies found that viral load monitoring was cost-effective. Studies used different thresholds to determine cost-effectiveness combined with variation in the unit costs resulted in marked heterogeneity between the results. The unit cost of viral load testing varied in the analysis from $5.80 to $103.88 per test, and the annual cost of first line ART and second line ART varied also from $108.18 to $462.47 to $239.31 to $2071.33, respectively (2017 USD). The range in the costs for viral load assays and ART is
Table 1. Studies estimating the cost-effectiveness of viral load (VL) monitoring

<table>
<thead>
<tr>
<th>First author</th>
<th>Location</th>
<th>Year studied</th>
<th>Key features modelled</th>
<th>Authors’ conclusion on cost-effectiveness+</th>
<th>Factors that make VL testing more cost-effective</th>
<th>Incremental cost-effectiveness ratio (ICER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn [21]</td>
<td>Tororo, Uganda</td>
<td>2001 to 2002</td>
<td>Randomized trial</td>
<td>Definite no</td>
<td>VL testing was not effective in this RCT (no evidence of health benefit)</td>
<td>Clinical + CD4 + VL monitoring vs. Clinical + CD4 monitoring: $5181 per DALY averted</td>
</tr>
<tr>
<td>Schneider [31]</td>
<td>Thailand</td>
<td>2001 to 2009</td>
<td>Heterogeneity in VL Virologic failure Effect of VL on differentiation of care</td>
<td>^Qualified yes</td>
<td>Lower cost of ART</td>
<td>Annual monitoring after single screen at six months vs. Supplying only first-line ART for ten years (with ART costs): $68,084 per QALY</td>
</tr>
<tr>
<td>Bishai [22]</td>
<td>Sub-Saharan Africa</td>
<td>2004 (Cost data)</td>
<td>Heterogeneity in VL Virologic failure</td>
<td>^Qualified yes</td>
<td>Second line treatment would have to be available Cost of VL testing would have to be reduced to $14 per test to have same median ICER as CD4 testing compared to clinical monitoring</td>
<td>VL vs. CD4 monitoring (second line unavailable): $16,139 per QALY</td>
</tr>
<tr>
<td>Vijayaraghavan [32]</td>
<td>South Africa</td>
<td>2005</td>
<td>Heterogeneity in VL Virologic failure Variation switching to second line in first line failures</td>
<td>Definite yes</td>
<td>Treating patients with VLs &gt;100,000 copies/ml to reduce HIV transmission by “highly efficient transmitters”</td>
<td>Use of VL testing every six months vs. WHO guidelines: $7860 per QALY</td>
</tr>
</tbody>
</table>

Increased VL testing frequency (every three months) vs. WHO guidelines: $41,286 per QALY
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<tr>
<th>First author</th>
<th>Location</th>
<th>Year studied</th>
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<th>Incremental cost-effectiveness ratio (ICER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pham [30]</td>
<td>Vietnam</td>
<td>2005 to 2013</td>
<td>Resistance, Virologic failure</td>
<td>^Qualified yes</td>
<td>VL testing every two years and individuals with VL &gt;1000 copies/ml and detectable HIV drug resistance placed on second line ART, Lower cost of second line ART, Low cost POC-VL and resistance tests</td>
<td>WHO recommendations for VL monitoring (six months after treatment initiation and every 12 months thereafter) vs. Status quo (no VL monitoring): $5243 per DALY averted</td>
</tr>
<tr>
<td>Kimmel [27]</td>
<td>Côte d’Ivoire</td>
<td>2006</td>
<td>Heterogeneity in VL Resistance</td>
<td>^Qualified yes</td>
<td>HIV RNA test &lt;$90, Decrease in second line efficacy due to time spent on failing first line ART is greater than 1% per month, Cost of second line ART &lt; $300</td>
<td>VL monitoring (test cost = $50 to $87) vs. Cotrimoxazole prophylaxis for opportunistic infections: $1990 to 2920 per YLS</td>
</tr>
<tr>
<td>Boyer [20]</td>
<td>Cameroon</td>
<td>2006 to 2010</td>
<td>Clinical Trial</td>
<td>Qualified no</td>
<td>Lower priced generic in-house assay, Use VL assay for patients with CD4 &lt;200 cells/µl</td>
<td>Clinical monitoring vs. VL + CD4 + clinical monitoring (Abbot RealTime HIV-1 assay): $4768 per LYG, Clinical monitoring vs. VL + CD4 + clinical monitoring (Generic assay): $3339 per LYS</td>
</tr>
<tr>
<td>Bendavid [24]</td>
<td>Cape Town area</td>
<td>2007</td>
<td>Heterogeneity in VL Virologic failure</td>
<td>^Qualified yes</td>
<td>Lower price of VL testing, Possibly reduced HIV transmission (not modelled), Fewer accumulated resistance mutations (not modelled), Higher rate of virologic failure</td>
<td>VL monitoring + CD4 vs. CD4: $5414 per LYG, Every three months vs. every six months: $100,000 per LYG</td>
</tr>
<tr>
<td>First author</td>
<td>Location</td>
<td>Year studied</td>
<td>Key features modelled</td>
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<tr>
<td>Phillips [34]</td>
<td>Lower to middle income countries</td>
<td>2008</td>
<td>Heterogeneity in VL Virologic failure Resistance Variation in switching to second line in first line failures</td>
<td>Qualified no</td>
<td>Lower cost of second line ART VL &gt;500 copies/ml vs. Switch after WHO stage four event: $1500 per LYG VL &gt;10,000 copies/ml vs. Switch after WHO stage four event: $4011 per LYG</td>
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<tr>
<td>Scott Braithwaite [16]</td>
<td>Sub-Saharan Africa</td>
<td>2008 (Cost data)</td>
<td>Virologic failure Heterogeneity in VL</td>
<td>Qualified no</td>
<td>ICER for VL testing better when first and second line costs are equal Use routine virological testing when ART is already initiated at 500 cells/µl and coverage targets have been met Low cost VL testing Six monthly VL testing, switching threshold at 1000 copies/ml is the only strategy on the efficient frontier</td>
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<tr>
<td>Estill [5]</td>
<td>LMIC (Cost data can be updated for specific setting)</td>
<td>2010</td>
<td>Variation in switching to second line in first line failures Resistance Effect of VL on differentiated care Virologic failure Heterogeneity in VL</td>
<td>Qualified no</td>
<td>Routine VL monitoring cost-effectiveness depends on cost of second line ART POC VL cost-effectiveness improved if first and second line ART prices are close Targeted VL monitoring is cost-efficient only if second line costs are much higher than first line, and routine VL monitoring does not prevent failure</td>
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<td>VL monitoring vs. Clinical monitoring: $951 to $5813 per DALY averted POC-VL (every six to twenty-four months) vs. CD4 monitoring (irregular every six months, every six to twenty-four months): $426 to $33,515 per DALY averted Lab-VL (every six to twenty-four months) vs. CD4 monitoring (irregular every six months, every six to twenty-four months): $984 to $8862 per DALY averted</td>
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<td>Hamers [26]</td>
<td>South Africa</td>
<td>2011</td>
<td>Virological failure</td>
<td>Definite yes</td>
<td>Reduced accumulation of drug-resistance mutations, reduced incidence of opportunistic infections and mortality, increased economic productivity, reduced HIV transmission</td>
<td>VL-only every six months vs. Symptom-based approach: $3183 per LYG VL-only every 12 months vs. Symptom-based approach: $5319 per LYG</td>
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<tr>
<td>Estill [25]</td>
<td>LMIC (Cost data can be updated for specific setting)</td>
<td>2012</td>
<td>Heterogeneity in VL</td>
<td>^Qualified yes</td>
<td>Include reductions in HIV transmission with suppression Lower cost of second line ART and VL Risk of virological failure with monitoring strategy (reduced by VL monitoring compared to clinical/CD4 monitoring) Use POC-VL test level of detection criteria of 1000 copies/ml to reduce unnecessary switches to second line ART</td>
<td>More accurate detection of treatment failure and faster, more appropriate switching to second line: $4010 to $9230 per QALY vs. clinical monitoring and $5960 to $25,540 vs. CD4 monitoring Taking transmission into account + More accurate detection of treatment failure and faster, more appropriate switching to second line: $2450 to $5830 per QALY vs. clinical monitoring and $960 to $2500 per QALY vs. CD4 monitoring Risk of virologic failure twice as high with clinical or CD4 compared to VL monitoring + Taking transmission into account + More accurate detection of treatment failure and faster, more appropriate switching to second line: $960 to $2500 per QALY vs. clinical monitoring and cost saving $2460 per QALY vs. CD4 monitoring</td>
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<td>First author</td>
<td>Location</td>
<td>Year studied</td>
<td>Key features modelled</td>
<td>Authors’ conclusion on cost-effectiveness</td>
<td>Factors that make VL testing more cost-effective</td>
<td>Incremental cost-effectiveness ratio (ICER)</td>
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<td>Keebler [15]</td>
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<td>Presents results from three different models</td>
<td>Qualified no</td>
<td>VL monitoring after high ART coverage is achieved</td>
<td>VL every 12 months vs. VL every 36 months: Braithwaite (20 years): $6018.83 per DALY averted</td>
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<td>Heterogeneity in VL</td>
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<td>Lower second line ART cost</td>
<td>HIV Synthesis (15 years): $3413.8 per DALY averted</td>
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<td>Resistance – HIV Synthesis model (Phillips), Braithwaite and colleagues</td>
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<td>Lower test costs</td>
<td>Estill (five years): $3760 per DALY averted</td>
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<td>Variation in switching to second line in first line failures</td>
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<td>Targeted VL strategy</td>
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<td>Virological failure</td>
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<td>Effect of VL on differentiated care</td>
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<td>Negoescu [28]</td>
<td>Uganda</td>
<td>2013</td>
<td>Virologic failure</td>
<td>^Qualified yes</td>
<td>Client centered and tailored to country GDP: Adjusting VL monitoring intervals of HIV patients on ART according to individual patient characteristics, disease dynamics, behavior, and GDP.</td>
<td>Adaptive VL optimized to 1 x GDP threshold vs. monitoring every 24 months: $491 per QALY</td>
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<td>Effect of VL on differentiated care</td>
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<td>Implementation in high resource settings</td>
<td>Adaptive VL optimized to 3 x GDP threshold vs. adaptive VL optimized to 1 x GDP threshold: $1311 per QALY</td>
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<td>Heterogeneity in VL</td>
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<td>Ouattarra [29]</td>
<td>Côte d'Ivoire</td>
<td>2013 to 2017</td>
<td>Virologic failure</td>
<td>Definite yes</td>
<td>Adaptive VL ICER &lt;1 x GDP if second line ART and VL costs decreased to $156 and $13</td>
<td>Adaptive VL vs. VL confirmation: $4100/YLS (2013 USD)</td>
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<td>Effect of VL on differentiated care</td>
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<td>Sensitive to initial CD4 count of cohort</td>
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<td>Heterogeneity in VL</td>
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<td>Lower HIV transmission rate due to monitoring (not modeled)</td>
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<td>Factors that make VL testing more cost-effective</td>
<td>Incremental cost-effectiveness ratio (ICER)</td>
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<td>Phillips [35]</td>
<td>Zimbabwe</td>
<td>2015 to 2025</td>
<td>Paper was primarily focused on whether use of drug resistance testing was likely to be cost effective as part of ART monitoring strategy. Variation in switching to second line in first line failures. Virologic failure. Resistance. Heterogeneity in VL. Effect of VL on differentiated care.</td>
<td>Qualified no</td>
<td>Most effective strategy for DALYs averted was VL monitoring without confirmation.</td>
<td>VL monitoring with no confirmation vs. no monitoring, no second line: $2113 per DALY averted.</td>
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<tr>
<td>Phillips [23]</td>
<td>Zimbabwe</td>
<td>2015 to 2035</td>
<td>Variation in switching to second line in first line failures. Virologic failure. Resistance. Heterogeneity in VL. Effect of VL on differentiated care.</td>
<td>^Qualified yes</td>
<td>With $22 viral-load test cost, annual savings of $30 needed to make program cost-effective. Reducing visits from every one to three months to every six months or every nine to twelve months should enable these savings. Reduction in non-ART program costs. Use VL monitoring less frequently than every 12 months (caveat: health risks with such infrequent VL monitoring not well understood).</td>
<td>DBS VL monitoring every 12 months vs. No monitoring: $326 per DALY averted (if used to differentiate care and reduce clinic visit costs).</td>
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</table>

^Qualified yes – the authors’ overall conclusion was that viral load monitoring was cost effective, but that this was conditional on the existence of certain conditions. +The author’s conclusions on cost effectiveness depend on the choice of cost effectiveness threshold – the appropriate threshold is now recognised as being lower than had previously been supposed, particularly when using the 1× or 3× GDP criteria. ART, antiretroviral therapy; DALY, disability-adjusted life years; GDP, gross domestic product; LYG, years of life gained; LYS, life years saved; QALY, quality-adjusted life years; VL, viral load; YLG, years of life gained; WHO, World Health Organization; LMIC, low- and middle-income countries.
due to agreements with manufacturers, volume of demand, advocacy, human resource costs, and calendar time of the study (with costs generally falling over time). Studies that did not include the transmission benefits of viral suppression may have underestimated the cost-effectiveness of viral load monitoring [27,29]. Neither clinical trial found a beneficial health impact of viral load monitoring on clinical outcomes [20,21], thus the change in costs was not balanced by an improvement in the health outcomes with the intervention. The clinical trials were conducted prior to lower cost viral load testing and ART recommended for all HIV-positive persons.

## 4 | DISCUSSION

We found three main factors that make it more likely for viral load monitoring to be cost-effective (Table 2): 1) Use of effective, lower cost approaches to viral load monitoring; 2) Ensuring the pathway to health improvement is established and that viral load results are acted upon; and 3) Simplifying HIV care and including viral load monitoring to facilitate differentiated care.

### 4.1 Effective, low-cost approaches to viral load monitoring

Several factors can ensure the cost of viral load testing and the fully loaded cost (all the costs of conducting a test) is as low as possible: choosing an efficient specimen for measuring viral load such as DBS, using an assay and threshold that strikes the right balance between the risks of missing detectable viral load and switching unnecessarily, and limiting the frequency of viral load monitoring [16,22–25,27,29–31]. In 2014, Roche introduced a ceiling price for PCR laboratory based viral load testing of $9.40 (and a fully loaded cost of $20) which, at a quarter of the

<table>
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<th>Characteristic</th>
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<td>1 Low average unit costs:</td>
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<tr>
<td>a VL assays,</td>
<td>Effective, low cost approaches to VL monitoring</td>
<td>[16,22–25,27,29–31]</td>
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<tr>
<td>b Other factors contributing to fully loaded costs for VL monitoring (e.g. personnel, transport, facility costs etc.),</td>
<td></td>
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<tr>
<td>c Dried blood spots (DBS) replacing plasma specimens</td>
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<td>d Second line ART</td>
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<td>1.2 Less frequent VL testing</td>
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<tr>
<td>2 Action based on VL results</td>
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<tr>
<td>3 VL informed differentiated care</td>
<td></td>
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<tr>
<td>2 Pathway to impact: Action based on VL results</td>
<td></td>
<td></td>
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<tr>
<td>3 Differentiated care for HIV</td>
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ART, antiretroviral therapy.
previous cost, has increased the cost-effectiveness of viral load testing [29]. Lastly, point-of-care viral load testing could well be more cost-effective if the real-time response to the results which such testing enables improves clinical care.

In addition to the costs of viral load testing itself, analyses have shown that downstream costs (in particular second line ART) notably affect the cost-effectiveness of viral load monitoring. Although costs of protease inhibitor based regimens have fallen markedly in recent years (from $600 to $205 per patient year in 2016 [40]), these are still very high for low resource health care systems – limiting the potential for viral load monitoring to be cost effective. The incremental cost-effectiveness ratio (ICER) of viral load testing changed from $4100 to $1500/year of life saved when considering a range of lower viral load testing and ART costs in Cote d’Ivoire [29].

Similarly, cost-effectiveness analyses that account for the decrease in transmission benefits with ART better estimate the full health gains compared to analyses only looking at individual benefits and cost.

4.2 Pathways to impact: action based on viral load results

There are inevitably challenges in implementing and acting upon viral load testing and these need to be considered in assessing cost-effectiveness. Specimens need to be transported in an efficient manner to accredited laboratories, results relayed to clinicians and clients, and the results acted upon promptly with adequate access to second line ART. Most analyses that find viral load monitoring to be cost-effective assume that the viral load results are acted on in a timely manner (either immediately or less than six months). Protocols that delineate the next steps for a client on ART with a detectable viral load for example adherence counseling, viral load retesting three months after adherence counseling, resistance testing (where available) if viral load is still detectable despite adherence, and switching to second line ART in a timely manner, increase clinical effectiveness and decrease the emergence and transmission of resistance mutations. Some clients may require more regular visits and monitoring for complex disease or comorbidities. Notably, even with viral load monitoring, switching to second line ART generally does not occur within the timeframe assumed by most mathematical models of HIV and the proportion of people who are on second line regimens is generally below 5% [23]. Phillips and colleagues estimated that even avoiding a three-month delay through point-of-care testing, could increase health benefits by 6% with no additional costs. Also, both randomized studies of the cost-effectiveness of viral load testing found viral load testing not to be cost-effective for monitoring [20,21], a note of caution that implementation must emulate the modelled scenarios to meet the cost-effectiveness thresholds. The cost-effectiveness of viral load monitoring hinges on adequate services to deliver clinical benefits.

4.3 Differentiated care for HIV

Differentiated care for HIV allows simplifying of protocols for persons well controlled on ART, with client responsive viral load testing (six months after initiation and then annually unless clinically indicated) providing feedback to inform ongoing individual and program effectiveness. This also supports viral load monitoring replacing CD4 count monitoring, spacing appointments, providing longer prescription refills, task shifting, community-based ART, testing using DBS specimens to simplify specimen transport, and using clinical care resources for complex clinical cases and clients who are not suppressed on ART. In this differentiated care context, viral load monitoring enables greater comfort with less clinical engagement. The cost of viral load testing can be offset by savings in the clinical visit costs. Thus, differentiated care with viral load monitoring can save costs with greater health gains compared to standard of care clinic management (for a simulated model population of Zimbabwe over 20 years, viral load monitoring and differentiated care had a cost saving of $139 million and 580,000 DALYs compared to CD4 monitoring, which represents a doubling of the health gain at more than a third less of the cost [23]). It is notable that the distinction between standard of care clinic HIV management and differentiated care is blurring as some, but not all, aspects of differentiated care are incorporated into clinic care such as chronic medication refills without clinic visits available for clients on ART in South Africa. Importantly, for differentiated care, viral load monitoring provides program level evidence on whether reduced clinical engagement impacts individual and public health outcomes.

Cost-effectiveness studies aim to inform the allocation of limited resources. This requires estimating the incremental costs of alternative interventions (e.g. viral load vs. CD4 vs. clinic-only monitoring) and the incremental health benefits (e.g. QALYs-gained or disability adjusted life years (DALYs)-averted); then assessing whether the cost-per-unit of health improvement represents sufficient value, compared to other claims on limited resources. These can all change depending upon how and where viral load monitoring is delivered, so any universal claims to cost-effectiveness are misguided and it is vital to understand the place of viral load monitoring within HIV programs and how it may facilitate design of programs to improve population health from within the resources available.

The results table (Table 1) illustrates that the ICER needs to be interpreted within the context of the analysis. First, the ICERs per QALY gained or DALY averted, even though each measure is in the same units, are not directly comparable unless the same strategies are compared, that is whether viral load testing is compared with clinical staging and/or CD4 count and underlying programmatic assumptions (indicated in the ICER column). Second, the threshold for what is considered cost-effective does vary as is illustrated in the interpretation of the results (conclusion column) which reflects the perspective and setting of the analysis.

4.4 Looking ahead: likely future programmatic changes that impact viral load cost-effectiveness

Lastly, notable programmatic changes are likely to impact cost-effectiveness of viral load testing, specifically changing to ART regimens with a high barrier to resistance [27] such as integrase inhibitors. The integrase inhibitor, dolutegravir, for example, has a higher barrier to resistance than current first line efavirenz based regimens, which could decrease the clinical benefits of viral load monitoring since resistance is encountered less frequently. The combination of ART formulations
and monitoring strategy should offer the greatest health gains for the cost. With alternative monitoring tests, for example detecting TDF/TAF in urine, viral load monitoring might only be required for clients without detectable TDF/TAF or other clinical concerns. As new regimens and models for care are rolled out, the cost-effectiveness of viral load monitoring will need to be reassessed on a continual basis.

5 | CONCLUSIONS

The cost-effectiveness of viral load monitoring is critically dependent on context. Viral load monitoring in differentiated care programs provides evidence that reduced clinical engagement, where appropriate, is not impacting health outcomes [23]. To achieve this goal of cost effective viral load monitoring, differentiated care programs will need to be scaled up to achieve the gains of cost saving – introducing viral load monitoring without differentiated care can result in lost opportunity for health gains through an alternative use of resources. As countries scale up differentiated care programs, data on viral load outcomes and cost are essential to evaluate the on-going cost-effectiveness of viral load monitoring in practice. Efforts to standardize this reporting and rapid analysis would facilitate the adoption of successful differentiated care strategies.

AUTHORS’ AFFILIATIONS

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COMPETING INTERESTS

The authors have no competing interests.

AUTHORS’ CONTRIBUTIONS

RVB, PR, and AP oversaw the review. RVB wrote the first draft of the paper, which was revised by all authors. NT did the electronic searches and reviewed the abstracts, with guidance from RVB. All authors contributed to design and execution of the review, as well as to the interpretation of findings. All the authors approved the final version of the paper for submission.

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Disclaimer: The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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