

Viral Load Monitoring as a Tool to Reinforce Adherence: A Systematic Review

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Objective: Viral load monitoring has been proposed as a tool to reinforce adherence, but outcomes have never been systematically assessed.

Design: A meta-analysis was conducted to systematically analyze the research on viral load monitoring as a tool to reinforce adherence. Viremic resuppression is defined here as a decrease in viral load beneath a particular threshold following viral load levels that have been elevated despite antiretroviral treatment.

Methods: Six databases were searched for studies published up to November 2012, which reported the use of viral load monitoring as a tool to identify patients in need of adherence support. Three conference abstract sites were reviewed for studies reported in the last 2 years. Randomized and quasi-randomized trials and observational studies, were eligible. No language or geographical restrictions were applied.

Results: Six retrospective and 2 prospective observational studies reported data from 8 countries: South Africa, the United States, Thailand, Mali, Burkina Faso, Swaziland, India, and France. Five studies reported on viremic resuppression, with a pooled estimate of 70.5% (95% confidence interval: 56.6% to 84.4%) resuppressed. The remaining 3 studies all reported declines in mean viral load. Delayed onset of routine viral load monitoring was associated with the emergence of drug resistance.

Conclusions: The clear trend of resuppression, following viral load testing and adherence support, demonstrates the utility of viral load as a tool to identify patients in need of enhanced adherence support.

Key Words: HIV, viral load, adherence, viremia

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INTRODUCTION

There is an increasing appreciation for the benefits of routine viral load monitoring as a tool to provide an early indication of risk for treatment failure and reinforce adherence.^{1,2} For patients in whom a detectable viral load is the result of poor adherence, timely identification of viremia provides an opportunity to reinforce adherence before the development of resistance mutations and, thus, maintain the efficacy of the patient's current antiretroviral therapy (ART) regimen.³ Subsequent follow-up viral load tests will document whether the patient is able to achieve viral suppression again⁴ or if the patient remains viremic, potentially triggering a genotype test to document resistance or an empiric regimen change.²

The World Health Organization (WHO)⁵ recognizes the importance of regular monitoring, including viral load, for reinforcing adherence to ART,⁶ and the 2010 WHO Guidelines for ART in resource-limited settings propose an algorithm for using viral load as a means for discriminating between patients in need of adherence support and those who require a switch to second-line therapy.⁵ Recognizing the benefit of this approach, the 2010 WHO guidelines also recommend that countries begin to phase in virological monitoring. However, capacity to implement routine viral load testing remains limited in many resource-constrained settings, leading to debate about the relative importance of viral load within a public health approach.^{7,8}

This systematic review assesses the impact of routine viral load monitoring on achieving virological resuppression in viremic patients.

METHODS

Using a sensitive search strategy as part of a predefined protocol (see **Appendix S1, Supplemental Digital Content**, <http://links.lww.com/QAI/A437>), we searched PubMed, EMBASE, CABS Abstracts, Cochrane Central Register of Controlled Trials, LILACS, and AMED databases up to November 2012 for studies that reported on the targeted use of an adherence intervention following an initial viral load and reported virological outcomes following the intervention. No language, date, or geographical exclusions were applied. We further searched the abstract databases of the International AIDS Society, Conferences on Retroviruses and Opportunistic Infections,

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N.F. conceived and designed the review, conducted the meta-analysis, and provided critical feedback; A.M. acquired articles, conducted full text searches, data abstraction, and drafted the article; K.B. conducted title and abstract search and full text searches, data abstraction, and drafted the article; T.R. provided critical edits; and J.C. provided substantial design support and edits to the manuscript.

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and the MSF Scientific Day, from 2011 to May 2013, to identify recent studies that have not yet been published in full. After an initial title screen, full text copies of potentially eligible articles were reviewed independently by 2 reviewers. A title search of references was performed on articles meeting the inclusion criteria to determine potential articles for inclusion, which were not identified using the initial database search. After all articles meeting the inclusion criteria were identified, data were abstracted by 2 independent reviewers according to the prespecified categories. Confirmations were requested from investigators when needed.

Articles were excluded if they had fewer than 2 viral load test rounds, if follow-up testing differed greatly between intervention and control groups (for comparative studies), if patients were antiretroviral naive or had been started on ART within the preceding 6 months, or if none of the outcomes of interest were reported. Viremia was defined based on thresholds defined by the studies. Articles were omitted from the review if they were judged to be at high risk of bias for the outcome of interest (ie, if other factors, such as changes in medication during the study, may have influenced resuppression rates). No restrictions were placed on the study design.

For studies reporting the proportion of patients resuppressing following an adherence intervention, data were pooled using random-effects meta-analysis following stabilization of the variance of raw proportions using a Freeman–Tukey type arcsine square-root transformation. Studies that did not have the same outcome measure (proportion resuppressed) were excluded from the meta-analysis, as these could not be directly compared statistically. All analyses were conducted using Stata version 12 (StataCorp, LP, College Station, TX).

RESULTS

Approximately 4279 titles were identified using the initial database search and taken for abstract review, of which 183 articles were read in full. Overall, 14 were identified, from which 6 met eligibility for the review; 2,047 conference abstracts were also screened and identified 2 additional studies for review (see **Appendix S2, Supplemental Digital Content**, <http://links.lww.com/QAI/A437>). Characteristics for the studies included are described in Table 1.

The selected studies were published between 2004 and 2013 and reported data from 8 countries: South Africa,^{9,10} the United States,¹¹ Thailand,⁶ Mali and Burkina Faso,¹² the Kingdom of Swaziland,¹³ India,⁸ and France.¹⁴ Five studies reported outcomes in terms of viremic resuppression in addition to viral load monitoring.^{6,9,10,13,15} Follow-up period for the included studies varied from at least 3 months^{13,15} to 6 months^{6,9,10} to 4 years.⁹ Of the 6 articles identified from the literature review for this study, 6 were retrospective cohorts^{6,8,9,11,13,14} and 2 prospective cohorts.^{10,12}

The studies defined different thresholds for viremia: >50 copies per milliliter^{6,8,13}; >200 copies per milliliter¹⁴; >400 copies per milliliter⁹; >500 copies per milliliter¹²; and >1000 copies per milliliter¹⁰; and 1 did not specify the viremic threshold.¹¹ Similarly, viremic resuppression was defined differently: <50 copies per milliliter^{6,8,11,12};

<100 copies per milliliter¹³; <200 copies per milliliter¹⁴; <400 copies per milliliter⁹; or <1000 copies per milliliter.¹⁰

Patient characteristics and reporting periods varied across studies. One study included children and adults,⁶ and the rest included adults alone^{8,10,11,13} or did not specify age.^{8,9,12,14} Although 1 prospective cohort collected data from the onset of treatment, the other 7 provided data starting with the detection of a raised viral load.^{6,8,9,11–14} All studies included patients who had already begun ART. Two studies noted that all patients had been enrolled in treatment for at least six months prior to the onset of viral load monitoring.^{6,12} One study provided additional unpublished data on resuppression in their cohort.⁹

There was substantial variability in the type and duration of adherence support interventions. These interventions included peer support, adherence counselors, peer counselors, educational sessions, home visits, adherence support tools, and short-term directly observed therapy.^{6,8–12,14}

Study quality was assessed according to modified Newcastle Ottawa criteria (see **Appendix S3, Supplemental Digital Content**, <http://links.lww.com/QAI/A437>) and was judged overall to be moderate. Most studies (6) were retrospective cohorts, but all provided objective outcome measures with appropriate statistical analysis; 3 discussed sources of bias and most (5) assessed generalizability of the findings.

All studies documented reductions in numbers of viremic patients between the first detectable viral load and subsequent viral loads. These reductions were statistically significant, where such analysis was done. One study reported data as time to event and estimated that, by 32 months, only 5.6% patients will have failed virologically (2 consecutive viral load tests over 1000).¹⁰ Five studies reported on the proportion of patients resuppressing after an adherence intervention; this ranged from 54.2% [95% confidence interval (CI): 46.3% to 62.0%]¹³ to 89.1% (95% CI 77.8–96.7%),⁶ with a pooled proportion of 70.46% (95% CI: 56.6% to 84.4%, $\tau^2 = 0.11$) (Fig. 1). The lowest proportion of resuppression was reported by Pirkle et al¹² in which only a third of participants achieved >1 log viral load reduction; however, this cohort had been on ART an average of 23.7 months before viral load monitoring was initiated, and there was a high rate of accumulated ART resistance mutations that had developed before the adherence intervention. The highest proportion of resuppression (90%) was reported by a study that focused on a subset of patients with viremia between 50 and 1000 copies per milliliter.⁶

DISCUSSION

This review found that, in all studies, the majority of patients in whom viremia is initially detected resuppress following an adherence intervention, and all studies showed a subsequent reduction in viral load levels.

Targeted adherence interventions triggered by viral load monitoring may allow patients to stay on more affordable, less complex, first-line regimens, with clear benefits for both the patient and healthcare system.^{3,16,17} On average, second-line HIV treatments are at least 3 times the price of first-line medications in low-income countries.¹⁸ Models predict that up to

TABLE 1. Description of Interventions and Outcomes

Study	Year	N	Study Design	Viral load Monitoring Schedule	Intervention	Outcome (Viremia)	Significance	Included in Meta-Analysis
Berki-Benhaddad et al ¹⁴	2006	15	Retrospective cohort	Baseline, months 1, 3, 9, and 12.	Personalized adherence support.	–Log 2.3 decreased viral load.	$P = 0.045$ (n = 15)	No
Calmy et al ⁹	2007	232	Retrospective cohort (comparative)	Baseline, 3 months, 6 months, and every 6 months thereafter.	Preparedness counseling, pillboxes, support groups, and a buddy system. Viral load testing used to identify patients who needed additional support.	77% patients who underwent an adherence intervention achieved viral load resuppression, defined as viral load <400 copies/mL		Yes
DeFino et al ¹¹	2004	45	Retrospective cohort	Baseline, months 3, 6, 9, and 12.	6–8 weekly one-on-one sessions with a nurse or counselor. Also included quarterly reinforcement, virological monitoring, pillboxes, pictorial medication schedules, and alarm reminders.	Median decrease in mean viral load from 180,190 to 49,206 copies/mL. Resuppression was defined as <50 copies/mL.	$P = 0.08$ (n = 45)	No
Khan et al ⁸	2013	40	Retrospective cohort	Baseline, 3 months, 6 months.	Structured client-centered adherence counseling and health education for patients and their families.	78% of those on second-line therapy with an elevated viral load and 78% of those subsequently on third-line therapy with an elevated viral load resuppressed.		Yes
Orrell et al ¹⁰	2007	43	Prospective cohort	Baseline, with testing every 8 weeks until resuppression.	Targeted intervention for those with elevated viral load, including pill boxes, dosing diaries, 3 educational sessions, and counselor home visits.	53% with viral load initially >1000 copies/mL reached full resuppression, defined as <50 copies/mL.		Yes
Parker et al ¹³	2013	200	Retrospective cohort	Baseline, 3 months.	Intensified adherence counseling.	47.5% patients had undetectable viral loads at the second viral load test.		Yes
Pirkle et al. ¹²	2009	56	Prospective cohort	Baseline and after adherence intervention.	1 month of mDAART administered along with weekly follow-up visits with a pharmacist or counselor.	35.7% decreased viral load 1 log; resuppression was not defined.		No
Wilson et al. ⁶	2009	40	Retrospective cohort	Baseline, every 3 months until resuppression, and every 6 months thereafter.	Viral load testing was used as a tool to assist in patients' adherence. Education materials and a counseling program were also offered.	90% of those with initially raised viral loads resuppressed after 3 months, defined as <50 copies/mL.		Yes

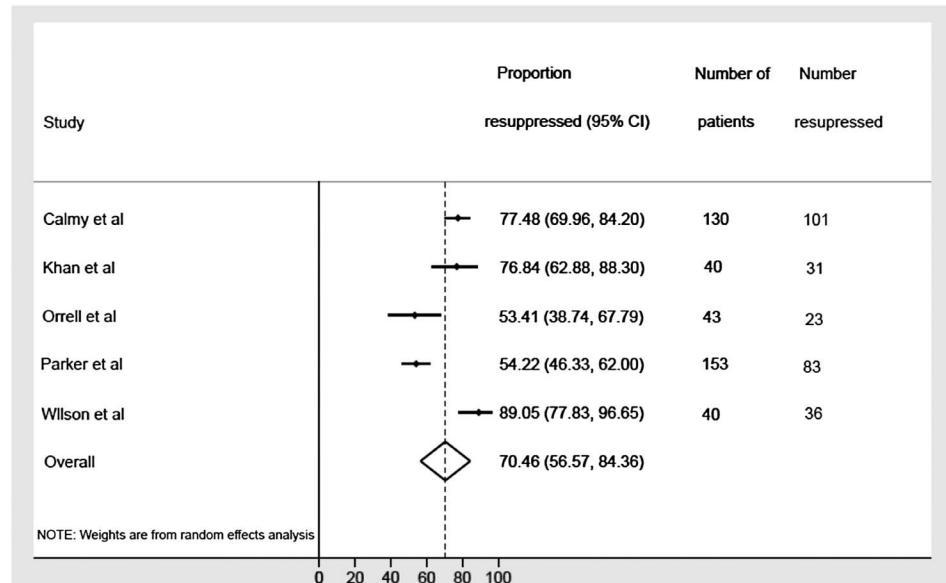


FIGURE 1. Meta-analysis of the pooled proportion of viremic patients resuppressing following an adherence intervention.

80% of drug-resistant transmission could be reduced by yearly virological monitoring.¹⁹ Timing of intervention is crucial. In 1 study included in this review, where routine viral load testing began later in the treatment cycle, more than 60% patients had already developed resistance mutations when viral load testing started,¹² suggesting that early viral load monitoring (ie, within 12 months of ART initiation) is critical for identifying early treatment failure. Of particular note is the 78% resuppression for patients suspected of failing second-line treatment; robust third-line options are not widely available in many low-income countries because of high cost, and viral load may be a particularly cost-effective intervention for these patients.

Although there is a clear rationale and recommendation for routine viral load testing, few low-resource countries have implemented this widely. A recent survey of 23 low- and middle-income countries found that only 4 incorporated routine viral load monitoring into their national guidelines, and only Brazil, Botswana, and South Africa actually have viral load testing readily available for this purpose.²⁰

As viral load monitoring is expanded, operational research is needed to inform the optimal adherence intervention, the frequency of viral load testing, the most appropriate virologic thresholds to use, and the optimal use of point-of-care technologies.²¹ The development of simpler, automated devices (whether point-of-care or laboratory based, using dried blood spots) is anticipated to greatly enhance the ability of resource-limited countries to implement viral load testing, particularly at peripheral sites.⁷

The aim of this review was to systematically assess the reported proportion of patients who resuppress following an adherence intervention, not to determine the causal effect of viral load on adherence. Such estimates of resuppression should be taken as indicative only and, in programs, can be expected to vary according to the presence of drug resistance (which may be influenced by regimen efficacy, prior treatment exposure, time on treatment, and prevalence of transmitted drug resistance) and the effectiveness of the actual adherence intervention.

Nevertheless, the findings of this review support the benefit of viral load testing as a tool to detect adherence problems and to allow substantial numbers of patients to achieve viral resuppression posttargeted adherence counseling. Additional studies can determine the optimal adherence–counseling package.

In conclusion, these observational studies show that routine viral load monitoring is beneficial when used as a tool to identify people in need of adherence interventions, the majority of whom resuppress and are able to continue their treatment after adherence support.

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