Commentary: The monitoring of adults and children on antiretroviral therapy in the 2013 WHO consolidated ARV guidelines

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The laboratory monitoring of patients on antiretroviral treatment (ART) is an important element of HIV treatment programs, and is one of the cornerstones for ensuring a successful and sustained response to ART. Previous WHO ART guidelines placed greater emphasis on treatment initiation, whereas monitoring was considered optimal but not a prerequisite for the rollout of treatment programs [1]. During the early years of the global AIDS response, this was a decision that was both pragmatic and strategic. Treatment access was a public health emergency, and WHO sought to simplify the approach to ART and thus provide member states with guidance that could be implemented without delay. There is little doubt that this was the right thing to do at the time. Global progress in scaling up HIV care and treatment services has been dramatic and unprecedented; many hundreds of thousands of lives have been saved, and close to 10 million adults and children are now receiving ART [2].

But at the same time, this public health approach has had a downside. Whereas treatment has expanded exponentially and the options available for first-line ART in low and middle-income countries (LMICs) are on a par with those in resource-rich countries, this is not the case for laboratory services. In order to achieve long-term benefit from ART – for both the individual as well as the community – viral replication must be controlled to the greatest extent possible for as long as possible. The only way to assess viral replication at present is notification of plasma HIV RNA or viral load. Studies have shown that absence of viral load monitoring results in delayed diagnosis of treatment failure, which in turn leads to immunologic decline, clinical events and accumulation of resistance mutations [3–5]. Systematic reviews undertaken as part of the WHO 2013 ART guidelines revision and published in this supplement have confirmed these observations. Tucker et al. [6] concluded that clinical monitoring alone is inferior to clinical and immunologic monitoring in terms of morbidity and mortality. Addition of viral load monitoring did not demonstrate improved mortality, but did decrease the time taken to switch to second-line therapy. Rutherford et al. [7] reviewed the sensitivity and specificity of the 2010 WHO CD4\textsuperscript{+} T-cell and clinical criteria for treatment switching and found that although they were moderately specific for diagnosing virologic failure, they had very poor sensitivity, implying that CD4\textsuperscript{+} T-cell alone would both over and underdiagnose virologic failure. Partly as a result of these systematic reviews, the revised 2013 ART guidelines provide for the first time, a strong recommendation to use viral load as the preferred method for monitoring patients on ART [8]. This recommendation, together with new guidance on how best to use CD4\textsuperscript{+} T-cells in combination with viral load as well as the frequency of monitoring (Table 1), is consistent with longstanding clinical practice in resource-rich settings, but represents a paradigm shift for the WHO guidelines.

In addition to the morbidity and mortality benefits of using viral load to monitor patients on treatment, routine use of viral load testing may prevent resistance from developing by identifying patients with poor adherence who can re-suppress viral replication with adherence interventions alone. In one cohort study in South Africa, although 7% of patients developed viral breakthrough during the first year of therapy, over two-thirds of these patients became undetectable following a targeted adherence intervention [9].

Although the new recommendations are supported by evidence and are in line with WHO principles of equity, they are not without controversy due to the high cost and implementation challenges of rolling out viral load in LMICs. One analysis of the cost-effectiveness of different

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monitoring strategies using current viral load test pricing and clinical data from a randomized trial in Uganda concluded that compared with CD4+ T-cell viral load was much less cost-effective because of relatively low clinical benefit and relatively high cost [10]. At the same time, nearly all studies note that viral load monitoring will become more cost-effective as the cost of viral load testing and second-line therapy declines [11].

Despite the fact that the overall quality of evidence based on Grading of Recommendations Assessment, Development and Evaluation criteria was judged to be ‘low’, there was consensus in the Guideline Development Group to issue a strong recommendation in support of the use of viral load, underscoring the importance of expanding viral load access. The rationale for using viral load as the preferred approach was to provide an early and more accurate indication of treatment failure, thus reducing the accumulation of drug-resistance mutations and improving clinical outcomes. This is a critical strategy for the long-term success of ART programs, but measuring viral load is not the only way to reduce drug resistance in the population. Implementation of routine viral load monitoring must be accompanied by efforts to prevent stock-outs through the continued support of healthcare systems and improved patient adherence.

In the coming months and years, the challenge for program managers will lie in how to implement these recommendations. Although we have seen significant success in scaling up access to other virologic tests such as DNA PCR for infant diagnosis, the advantage with these qualitative assays is that they can be performed using dried blood spots (DBS). Although DBS have been used successfully with various viral load platforms, there are known to be several limitations. DBS contain cell-associated RNA and DNA which may be detected by the viral load assay, resulting in inaccuracies and false-positive tests when viral load is undetectable in plasma. In addition, the volume of blood in a DBS is small, thus decreasing the sensitivity of viral load testing. WHO guidelines currently call for a viral load cut-off of 1000 copies/mL to make a determination of virologic failure, but higher thresholds may be necessary when using DBS which may in turn reduce the clinical and programmatic benefits of using viral load in the first place. There is an urgent need for research to establish consistent and reliable cut-offs for DBS viral load as well as for newer point-of-care viral load assays which are under development.

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#### Conflicts of interest

None declared.

### References


