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Expansion of Viral Load Testing and the Potential Impact on Human Immunodeficiency Virus Drug Resistance

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Abstract

Increasing the volume, strengthening the quality, and proactively using data of human immunodeficiency virus (HIV) load testing are pivotal to limiting the threat of HIV drug resistance (HIVDR) accumulation, and allow for optimal case-based HIVDR surveillance. Triangulation of viral load (VL) and HIVDR testing data could be pursued to answer key questions and translate data and results for program and public policy. Identification of virologic failure and early management mitigates the greater risk of HIVDR. Routine VL monitoring and evaluation systems are necessary, and countries should consider reviewing system requirements, structural needs, and procedural and technical factors for the entire VL cascade, with special emphasis on post-test result use.

Keywords

viral load; virologic failure; human immunodeficiency virus (HIV) drug resistance

Through adoption of a public health approach, access to antiretroviral therapy (ART) in resource-constrained settings (RCSs) has dramatically improved, with 19.5 million people living with HIV receiving ART globally in 2016 [1], an increase from 7.5 million in 2010 [2]. Key enablers of successful expansion have been the use of standardized nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based ART regimens [3] and limited laboratory monitoring of the ART response. Programs in RCSs have traditionally relied on either CD4 counts (immunologic criteria) or clinical criteria to determine patient response to ART, both of which are recognized as poorly predictive of ART failure [4, 5]. This evidence prompted the 2013 World Health Organization (WHO) guidelines to recommend routine viral load monitoring (VLM) for detection of treatment failure in patients on ART in RCSs [6].

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The limited use of VLM and subsequent continued exposure to failing ART and prolonged viremia may lead to an accumulation of drug resistance mutations (DRMs) and higher rates of immunosuppression and mortality [3, 7–9]. Additional negative consequences of virologic failure (VF) include the higher probability of transmission and potential transmission of resistant viruses with subsequent limited efficacy of first-line ART [10]. Timely detection of treatment failure is critical to individual clinical outcomes, preservation of second-line treatment options, and lower rates of mortality [8, 9]. Efforts to expand viral load (VL) testing to allow for routine and not targeted VLM are underway, facilitated by recent technological advances that allow simplification and decentralization of specimen transport and processing, such as the use of dried blood spots (DBSs) for VL quantification [11, 12].

Although DBS use expands access to VL testing, it does not reliably quantify viremia at <1000 copies/mL. Viral load studies from high-income countries have shown that patients with low-level viremia (LLV, commonly defined as VL between 50 and 1000 copies/mL) [13] harbor DRMs that confer resistance to the current ART regimen, which ultimately leads to treatment failure and decreases future therapeutic options [14–16]. There are limited data on the prevalence of LLV in RCSs [17]. A study of 1 cohort from South Africa found LLV in 12% of patients per year, where 27% of patients with LLV accounted for 39% of VF [18]. Given the potential for increased risk for VF of first-line ART in the setting of higher VL and longer duration of LLV, whether VF thresholds should be lowered in patients on ART in resource-limited settings is yet to be determined.

Expansion of VL testing in RCSs has the potential for major impact on both the emergence and monitoring of human immunodeficiency virus (HIV) drug resistance (HIVDR), an issue of particular concern in RCSs given the widespread use NNRTIs, which have a low genetic barrier to resistance [3]. Other factors contributing to the selection and transmission of HIVDR include treatment interruptions secondary to poor adherence, interruption of ARV commodities supply, drug–drug interactions, and delayed switching to second-line ART in the setting of VF [19]. Viral load suppression (VLS) confirmation may prevent DRM development and trigger enhanced adherence counseling and subsequent switch to a second-line protease inhibitor–based regimen [20, 21].

In RCSs, the efficacy of national HIV treatment programs can be compromised by the emergence and spread of HIVDR [22]. Models have revealed significant impact of HIVDR on estimated AIDS deaths, HIV incidence, and ART program costs [10]. Pretreatment HIVDR (PDR), even at relatively low levels, has been linked with additional burden of new AIDS deaths and additional costs [23]. Assessment of patient-level HIVDR through individual genotypes is not feasible in RCS due to high cost, low throughput, and lack of adequate laboratory infrastructure; therefore, HIVDR monitoring in these settings has relied on national-level surveillance. Countries have been encouraged to develop coordinated and resourced national strategies to prevent, monitor, and respond to HIVDR [24]. Cross-sectional acquired drug resistance (ADR) surveillance surveys have been proxies for national viral suppression and have highlighted the high rates of ADR in people failing first-line ART, high rates of VF and ADR in children and pregnant women on ART, and increasing rates of PDR in some countries with more mature ART programs [25].

AVAILABLE DATA TO MEASURE THE STATE OF VIRAL LOAD MONITORING EXPANSION

With expansion of VLM, routine programmatic data may serve as another source for estimating national and program-specific VLS. Several key stakeholders in the HIV/AIDS response have developed indicators to track VLS among persons living with HIV (PLHIV) on ART using VL tests conducted for clinical monitoring. However, in RCSs where routine VLM testing expansion is underway, the analysis, utilization, and generalizability of the data may be limited due to variability in national VL testing guidelines, VL testing coverage, data collection, patient tracking systems, and frequency of reporting.

Review of VL indicators from the President's Emergency Plan for AIDS Relief (PEPFAR) and WHO highlight some key differences [26–28]. WHO has tackled some of the challenges in generalizing VLS by creating an individual indicator for VL coverage (VLS.2) among PLHIV newly initiated on ART and another indicator (VLS.4) to assess VL coverage among all PLHIV on ART. Alternatively, PEPFAR has developed an indicator (TX_PVLS) that determines VLS among all PLHIV on ART receiving VL testing, tracks scale-up of routine VLM, and may serve as a proxy for programmatic VL coverage when compared with a PEPFAR treatment coverage indicator (all PLHIV on ART). Both organizations primarily rely on patient records or ART registers as data sources, with laboratory data as an alternative source. Viral load testing data from laboratory information management systems can be extracted and deduplicated to account for multiple tests for a subset of patients. Application of this method has had variable success [29]. This process is also hampered by poor data quality and by the absence of electronic medical records (EMRs) or unique patient identifiers.

Challenges with collecting and interpreting VL data reported by countries include variable capture and accuracy of demographic and other key variables in the VL requisition form and limited and nonstandardized capture of VL test dates and results in clinic records in systems that are not electronically searchable. Even with novel adjustments in data collection, the challenges of interpreting and extrapolating findings to PLHIV on ART remain. To estimate VL coverage using routine programmatic data, other data elements are required (eg, number of patients eligible for and receiving VL testing). To account for the impact of variable VL testing guidelines, the PEPFAR indicator defines patients eligible for VL testing as those on ART for at least 6 months. The WHO cross-sectional VL indicator (VLS.4) does not account for the proportion of all PLHIV on ART eligible for VL testing. Although indicators from both organizations assume that VL test results recorded in the patient chart or EMR are proxies for VL tests performed, this may not be the case.

In 2015, the South African National Health Laboratory Services (NHLS) and others estimated VL coverage and suppression by deduplicating laboratory test data [29]. They demonstrated a significant difference between estimates of VL coverage using the national patient EMR (*Tier.net*) versus the NHLS deduplication algorithm (46% vs 75%) and striking variability in rates of VLS by age, sex, and geography—20% of individuals aged 15–24 years had VL >10 000 copies/mL; in 3 provinces, VLS was ≤75%; and in 200 clinics among

patients receiving a VL test, VLS was <50%. Findings from the NHLS deduplicated dataset emphasize the need for integrated data health systems that allow for subpopulation analyses.

HARNESSING THE DATA

In recently completed population-based HIV impact assessments in Zambia, Zimbabwe, and Malawi, the prevalence of VLS in adult PLHIV who self-reported ART use (adults aged 15–64 years) was 89.2%, 86.5%, and 90.8%, respectively [30]. These countries are making great strides toward achieving the UNAIDS 90-90-90 targets. In these 3 countries, female and older adult PLHIV had higher rates of VLS than male and younger adult PLHIV. Younger adult males (aged 15–24 years) had the lowest VLS according to these national surveys, which provide critical information about potential for drug-resistance development and public health impact.

Countries like South Africa and Mozambique have demonstrated the utility in both developing data systems and triangulating data from multiple sources to perform meaningful data analyses [29, 31]. Other studies have demonstrated the potential of mathematical models and algorithms applied to EMRs to optimize patient management [32].

CALL TO ACTION

Viral load and HIVDR are closely intertwined; increased VL testing and strengthening the quality and use of VL data can play a pivotal role in both decreasing emergence of HIVDR and allowing for more optimal HIVDR surveillance in the future (eg, case-based). Higher rates of VF serve as signals that may impact HIVDR and need to be identified and managed early to mitigate the risk. The expansion of routine VLM and strengthening of VLM and evaluation systems offer a strategic opportunity for countries to review the system requirements, structural needs, and procedural and technical factors for the entire VL cascade, with special emphasis on post-test result utilization. Overcoming limitations to VL expansion across the entire system (such as sample-processing backlogs; fragile systems for an effective and sustainable VL cascade; limited patient and provider demand; and lack of telecommunication infrastructure, standard procedures for returning VL results to clinical record systems, and proper interpretation, quality assurance, and data use) is crucial. Site-level clinical mentoring, supportive supervision, and identification of ART program factors that be adjusted to minimize the emergence of VF and HIVDR and optimize treatment outcomes are essential and should be pursued concomitantly with HIVDR surveillance efforts.

To maximize utility of VL as a monitoring tool, preserve treatment options, and limit the threat of widespread HIVDR, scaling up routine VLM requires collaboration between stakeholders. The clinical, laboratory, and strategic information stakeholders should be convened to routinely review their current VL data collection systems (eg, forms, registers, lab information systems, EMR, patient databases), agree on VL data priorities, and develop a way forward for monitoring systems to routinely provide disaggregated VLS program data. Despite current limitations of available VL data, efforts to strengthen the collection, analysis, and utilization of data to inform and improve the quality of HIV services and

patient outcomes are crucial. Ongoing VL and HIVDR data triangulation efforts may answer key program questions and translate data and results for program and public policy. Collectively improving our VL and HIVDR intelligence is more critical than ever.

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