Stockholm Evaluation Unit

VIRAL LOAD MONITORING

MSF OCB, Gutu district, Zimbabwe

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SHORT VERSION

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ACRONYMS

AE	Adverse Events (related to medication)
ART	Antiretroviral Therapy
CAG	Community ART Group
CHAI	Clinton Foundation HIV/AIDS Initiative
DBS	Dried Blood Spot
DR	Drug Resistance
EAC	Enhanced Adherence Counseling
GF	Global Fund
HF	Health Facility
HTC	HIV Testing & Counseling
HVL	High Viral Load [in this document HVL is VL ≥1000 copies/mL]
IQR	Inter-Quartile Range
LLV	Low Level Viremia [in this document LLV is VL 40-999 copies/mL]
LTFU	Lost To Follow-Up
MSF	Médecins Sans Frontières
M3	Month 3
MOHCC	Ministry of Health & Child Care
NGO	Non-Governmental Organization
NMRL	National Microbiology Reference Laboratory
OI/ART	Opportunistic Infection/ Antiretroviral Therapy
PEPFAR	President's Executive Plan For AIDS Relief
TAT	Turnaround Time
TDR	Transmitted Drug Resistance (same as Primary Drug Resistance)
UVL	Undetectable Viral Load
VL	Viral Load

EXECUTIVE SUMMARY

Context: MSF launched an ambitious project to establish routine viral load monitoring for patients on antiretroviral therapy beginning in 2013 in Gutu District, Masvingo Province, Zimbabwe. This evaluation of the viral load (VL) monitoring system was commissioned in order to more fully understand the experience and outcomes of the introduction and scale-up of VL in one district of Zimbabwe, but also undertaken with a view to the national scale-up of VL monitoring, and the general issue of VL monitoring in sub-Saharan Africa in light of the UNAIDS 90-90-90 targets.

Scope: In order to understand all aspects of the VL monitoring system, the entire VL pathway was examined from the point of requesting a VL measurement at a health facility in Gutu District to the NMRL virology laboratory in Harare where the test is performed, following the delivery of results to health facilities (HF) and patients, and the response to VL results in terms of the management of patients on ART. In addition to examining these operational aspects, it was important to examine the logic of the system insofar as it is based on contestable assumptions about the timing of VL measurements and the response to specific levels of VL elevation. The operational system, even if perfectly executed, cannot overcome shortcomings inherent in the theoretical framework. A parallel theme running throughout the evaluation was to assess the independence and potential sustainability that the VL monitoring system demonstrates. Since variability from site to site had been noted both in the uptake of VL monitoring and in the proportion of a HF cohort that was virologically suppressed, the evaluation entailed a careful search for differences between sites that might be explanatory.

Methods: The evaluation exercise entailed a review of existing project reports and data, discussion with MSF team members in Zimbabwe, and site visits to the NMRL virology laboratory in Harare and 9 HF in Gutu District, where personnel based at each site were interviewed. Some existing data & data analyses were used and some new data extraction and analysis was performed to enable the evaluation questions to be addressed. A search of the published literature relevant to the evaluation questions was performed and the references have been integrated into the report.

Uptake of VL measurement at HF: The focus was on uptake of the first month 3 (M3) VL since this is the most crucial VL measurement in terms of preservation of the first line regimen through the avoidance of antiretroviral drug resistance. Uptake of M3 VL was examined in 2 separate ways: (1) File reviews at 6 major HF, where an average of 66% of files had evidence of M3 VL for ART initiations in Q1 and Q2 of 2015 (and 34% did not); and (2) TIER.net data for 10 monitored sites; where quarter-to-quarter variation in the proportion of new ART initiators with an M3 VL was found to be 54%, 57% & 45% in Q4 2014, Q1 2015 & Q2 2015, respectively. To complement these data, the TIER.net database was used to find the proportion of ART patients at each of the 10 monitored HF who had no evidence of any VL measurement; the proportion with any VL varied from 5.1-21.4% of the ART cohort.

VL laboratory services at supra-District level: A concerted, multi-partner effort has been made to build the VL laboratory service which meets current district needs, but requires input from other partners to reach national targets for VL monitoring. The experience to date has shown that the system is vulnerable to technical problems leading to service interruptions, and serious backlogs in sample processing and reporting of results. Data on turnaround time (TAT) for VL results was extracted for 6 major health facilities for 3 consecutive years: the median (IQR) TAT for the 6 facilities was 22 (17-28) days in Q3 2013, 25 (18-36) days in Q3 2014, and 40 (23-49) days in Q3 2015. The effects of a protracted service interruption in Q3 2015 are clear from these data. Although it is reasonable to anticipate that with an expanded number of VL platforms in Zimbabwe and a more functional service contract to maintain them such delays will be less likely in future, there are a number of remediable process inefficiencies relating to data entry in the virology laboratory which, if addressed, could increase the efficiency of operations.

Aspects of virological suppression and the interpretation of VL results for patient management in Gutu District: Patient education is the primary resource used to support adherence to ART, given that other

methods are not routinely used except when group support is indirectly provided for already adherent patients assigned to a Community ART Group (CAG).

High VL (HVL) at M3 has several potential causes: it may reflect high (unmeasured) baseline VL – this may apply to roughly 5% of the cohort of ART initiators at M3; or possibly primary antiretroviral drug resistance – although we do not have a precise estimate in Zimbabwe it is likely in the range of 0-4%. Most patients with HVL at M3 are presumed to have poor adherence to ART, and the higher the VL value, the more likely that is actually the case. The standard programmatic response to HVL at M3 is Enhanced Adherence Counseling (EAC). The effectiveness of EAC has been questioned in a recent study, and data from a 2014 VL cascade analysis in Gutu District was used to further dissect the programmatic experience. When the initial VL was 1000-9999 copies/ml, 68% of patients had a follow-up VL <1000 copies/ml following EAC, but if the initial VL was >10,000 copies/ml only 14.0% suppressed (<1000 copies/ml) after EAC. Further analysis of the timing of EAC after the initial HVL (1000-9999 copies/ml) showed that those who subsequently suppressed their VL had EAC at a median of 59 days after the HVL was detected, whereas those who did not suppress their VL had EAC at a median of 180 days after the initial HVL was detected. These data suggest that EAC is more likely to be associated with subsequent viral suppression if pre-EAC VL is <10,000 copies/ml and EAC occurs within 2 months.

Variability in proportion with HVL was analysed with univariate & multivariable logistic regression (for 6 major sites in Gutu District). This showed that HVL at the first VL measurement was independently predicted by younger age (those >20 year of age were 62% less likely to have HVL); male sex (women were 25% less likely to have HVL), and when reason for testing was not 'routine' – meaning usually targeted and often post-EAC- then the odds of HVL were nearly doubled. There was no independent association with time on ART, or with a particular HF.

Variability in later VL measurement was evaluated among patients with a high second VL measurement (VL2), by looking at their subsequent (VL3) VL values. Only about 50% of such patients suppressed their VL on the VL3 measurement. Logistic regression was again employed to analyse potentially associated factors: it showed that, male sex was no longer independently predictive and although age >20 was associated with suppression it was of borderline significance. The only independent predictor of HVL at VL3 was the magnitude of the VL2 elevation: compared to the reference category (VL2 ≥3 logs but <4 logs) those with VL2 ≥4 logs but <5 logs were 3.6 times more likely to have HVL at VL3, and those with VL2 ≥5 logs were 9.8 times more likely to have HVL at VL3. This implies that elevation of VL2 and VL3 is more strongly associated with virological factors.

Groups with theoretically increased risk of HVL: Patients with low level viremia (LLV; here 40-999 copies/ml) are known to have an increased incidence of virological failure (this is well documented in published literature). Data on the evolution of VL was examined among those with LLV in the Gutu cohort: 13.5% of patients on ART have LLV on their first VL measurement. Such patients get a follow-up VL routinely at 12 months and for 21.9% the follow-up VL is persistently in the LLV range, but for 15.1% it is elevated ≥1000 copies/ml; of those with a 2nd routine VL in the LLV range, a 3rd routine VL was persistently in the LLV range for 24.1% and ≥1000 copies/ml for 15.2%. Thus, the project data illustrate what the literature describes: progressive accumulation of virological failure among those with LLV. In this system LLV does not prompt EAC or targeted (early) VL follow-up.

Option B+ women may be at risk for poor adherence related to several social and demographic risk factors but a previous analysis (data period April 2013- June 2015) showed no greater proportion of HVL than among non-PMTCT women initiating ART.

Intolerance to specific antiretroviral agents could have compromised adherence and be associated with HVL but data suggest that switching of potentially problematic agents (EFV, AZT) is rare and this implies that intolerance is not likely to be a significant contributor to HVL in the Gutu cohort.

TB co-infected patients are reported in the literature to be at increased risk of virological failure. Limited data are available on co-treated patients; the active cohort of TB patients has a similar proportion with HVL as the general ART cohort (13.2%) but 23.2% of TB-HIV patients were LTFU by Q3 2015 and of those

with a VL value the proportion with HVL was much higher. While not conclusive this could suggest an association between poor virological control and poor outcomes with TB-HIV co-infection.

Strengths and weaknesses of the current VL monitoring system with regard to the Undetectable Viral Load (UVL) objective: The VL monitoring system has structural strengths (autonomy of NMRL, plans and funding for expansion of VL services, use of DBS technology, SMS results delivery, CAGs to decrease clinic burden) but suboptimal uptake of M3 VL needs to be addressed, and TAT for results has been vulnerable to service interruptions so far.

HF staff (including Primary Counselors) are human resource strengths but supervision and mentorship for them are of variable quality; the VL benchmarks are often missed partly due to this. Counselors cannot address all issues underlying poor adherence, more comprehensive psychosocial care programs are needed. Nurses need clearer advice on the management of HVL and the process for authorization of switch to 2nd line ART needs streamlining to avoid delays.

VL monitoring is patient friendly, with direct transmission of results to patients via SMS and the offer of CAG which simplifies medical follow-up and enhances social support. Young people need more options for adherence (and social) support. LTFU needs to be systematically addressed.

Theoretically, it appears that 3M VL is the optimal timing; when patients do have persistent HVL despite EAC evidence suggests they can still respond well to 2nd line ART. Prolonged failure on 1st line ART is associated with increased mortality. Low level viremia deserves to be treated just as higher elevations in VL to avoid overt failure.

Sustainability prospects are overall good with solid plans and funding arrangements centrally for taking over project VL needs, and a high level of engagement of MoHCC at District level in supervision and service provision. Transport of specimens to the laboratory needs to be independent of MSF but steps are being taken to address that. More use of VL monitoring will mean more need for 2nd line ART (with its cost implications) but the alternative is worse: increasing resistance to the 1st line regimen and poorer outcomes if patients remain on 1st line despite virological failure.

Conclusions:

1. The project strategy is appropriate to the UVL objective providing M3 VL is emphasized.
2. Appropriate and timely adaptations closely related to partners have enhanced the capacity and prospects for sustainability of the VL monitoring system.
3. The UVL objective has been achieved to a moderately high degree considering the pilot nature of the project, and results are expected to improve over time.
4. Activities were carried out as planned except for temporary outsourcing of VL measurement to South Africa.
5. Several factors threaten the achievement of the UVL objective, including delayed measurement of VL1, or delayed response to HVL at VL1; failure to systematically address low level viremia; higher risk of HVL among patients restarting ART after LTFU; and most importantly poor adherence related to psychosocial factors and inter-related stigma, particularly among young people – this demands a comprehensive approach to psychosocial care to move beyond the limits of one-to-one counseling.
6. Limitations include the questionable (perhaps conditional) effect of EAC, and the importance of addressing retention in care/ LTFU hand in hand with adherence support.
7. Opportunities exist to enhance patient support and patient autonomy with expanded use of SMS –based systems, community groups, alternative drug refill systems, and enhanced psychosocial care options (as noted above).
8. The systematic issues most related to effectiveness (in obtaining UVL) are timing of VL1, rapid TAT for VL results, systematic switching of patients failing 1st line ART, and more comprehensive psychosocial support, especially for young people.
9. VL uptake can be improved with a variety of flagging or systematic reminders.
10. Site visits and mentorship could be used to transfer lessons from high performing clinics.

11. Low coverage of VL is often seen with frequent personnel changes.
12. It can be overcome with consistency in personnel and systematic reminders.
13. VL monitoring has good prospects for sustainability if specimen transport is independent of MSF.
14. Sustainability overall can be enhanced by streamlining data entry at the virology laboratory for efficiency.
15. Training related to expansion of VL lab services with contingency plans to keep TAT <30 days. National consensus on ART switching rules –and training on this - is imperative.
16. MSF can support the activities noted in points 5-15 to enhance outcomes in Gutu District.

Recommendations:

⇒ 1. Optimize the systematic uptake of M3 VL using systematic flagging or reminders
⇒ 2. Advocate for a national adoption of M3 VL instead of M6.
⇒ 3. Avoid prolonged continuation of 1st line ART with HVL; switch to 2nd line systematically.
⇒ 4. Manage low level viremia (40-999 copies/ml) with EAC and early post-EAC follow-up VL.
⇒ 5. Diversify the range of psychosocial supports for patients, involving local NGOs, community groups, PLWA groups, and adding evidence based methods for adherence support.

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