Curr Trop Med Rep (2017) 4:1–5
DOI 10.1007/s40475-017-0098-2

Optimizing Treatment Monitoring in Resource Limited Settings in the Era of Routine Viral Load Monitoring

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Published online: 16 February 2017
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Abstract
Purpose of review Routine viral load monitoring (VLM) for patients on antiretroviral treatment (ART) is being scaled up in resource limited settings.
Recent findings VLM potentially has several roles in improving HIV care and includes identifying patients with treatment failure and in need of second-line ART. VLM can also be used as a tool to improve adherence to ART, with 60% of the patients with detectable viral load achieving suppression following ART adherence counseling. VLM may play a role in optimizing differentiated care strategies, by identifying patients who need more close follow-up and adherence support and those who need minimal support. Finally, by ensuring that patients achieve viral suppression, VLM plays an important role in prevention of transmission to partners and infants.
Summary Early reports indicate that acting on viral load results to facilitate timely switching is still an ongoing challenge with delayed switches still being common.

Keywords Viral load monitoring · Coverage · HIV care · Treatment failure · HIV prevention

This article is part of the Topical Collection on *HIV in the Tropical Setting*

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Introduction

Access to antiretroviral treatment (ART) for HIV-infected individuals has rapidly expanded in low- and middle-income countries (LMICs) since the inception of free public-sector ART initiatives in 2002. There are currently more than 17 million people receiving ART globally, 12 million of whom live in sub-Saharan Africa, which is the most affected reason [1]. In order for HIV treatment to be effective in restoring immune functionality by increasing CD4 T cell count and in reducing HIV-associated mortality and morbidity [2], ART should control viral replication, and ultimately, patients should achieve viral suppression.

Therefore, periodic viral load (VL) testing is considered the gold standard approach for ART monitoring in HIV-positive patients and in countries where VL testing is available; prospective VL test, along with CD4 count measurements, has been used to monitor the effectiveness of ART [3]. Patients with HIV VL measurements above the levels of detection should be counseled for treatment adherence and, if viremia is persistent, should be switched to an effective second-line ART regimen.

However, in LMICs, due to cost and complexity of laboratory assays, viral load monitoring (VLM) has not been historically recommended by WHO; in contrast, the guidelines [4] proposed the following immunological criteria for diagnosing ART failure: (1) patients with a persistent CD4+ <100 cell/μl after 1 year on ART; (2) patients with 50% count fall from the peak CD4+ count while on ART; (3) CD4+ cell/μl less or equal than baseline—all without a concomitant infection to cause transient CD4+ count decrease. However, multiple observational studies from sub-Saharan Africa have demonstrated that immunological criteria to identify confirmed

viral treatment failure have low sensitivity, which can lead to a delay in identifying viral failure and in the accumulation of genotypic resistance mutations [5)], and low specificity, which could result in switching unnecessarily patients with undetectable VL to second-line treatment, resulting in unnecessary program costs [6–13]. Additional benefits of VLM include the opportunity of objectively measuring adherence and identifying patients in need of ART adherence support counseling [14].

Starting in 2006, the WHO guidelines have gradually shifted by suggesting the use of VLM in tertiary health care centers [15], subsequently using a scale-up approach [16], and finally, VLM has been recommended by the 2013 WHO guidelines as the preferred tool to monitor patients on ART [17]. Additionally, in 2014, UNAIDS launched the "90-90-90" targets, which are (1) to increase to 90% of the number of individuals infected with HIV aware of their serostatus; (2) to link and start on ART 90% of the individuals who were tested positive for HIV infection; (3) to achieve viral suppression, defined as viral load below the detection threshold, in 90% of the patients started on ART [18].

In this paper, we review the recent literature in the implementation of viral load monitoring in RLS, the current practices in the use of viral load testing, and future technologies and potential roles of viral load monitoring.

Access to Viral Load Testing

Results from a survey conducted in 122 LMICs by WHO in 2012/2013 revealed that only 20% of ART patients receives VL testing [19]. While in the majority of the LMICs VLM, either targeted or prospective, is recommended by the national guidelines, in practice, it is not performed because of limited availability [20]. With the support of CDC and other US government agencies and as part of the President's Emergency Plan for AIDS Relief (PEPFAR), seven countries in Sub-Saharan Africa (Côte d'Ivoire, Kenya, Malawi, Namibia, South Africa, Tanzania, and Uganda) updated the national guidelines in line with those of WHO and started systematically to scale-up VL testing as a national monitoring strategy for patients on ART [21].

The coverage reported in year 2015 widely varied from 3% (Côte d'Ivoire) to 95% (Botswana); overall, the majority (6/7) of the countries did not achieve the targets set by the individual governments [21]. While the level of coverage highly depended on the level of pre-implementation coverage, other factors contributed to the low slow implementation of VLM, such as lack of an operational budget, human resource constraints, lack of knowledge and training, and difficulty in transporting samples. Lack of knowledge and training, resulting in providers not requesting for VL testing, has also been identified as an obstacle in scaling up VLM [21].

The Role of Viral Load Monitoring in Improving HIV Care

Monitoring to Identify Treatment Failure

Currently, the WHO guidelines recommend that periodic VL testing should be used to monitor all patients on ART with VL tests performed every 6–12 months [17]. Treatment failure is defined by WHO as 2 consecutive VL measurements greater than 1000 copies/ml if the measurement is performed on blood or plasma and 3000–5000 if performed on dried blood spots (DBS), due to suboptimal sensitivity of DBS at lower thresholds. According to the suggested algorithm, any patients with a first VL measurement >1000 copies/ml should (1) be evaluated and counseled for ART adherence concerns, (2) repeat VL test after 3–6 months, and (3) switched if VL is persistently >1000 copies/ml [17].

In order for VLM to improve outcomes of patients on ART, it is crucial that an intervention or action is taken for those patients with VL measures above the recommended threshold, namely, if patients present with a first VL >1000 copies, they should receive adherence counseling, and patients with confirmed viral failure (2 consecutive measurements >1000 copies/ml) should be switched to second-line ART.

As previously mentioned, the UNAIDS has set diagnostic and treatment goals to be achieved by 2020, known as the 90-90-90 targets; however, early evaluations of the impact of routine VLM suggest leakages [22•] [23] along the WHO-suggested algorithm, compromising the target of achieving viral suppression in 90% of the patients on ART. Between 14 and 27% of the patients with a first VL >1000/ml did not receive adherence counseling, while 28–30% did not have a repeated VL test; in a survey conducted in Swaziland, only 14% of the patients with confirmed viral failure were switched to second-line ART [22•]. These evaluations clearly demonstrate that the benefits of the scale-up of VLM could be jeopardized by practices not complying with the guidelines. While reasons for this still need to be accurately explored, it is likely that the same factors contributing to low coverage, such as financial and human resource constrains, lack of training, and difficulties in distributing laboratory results, are as well influencing the suboptimal management of viral load results [21].

In patients with persistent viremia who are not switched to second line, there is an increase in mutations of both nucleoside and non-nucleoside reverse transcriptase inhibitor drugs (NRTI and NNRTI) used in combination as first-line treatment overtime [24, 25]. Given the limited choice of drugs for second-line treatment and to the lack of resistance testing to guide switch to an effective treatment in most settings, the

accumulation of resistance may compromise the efficacy of second-line regimens and therefore clinical outcomes [26]. Additionally, delays in switching to an effective regimen may negatively impact patient outcomes, particularly morbidity and mortality. In resource limited settings, few studies have been conducted in this area in patients with confirmed viral failure. Earlier work suggests an increased morbidity in patients meeting the immunologic WHO criteria for treatment failure, with patients not promptly switched to second-line treatment having a twice the risk of experiencing opportunistic infections compared to patients switched to second line within 3 months [27]. In a large multisite analysis conducted across Sub Saharan Africa where a large proportion of patients were monitored using routine VLM, the cumulative mortality of patients remaining on a failing first-line treatment was three times higher as compared to patients switched to second-line treatment (11.7 versus 4.2%) [28]. Of note, the cumulative mortality of patients switched was still double the mortality of those on a non-failing first-line regimen; hence, the importance of reinforcing adherence while on first line to ensure long durability of first-line ART. Similarly, rates of being lost to follow-up in patients on failing first line were three times higher as compared to patients promptly switched to second-line therapy (14.4 versus 4.9 per 100 person-years) [28].

Viral Load Monitoring to Improve Adherence

Expanded access to VLM in LMIC represents an important tool for clinicians to identify adherence problems earlier and to intervene with the goal to achieving viral re-suppression. Data from South Africa and Uganda suggest that the majority of patients who have a detectable VL in the first 6 months of treatment will re-suppress after adherence counseling interventions. Early evidence from Khayelitsha, South Africa, suggests that at least 60% of patients who had a detectable VL (>400 copies/ml) at 6 months would re-suppress at 12 months after an adherence counseling intervention [29]. Data from a larger study of 1841 patients in Uganda, with access to early VLM and an enhanced adherence session for those with detectable VL at 6 months, suggest that 60% would achieve VL suppression at 12 months and remained suppressed up to a median follow-up time of 60 months [30]. This evidence supports the use of early VL monitoring as a strategy to improve adherence to ART and ultimately preserves efficacy of low-cost first-line regimens in LMIC. Clients started on ART during the first years of PEPFAR are now entering their second decade on treatment with many still on first-line regimens: VLM is becoming even more important to identify adherence challenges as the potential for treatment fatigue grows. As countries continue to scale-up VLM, timely reporting of results to clinicians and appropriate adherence interventions targeted to patients with non-suppressed VL will be important components of treatment success.

Point of care (POC) technologies have the potential to revolutionize treatment monitoring strategies in areas where laboratory access is limited due to cost or geographic location. By moving these technologies closer to the patient, POC VLM would allow clinicians to immediately identify and act on adherence challenges at the same patient visit, reducing the risk of prolonged treatment failure among clients needing second-line therapy and potentially limiting the accumulation of drug resistance. POC technologies overcome many of the logistical challenges faced by centralized laboratory services including transport of specimens and delayed return of results. Although the POC subject is beyond the scope of this paper, several POC technologies are in various stages of development and may prove to be of enormous benefit to both patients and providers.

Monitoring Frequency, the Role of CD4, and the Use of VL to Facilitate Differentiated Care

The optimal frequency of VLM has not been well studied in RLS and at present is often guided by international guidelines and resource availability. Most countries are following the current WHO guidelines which suggest performing an early VL within at least 6 months of ART initiation followed by a second VL at 12 months and then monitoring annually if virologically suppressed [17]. Routine CD4 monitoring at least every 6 months until recently has been the recommended standard of care in RLS; however, several recent studies have questioned the value of routine CD4 monitoring among clients on ART who have achieved viral suppression [31–33]. This has led to a modification in the WHO guidelines to consider stopping routine CD4 monitoring among clients on established ART defined as virologically suppressed (VL <1000 copies/ml), on ART for at least a year, and with a good knowledge of the importance of maintaining optimal adherence. Reductions in CD4 monitoring frequency could partially offset the additional costs incurred by countries currently scaling up VLM. Both providers and patients have become accustomed to routine CD4 monitoring and both will need to be sensitized to the utility of VLM as the ultimate tool to monitor treatment success on ART.

The scale-up of VLM in RLS presents several opportunities to facilitate differentiated care for those on ART. By identifying individuals with adherence challenges early in the course of treatment, providers now have the ability to focus time and resources on clients most at need for adherence support. Likewise, clients with good adherence histories supported by successful VL suppression on treatment may be seen less frequently and result in cost savings and reduced client waiting times. As VLM scale-up continues, the optimization of differentiated care strategies using VLM is a critical area of

implementation science to inform future treatment monitoring guidelines.

The Role of Viral Load Monitoring in Prevention

Finally, VLM potentially plays an important role in HIV prevention to both sexual partners and infants. Reduction in transmission to sexual partners in patients on ART as compared to patients not on ART has been demonstrated in several observational and clinical trial studies [34•], with a 95% risk reduction of transmitting HIV to sexual partners compared to individuals not on ART [35]; additionally, a meta-analysis of three cohort studies with confirmed suppression at the time of HIV transmission showed minimal transmission (incidence 0 per 100 person-years, CI 0–0.05) [34•].

Similarly, the use of triple antiretroviral (ART) therapy during pregnancy has been proven to be highly effective in reducing mother-to-child HIV transmission from 15 up to 45% with no treatment at all to below 5%; particularly suppressed viral replication has been proven to prevent mother to child transmission [36] with virtually zero transmission of HIV under circumstances of sustained viral suppression [37]. Preliminary data from the PROMISE study, which enrolled 2431 pregnant women from India and Africa, demonstrated that ART is also very effective to prevent HIV transmission to the infants also during the breastfeeding period, with a probability of transmission of 0.3, 0.5, and 0.6% at ages of 6, 9, and 12 months.

VLM can guide targeted interventions for those with high viremia, including reinforcing adherence to achieve suppression, and emphasis on use of condoms for those in a discordant relationship, and finally, timely switch to second line in order to suppress viral replication. Therefore, implementation of VLM and use of viral load results as a tool to ensure suppression may be an important implication for controlling the HIV epidemic; for example, it has been estimated that routine viral monitoring in Malawi could prevent over 350,000 new infections if efforts are made to guarantee viral suppression [38]. Similarly, ensuring sustained suppression in pregnant women could contribute to the reduction of pediatric HIV, and the goal of the UNAIDS targets of achieving an "HIV-free generation."

Conclusions

Viral load monitoring has the potential of improving individual HIV care, optimizing health systems by using resources for those in need of more support (differentiated care), and reducing the burden of the epidemic by preventing new infections. All these potential benefits could be jeopardized by non-compliance with proposed VLM algorithms, delayed switches, and low viral load coverage.

Compliance with Ethics Standards

Conflict of Interest Castelnuovo Barbara and Steven J. Reynolds declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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