



VIRAL LOAD MONITORING

MSF OCB, Gutu district, Zimbabwe

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DISCLAIMER

The author's views expressed in this publication do not necessarily reflect the views of **Médecins sans Frontières** or the Stockholm Evaluation Unit.

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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.

PROJECT BACKGROUND

INTRODUCTION

Since January 2011, MSF has been supporting Ministry of Health and Child Care (MoHCC) in Gutu District, Masvingo Province, to increase access to quality HIV/TB care and this through decentralization of ART diagnosis and treatment from hospital to clinics using a mentoring approach.

Overall ART coverage has increased dramatically since 2013 such that by the end of 2014 30 of 31 health facilities offered ART (using the updated WHO threshold of CD4 <500). ART coverage for adults was 78.6% for Q2 of 2015.

In line with the WHO's 90-90-90 target, a key indicator in MSF's Gutu project is for 90% of all patients to have a suppressed VL. The current threshold in Zimbabwe for suppression is 1000 copies/ml. In Gutu, routine VL screening has been implemented since early 2013 and by the end of 2014, 73% of patients who had been on ART for more than three months were found to have been monitored using viral load and this has since improved. However, there is some variation between clinics – at the end of quarter 1 in 2015, 6 of the 29 clinics were noted to be sending fewer viral loads than would be expected based on their cohort size. The Q2 2015 Narrative Report notes that the proportion of routine first VL results >1000 copies/ml was 13%. There is substantial inter-site variability in the proportion of the cohort with suppressed VL.

Gutu District is one of the first in Zimbabwe to implement routine VL monitoring for patients on ART. This entailed the creation of new systems within an already resource-constrained setting. The mode of engagement chosen by MSF for Gutu District is deliberately aimed at avoiding the creation of a parallel and/or highly resourced system with low prospects for sustainability post-MSF. The accomplishments of this project should be interpreted as those of a pilot project.

OBJECTIVES OF THE PROJECT

General objective

Morbidity and mortality due to HIV/ AIDS/ TB are reduced in Gutu District

Specific objective

The population in Gutu district benefits of increased access to quality OI/ART & TB/ MDR TB services offered by MOH with support of MSF.

Expected result 1 : Increased number of adults & children access TB / DR-TB and HIV care (new 2013 WHO guideline) maintaining the mobile mentoring approach integrated in MOHCW.(light approach)

Expected result 2: Undetectable VL, quality care for clients with Opportunistic Infections and acceptable cure rates and success rates for TB are achieved through quality HIV / TB services with good retention in care

Expected result 3: HIV / TB funding is ensured, (advocacy), policy allows initiations < 500 and no ART drug gaps are faced at district level.

This evaluation is primarily focused on Expected result 2 (where 'undetectable' refers to VL < 1000 copies/ml).

EVALUATION METHODS & LIMITATIONS

PURPOSE AND OBJECTIVES OF THE EVALUATION

Purpose: Conduct an evaluation of the viral load component (since inception but in particular since mid-2013) of the Gutu District HIV/TB project to directly contribute to an immediate improvement of the project, as well as to understand the prospects for viral load monitoring sustainability after MSF departure.

The objectives are to answer the following questions:

- Is the strategy appropriate in order to achieve the UVL objective?
- Were appropriate and timely adaptations made in response to changes in the environment?
- To what extent has the UVL objective been achieved across the project?
- Were the related activities carried out as originally planned?
- What were reasons for achievement or non-achievement of the 90% UVL target?
- What are the limitations/opportunities inherent in the approach?
- What can be done to make this component of the intervention more effective?
- Can the factors contributing to a high proportion of undetectable VL in the 'high performing' clinics be replicated in other clinics? If so how?
- How can 'low performing' clinics learn from 'high performing' clinics within Gutu and in Zimbabwe generally?
- What factors can be identified that contribute to a low coverage of VL monitoring in the Gutu clinics?
- What measures are needed to increase coverage of VL monitoring in places where it is a problem?
- How sustainable will VL monitoring be for clinics after the departure of MSF?
- What factors will affect the sustainability of VL monitoring?
- What further training will be needed to improve the sustainability of VL monitoring?
- What else could MSF do before the end of the project in Gutu that will improve the sustainability of VL monitoring?

METHODOLOGY (OUTLINE)

- Review of project history & plans
- Reports and existing data analyses
- Literature review
- Descriptive statistics regarding demographics of cohort, and VL outcomes & patterns
- New analysis of existing data on VL determinants and VL outcomes
- Data sampling at sites regarding uptake of VL and management of HVL
- Observation/ interviews at the NMRL VL laboratory
- Observation/ key informant interviews at 9 health facilities & in MSF team regarding OI/ART clinic organization, patient files, VL scheduling & response to VL results
- [A detailed list of site visits and informants is provided in Annex II & III]

LIMITATIONS

There is currently no digitized information on distance of patient residence from health facility, which can only be determined by perusal of the patient OI/ART file and estimation of the distance based on

the area of residence. Distance may be a factor that influences VL uptake or adherence but I was unable to evaluate it here.

Data on TB-HIV co-infection and co-treatment is not available in a unified database; a limited analysis of virological outcomes was possible.

There are no electronic data on lateness of attendance or defaulting (only on loss to follow-up). A published study from MSF (Bastard M, 2012) found that that lateness for appointments predicted virological failure and antiretroviral drug resistance.

FINDINGS

UPTAKE OF VL SERVICES AT HEALTH FACILITIES IN GUTU DISTRICT

Attitudes among HF staff are positive – the VL testing algorithm is, in general, well understood and there was no indication of any opposition to VL monitoring (on the basis of increased workload or any other potential argument).

In practice routine VL measurements are frequently missed, particularly (but not only) the M3 VL after initiation.

Periodic knowledge assessments have been performed among all nursing staff working (full or part-time) in the OI/ART clinic at each location; although there is person-to-person and site-to-site variability in knowledge, particularly around areas like paediatric HIV treatment, this does *not* correlate with VL uptake at a facility.

It appears that at least some nurses may not realize that even if the 3M VL is missed it is still important to collect blood for VL as soon as possible after, not to simply wait for the 12M VL

The M3 VL appears to be frequently missed because there is currently no systematic flagging system to indicate that it is due. Staff at HF use a variety of methods to remind themselves when a VL is due-, but these are themselves prone to inconsistent use in most locations visited:

- Noting the ART initiation date is 3 months prior thus 3M VL is due.
- Note need for VL in patient's own health book.
- Note need for VL in Booking Diary when next visit is booked.
- Keep separate VL register with entry made at time of venipuncture.
- Keep separate VL book based on information written on the stub of the VL Request Form (sometimes filled in later).

The HFs with the highest VL uptake used method 4 or 5.

In the absence of a systematic reminder to collect the M3 VL specimen, adherence to the VL algorithm depends on:

- The familiarity of staff with the VL algorithm (may be low for some part-time staff),
- Personal organizational skills (variable) and
- Workload (cohort size and number of patients per clinic day).

Although M3 VL was evaluated in detail *because it provides the most recent data on VL uptake and because it is arguably the most time-dependent VL* (Kerschberger, 2015), missed VL occurs at all other times as well, whether routine (e.g., M12, M24, etc.) or targeted (post-EAC, post HVL). Uptake of VL testing was examined in 3 different ways, as illustrated in Tables 1, 2 & 3

The effect of delayed or missing M3 VL is a lost opportunity to intervene if there is HVL.

A recent MSF publication notes that VL1 at 3 months is associated with 22% less Virologic failure than VL1 at 6 months (and a 27% risk reduction for switch to 2nd line ART). The authors estimated a 9% increase in risk of failure for each month of delay after 3 months. (Kerschberger, 2015).

Table 1: File Review at facility regarding VL uptake: 2015 Q1 & Q2 ART initiations (*Q2 only)

Facility	M3 VL done n (%)	M3 VL missed n (%)	LFTU prior to M3
Gutu Rural H*	28 (62)	17 (38)	13
Serima Mission H	16 (70)	7 (30)	1
Gutu Mission H	34 (94)	2 (6)	6
Chinyika HC	13 (45)	16 (55)	~5
Chimombe HC	12 (38)	20 (62)	N/A
Mutero Mission H	18 (100)	0 (0)	N/A
	121 (66)	62 (34)	

Table 2: Uptake of 3M VL1 among 10 TIER.net sites, looking at quarterly variability in VL uptake

Period	# ART initiations	# with 3M VL1 in TIER.net	# with 3M VL1 in VLIS	% 3M VL1
2014 Q4	259	152	140	54
2015 Q1	296	143	170	57
2015 Q2	225	54	102	45

Table 3: Proportion of active ART cohort who have never had a VL (based on TIER.net) as of end of Q3 2015

Site	Active	LTFU (% of Active)	Active with no VL ever (% of Active)
Serima	667	31(4.6)	83(12.4)
Gutu Rural Hospital	1713	584(34.1)	366(21.4)
Cheshuro	604	37(6.1)	73(12.1)
Chimombe	689	59(8.6)	74(10.7)
Chitando	655	29(4.4)	91(13.9)
Soti Source	189	15(7.9)	10(5.3)
Matizha	523	67(12.8)	73(14.0)
Chinyika	599	28(4.7)	102(17.0)
Magombedze Chitsa	252	10(4.0)	18(7.1)
Chepiri	182	11(6.0)	18(9.9)

VL LABORATORY SERVICES AT SUPRA-DISTRICT (HARARE) LEVEL

Planning and management of VL services:

Ownership is within the MOHCC (and the NMRL - which sits within this ministry).

MSF & CHAI played major roles within the VL Technical Working Group, along with other NGOs, in the elaboration of a national roll-out plan.

MSF contributed to the writing of the WHO 'VL Implementer's Guideline' to promote implementation of the national roll-out plan.

Funding of VL services

Introduced by MSF using UNITAID funding (for the 2013-2015 period – but MSF has a no-cost extension and may use existing funds until mid-2016); continuation funding post-2015 will be covered by the Global Fund grant for the 2014-2016 period; it is anticipated that the next GF application (for 2017-2019 period) will provide for continued VL monitoring. PEPFAR also contributes to VL funding, although minimally, partly through budget line shifts away from CD4 testing to VL testing.

MSF collaboration with UNITAID was part of a USD 28M initiative involving MSF-OCB, -OCP & -OCG in several African countries, aimed at optimizing synergy between the market development aims of UNITAID and the patient-centred & population health-focused aims of MSF. This was recently evaluated positively (by MSF) and is seen to have benefitted GF budgets through competition-induced price reductions in HIV-related technologies.

This has stimulated MSF operational research, for example on point-of-care VL using Xpert™.

MSF (HOM, MedCo) participates in GF meetings, and supported the GF application for 2014-2016 which included lines for VL machines and reagents. MSF has also supported applications for 'Incentive Funding' – a mechanism introduced by GF to allow greater responsiveness to new needs between regular 3-year GF funding cycles, which could be used for VL related costs.

Human resources

MSF currently funds 6 laboratory scientists and 4 data officers working at the NMRL VL laboratory; funding of these positions should be taken over by the MOHCC after UNITAID funding ends (using GF grants).

Technical capacity: will only cope with the addition of other VL machines in Zimbabwe; had uptake been optimal the laboratory may have been overwhelmed.

Delays in increasing VL laboratory capacity by MOHCC are related to protracted discussions between the UNDP (the GF Principal Recipient, in Zimbabwe), BioMérieux (the vendor of the current NMRL VL platform - the one most likely to be selected for roll-out since it is the only platform validated for VL on DBS) and Department of Laboratory Services within MoHCC; this is beyond the control of MSF.

Associated Public Health Laboratories (US) has funding for incentive-based payments to laboratories, particularly 6 high-throughput labs and they will be incentivizing VL over CD4 tests.

Inefficiencies

Registration data is not communicated electronically to VL laboratory requiring the lab staff to re-enter patient identifiers.

Every VL result requires a manual multiplication (by a factor of 1.8) due to sample type; this requires an employee to double check all calculations. The manufacturer has been requested to build in this calculation but has so far not done so.

Final data entry entails a large number of data fields making it error prone. For this reason double data entry was performed (estimate 45 discordant entries per 200 patient files created - although most in non-critical data fields such as exact spelling of name).

From the perspective of the health facilities, results are not delivered in order of sample (DBS) submission – the lab does not seem to be processing and reporting on a first in/first out basis, although they have been instructed to do so.

Service interruptions: these illustrate the vulnerability of a system relying on a single VL machine, and the effect that long turnaround times for results have on patient management (see later section on optimal timing of VL and responsiveness to HVL).

Table 4: Turnaround times for VL results: Interval between date of venepuncture and date result posted in VLIS (median with IQR) for 3 different calendar quarters

Facility	Q4 2013	Q3 2014	Q3 2015*
Majada	20 (15-22)	21 (15-30)	48 (32-51)
Gutu Rural Hospital	21 (16-23)	20 (14-33)	33 (25-45)
Gutu Mission Hospital	23 (16-28)	24 (18-30)	42 (21-48)
Cheshuro	27 (21-30)	39 (27-43)	42 (22-52)
Serima Mission H	28.5 (20-35)	25 (18-36)	42 (26-52)
Mutero Mission H	27 (22-29)	30 (16-42)	51 (32-55)
Overall for 6 facilities	22 (17-28)	25 (18-36)	40 (23-49)

**During this period the NMRL VL laboratory had repeated interruptions of service related to malfunctioning of the BioMérieux NucliSens machine; delays might have been even greater had ~5000 DBS specimens been sent to Durban, South Africa for processing while the NMRL machine was not running.*

Mitigating factors: (1) the SMS results delivery system is very advantageous if used optimally by health facilities and patients electing to receive SMS result messages, (2) the main cause for delay was machine breakdown which was mitigated by outsourcing tests to a lab in South Africa.

ASPECTS OF VIROLOGICAL SUPPRESSION AND THE INTERPRETATION OF VL RESULTS FOR PATIENT MANAGEMENT IN GUTU DISTRICT

Supporting adherence to ART

Early adherence is known to predict virological failure (Ford, 2010) – bolstering the rationale for early intervention. Adherence is positively associated with the magnitude of VL reduction (Muyingo, 2008).

Pre-ART counseling in Gutu District is not formally evaluated; counselor mentors have the impression of good retention of facts by patients, but more variability in motivation to take ART.

HF not large enough to warrant a Primary Counselor are at a disadvantage; other staff members provide counseling (if trained to do so) but their time is limited by other duties, (including HTC); counselor mentors state there is a need for more primary counsellors;

- Patient literacy level is high so printed materials are used
- SMS adherence support is not used (only for VL results)
- Treatment support for children & adolescents: it is recognized that young PLWHA need extra support for adherence to ART
- Peer support is important but disclosure is problematic due to stigma
- Medication doses can be directly observed for young children but adolescents may simply discard their medication discreetly

It is generally assumed that post-EAC VL is reflective of the effectiveness of EAC, but that is only partly true due to variable contribution of primary or secondary resistance:

- A recent MSF publication found that EAC was not associated with the likelihood of re-suppression (Jobanputra, 2015) Other authors have reported adherence-related re-suppression after virological failure (Gupta, 2014).

Determinants of HVL at M3

Delayed suppression due to high baseline VL;

- This can be generally speculated to occur in children and/or patients with low CD4 counts or clinically advanced disease, in whom VL is likely to be higher than average (Kantor, 2015; Fox, 2012).
- Analysis done by Epicentre/MSF of data collected from population viral load surveys (in Kenya, South Africa and Malawi) shows a very reliable inverse correlation between CD4 and VL among untreated patients; thus some patients could be predicted to have high baseline VL on this basis
- Baseline VL is considered to be distributed log-normally and usually centred around 4.8 or 4.9 logs; about 10% of patients can be expected to have BL VL of 6 logs or higher of whom only about half (meaning about 5% of the total initiating ART) will have VL suppressed to 1000 copies/mL 3 logs) by 90 days on ART (Richard Harrigan, personal communication); other authors have estimated that if baseline VL is 6 logs, time to suppression below 50 copies/ml will be 113 ± 15 days (Rizzardì, 2000).
- Any such adult patients should be suppressed by M6 (the situation may be different for children).

Primary (transmitted) drug resistance: difficult to quantify accurately but perhaps 0-4% in Zimbabwe (Manasa, 2012; Kantor, 2015; Wadonda-Kabondo, 2012] although may be increasing (Cambiano, 2013);

- Some of these patients may suppress to <1000 copies/mL initially due to residual activity in their regimen but will later acquire further resistance and have VL rebound. This could result in a 3M VL <1000 copies/mL but a 12M VL >1000 copies/mL.
- Poor adherence which may promote further acquired drug resistance.
- Very high M3 VL (>5 logs) usually means little or no ART has been taken.
- Intermediate VL (3-4.9 logs) may reflect poor adherence with or without resistance, but VL above 4 logs are increasingly unlikely to simply present delayed suppression due to very high baseline VL.

Clinical response to HVL: In practice, although there is some awareness of potentially delayed suppression due to high (unmeasured) baseline VL and of acquired DR, nurses and counselors work with the assumption that high 3M VL reflects poor adherence. This is reasonable practice as they do not know pre-treatment viral load and/or if primary drug resistance is present and both these factors are beyond their control anyway.

Further analysis of the 2014 Gutu VL cascade data to look at VL suppression post-EAC showed that the likelihood of post-EAC suppression appeared to be related to the magnitude of VL1 and possibly to the interval between VL1 and the first EAC session;

- If VL1 was ≥ 4 logs then VL2 was <1000 only 14% of the time, compared to 68% of the time if VL1 was between 3 but <4 logs, which may reflect high baseline (pre-treatment) VL in this group, and/or greater resistance potential with higher VL and/or greater risk of continued poor adherence (see Table 5).

- Among the subgroup of patients with VL1 >3 log but <4 logs, the median (IQR) interval was much shorter among patients who suppressed post-EAC than among those who did not suppress post-EAC (see Table 6).
- These points together suggest that a VL1 value ≥ 4 logs and/or a long interval between high VL1 and EAC (with any elevation of VL above 3 logs) are associated with a low proportion of post-EAC VL suppression <1000 copies/mL.

Table 5: Suppression of HVL1 after at least 1 EAC session; 91 subjects with VL2 value after at least 1 EAC session

VL1	VL2 (post-EAC) <1000	% VL2 <1000
1000-9999 (41)	28	68.3%
>10,000 (50)	7	14.0%

Table 6: Further analysis of VL1 <10,000 group – note interval between VL1 and first EAC

Subgroup	VL1 Median (IQR)	VL1-EAC interval Median (IQR)
28/41 with VL2 <1000	2275 (1237-3242)	59 (25-87)
13/41 with VL2 ≥ 1000	2548 (1593-4184)	180 (69-394)

Reasons for variability between sites in the proportion of HVL values

Univariate logistic regression followed by multivariable logistic regression modelling of VL1 outcomes shows that VL1 HVL is independently predicted by;

- Younger age - patients older than 20 were 62% less likely to have HVL.
- Male sex - women were 25% less likely to have HVL.
- Reason for VL testing ‘not Routine’ (targeted, often post-EAC) – a non-routine VL test was almost twice as likely as a routine VL test to be a HVL (adjusted OR 1.86 for non-routine VL to be HVL, compared to routine VL).

Variables that were not independently associated with high VL1 were ‘Time on ART’ or ‘Health Facility’, meaning that inter-site variation in the proportion of HVL is related to the sex/age composition of the cohort and the proportion of targeted (non-routine) VL tests among total VL tests.

This analysis is consistent with earlier analysis of data from Buhera & Gutu Districts (July 2013 – December 2014) based on VL from 1751 children <15 years of age; VL1 values were ≥ 1000 copies/mL in 39.8%, 29.4%, and 39.1% of children aged 1-4, 5-9, and 10-14, respectively

Variability in later VL measurements

Since suppression of VL2 after elevated VL1 includes adherent patients with high pre-treatment baseline VL, we also looked at variability in later virological suppression with the hypothesis that suppression would be less frequent, and it may have different predictors.

This was evaluated by looking at VL3 outcomes among patients with elevated VL2 values ≥ 1000 copies/mL; most of these patients will have received EAC (usually required before the VL is ordered) but we did not have data on EAC session dates for this analysis

Univariate and multivariable logistic regression modelling was performed to evaluate predictors of HVL at VL3 (here we mean that VL3 is the follow-up VL measurement obtained after HVL is found at VL2, and the patient is not switched immediately);

- The overall proportion of suppression at VL3 after elevated VL2 was about 50% (this included 3 subjects of 214 who had switched to 2nd line ART so the LR was restricted to those 211 remaining on 1st line ART).
- In this model male sex was no longer a significant independent predictor; reason for test was not included as a predictor since all were non-routine because VL2 was elevated for all subjects in this sub-analysis.
- The only significant independent predictor of high VL3 was the magnitude of VL2 elevation; compared to patients with VL2 ≥ 3 logs but < 4 logs (the reference category), those with VL2 ≥ 4 logs but < 5 logs were 3.6 times more likely to have high VL3, and those with VL2 ≥ 5 logs were 9.8 times more likely to have high VL3; age > 20 was associated with half the risk of high VL3 but with only borderline significance.
- This suggests that continued VL elevation of VL2 and VL3 is more strongly associated with virological factors.
- The proportion of suppression of VL3 is much lower than the initial proportion of suppression seen in VL1 values.

Evidence suggests that high levels of resistance are associated with failure of first line ART (Pinoges, 2015; Manasa, 2013)

Regimen switching was uncommon in this group despite persistent HVL.

GROUPS WITH THEORETICALLY INCREASED RISK OF HVL

Patients with Low Level Viremia (LLV = 40-999 copies/mL here)

The current DBS VL measurements employ 2 DBS per specimen to provide a total specimen of 100 microlitres; results were validated against plasma VL for values > 500 copies/mL (by MSF).

Virologic failure due to antiretroviral drug resistance (DR) is well documented in patients with VL < 1000 copies/ml; among 1965 patients with persistent LLV of < 1000 copies/ml, 30% had regimen-compromising DR mutations (cited in Ryscavage P, 2014); in another study the cumulative incidence of virological failure at 1 year, after 6 months of LLV was 24.2% for LLV 200-499 copies/ml and 58.9% for LLV 500-999 copies/ml (Laprise C, 2013).

The MSF/NMRL Viral Load Information System (VLIS) provided data from all Gutu District sites for the following descriptive analysis;

- Among 5551 VL1 values (first VL measurements) in VLIS, 13.5% fall within 40-999 copies/ml (LLV).
- A 2nd routine value (1 year after the 1st) is available for 324 subjects with a VL1 in the LLV range;
 - The 2nd VL was persistently 40-1000 copies/ml for 21.9% of subjects
 - The 2nd VL was ≥ 1000 copies/ml for 15.1%
- A 3rd routine value (1 year after the 2nd routine VL) is available for 79 subjects with a 2nd VL in the LLV range;
 - The 3rd VL was persistently 40-1000 copies/ml for 24.1%
 - The 3rd VL was ≥ 1000 copies/ml for 15.2%

These data are consistent with what the literature suggests: HVL > 1000 copies/ml accumulates with persistent LLV 40-1000 copies/ml, so LLV is a marker for risk of virological failure (VL > 1000 copies/ml).

LLV does not currently prompt measures to assess or enhance adherence or any non-routine follow-up VL measurements; transmission is possible at VL levels of <1000 copies/ml [same reference].

Option B+ women

Because these women are asymptomatic, often young, often newly diagnosed with HIV, and often have not disclosed their HIV status to partners they may be at increased risk of default, loss to follow-up or poor adherence to ART

A previous analysis of the Gutu Option B+ cohort between April 2013 and June 2015 showed similar proportion of pregnant and breastfeeding Option B+ mothers with 3M VL <1000 copies/mL as non-PMTCT women initiating ART

Patients with intolerance to specific antiretroviral agents

Intolerance leading to poor adherence could be associated with HVL

There are no electronic data on AE per se

There is data on switching of single ARV agents – which may be a proxy for intolerance;

- EFV: there were only 12 single-agent replacements of EFV with NVP suggesting that serious intolerance to EFV is uncommonly reported; other changes were in the context of switching to 2nd line so unlikely to be AE-related.
- AZT: there were no single-agent replacements of AZT; all changes were in the context of switching to 2nd line ART (i.e., not AE-related).
- These data imply that AE from these 2 commonly used agents are an unlikely cause of HVL in this cohort, since if there were a large number of unreported AE resulting in poor adherence or defaulting/LTFU then we would expect more reported AE too. This is consistent with a recent study from Mozambique indicating that AE were not the cause of poor adherence (Maixenchs, 2015).

TB-HIV co-infected patients

Symptoms, pill burden and potential drug-drug interactions could be associated with virological failure

A study in SA (El Khatib et al, 2010) found that patients on concomitant TB treatment were 6 times more likely to be viremic than ART patients not on TB treatment

The cohort of Gutu ART patients treated for TB from 2013 to present was evaluated with respect to virological outcomes:

- Of the currently active cohort of patients with co-infection the overall proportion with HVL was 13.2% which is similar to the general ART cohort
- Of note, 23.2% of TB-HIV patients had died or were lost to follow-up by Q3 of 2015
- Only 24 of those who died or were LTFU had a viral load in TIER.net but this was HVL in 28.6% in 2013 and 47.1% in 2014 (no deaths or LTFU with VL value in 215); this suggests a possible association with lack of virological control and a bad outcome with TB-HIV co-infection

Patients living at a long distance from the nearest health facility

There is evidence that rural location is associated with poorer adherence than urban locations, and that uptake of ART is lower as distance from the HF increases (Cooke, 2010)

There is no database with information on distance of residence from HF; patient files were reviewed at 1 HF to explore the feasibility of such an analysis but these data are very time-consuming to collect and code for distance

The Community ART Groups (CAGs) are a growing programmatic response which partly addresses the inconvenience of long distances for patients. Because only adherent patients with VL <1000 copies/mL can join a CAG it is not clear to what extent a mechanism like a CAG might avert poor adherence among early poorly adherent patients living at some distance (>5 km) from the nearest HF.

Patients who stop (default or LTFU) ART and restart 1st line ART

Literature suggests high risk of DR and increased risk of virological failure.

Close monitoring of VL is strongly advised among patients who return after default or LTFU to detect virological failure due to acquired antiretroviral drug resistance.

STRENGTHS AND WEAKNESSES OF THE CURRENT VL MONITORING SYSTEM WITH REGARD TO THE UVL OBJECTIVE

Structural issues

Strengths

- High degree of autonomy of NMRL as lead agency.
- Feasible funding plans for expansion and continuity of VL services in Zimbabwe in the coming years.
- Use of DBS specimens is appropriate technology to allow decentralized VL measurement.
- SMS results delivery system helps keep TAT lower than paper results delivery.
- Capacity to decrease clinic burden by formation of CAGs for stable patients with VL<1000 copies/mL will manage burden of increasing total cohort size.

Weaknesses

- Low uptake of 1st VL measurement at 3 months according to algorithm (arguably the most important VL measurement).
- Vulnerability to service interruptions – increased TAT.
-

Human resource (including management) issues

Strengths

- Skilled staff who understand the utility of VL.
- Presence of primary counselors at larger centres with GF funding.

Weaknesses

- Variable supervision and mentorship quality, insufficient emphasis on VL-related benchmarks for uptake in general cohort (i.e., not missing the 3 month and 12 month VL benchmarks).
- Limitations of counseling at HF: for complex psychosocial situations that underlie poor adherence, particularly for those <20 years of age. Some situations will require more than individual counseling.
- Limitations of counselors per se: the education and training of Primary Counselors is stipulated by the MOHCC and may be insufficient for counseling complex patients.
- Lack of comprehensive psychosocial care approach to adherence support – beyond facility-based 1:1 counseling.

- Lack of clarity or experience in management of persistent HVL – resulting in prolonged HVL on 1st line ART and low rate of switch to 2nd line ART; a study based on experience at 5 sites in South Africa found that overall 10.1% of patients had switched ART regimens by 5 years on treatment (Fox, 2012).
- Authority to switch to 2nd line ART is restricted to clinicians or mentorship teams; this can be made more efficient by presenting the responsible person(s) with a concise summary of pertinent facts for regular (weekly) review re: possible switch.

Patient-level issues

Strengths

- Detection of treatment failure before immunological or clinical deterioration should minimize HIV-associated morbidity & mortality, if used to guide switching to 2nd line ART (although this is not working to potential yet).
- High uptake of SMS VL results message option among (majority of) patients with mobile phone – usually followed by patient initiated visit to HF if HVL indicated.
- Allows entry to CAGs which have stimulated patient support groups (and with patient-initiated and managed income generation activities) – decentralized psychosocial support.

Weaknesses

- May divert necessary attention to LTFU: the problem doesn't disappear – it moves to the preceding '90' target (coverage of ART); LTFU should be tracked and analyzed along with HVL proportions since patients LTFU are by definition not virologically controlled [consider 'Intention to Treat' type analysis].
- Limited psychosocial support options for <20 year olds with HVL – no HIV+ peer support mechanisms yet.

Epidemiological & virological issues relevant to effectiveness

Strengths

- 3M VL appears optimal for early VL monitoring to minimize resistance to 1st line ART.
- Some patients attain VL <1000 copies/ml with EAC even if VL >4 logs (and some respond even if VL is higher – albeit less frequently).
- Although resistance is high among patients failing 1st line ART, effectiveness of PI-based 2nd line ART still preserved so a good response can be anticipated after switch to 2nd line if adherence is good (Paton/the EARNEST Trial Team, 2014; Hosseinipour, 2013).

Weaknesses

- Persistent low-level viremia (VL 40-999 copies/ml) is associated with antiretroviral DR and virological failure but its presence provokes no change in patient management, no EAC and no VL follow-up; this raises a question about setting the VL goal at <1000 copies/ml – it may be suitable for global program assessment but not for individual patient management.
- Prolonged viremia increases resistance over time with potential weakening of 2nd line ART through cumulative cross resistance affecting NRTI potency.
- Risk of death increases among patients failing 1st line (but not switched).
- Avoid switching to ABC for failure when VL >6 logs (high risk of failure).

Approach to sustainability of the VL monitoring system post-MSF involvement

Strengths/ Central Level

- National roll-out plan.
- MOHCC acceptance of VL as preferred monitoring technology.
- Feasible funding arrangements foreseen for handing over of Gutu District VL cohort.
- Some CD4 budgeted amounts will be shifted to VL.
- Sufficient skilled staff at NMRL to run system.

Strengths/ District Level

- Sufficient staff at HF level to continue VL monitoring system.
- District Medical Officer takes principal responsibility for supervision and mentorship of HF personnel, including VL monitoring (taken over from MSF).
- Largely literate and treatment-educated population increasingly able to demand VL (stimulated by SMS VL messages).
- Mostly MOHCC-run system for specimen collection within Gutu District (MSF currently supplements only the fuel budget).
- Exploration of decentralized VL technologies ongoing (in MSF but supports MOHCC) – could be used to prioritize testing of patients who most need rapid turnaround time (e.g., persons <20 years of age, any targeted VL, including post EAC, M3 VL, VL for pregnant women).

Limitations/Weaknesses/ Central Level

- Weaknesses inherent in 1st line regimen (low genetic barrier to resistance).
- VL monitoring budget will be affected if drug costs rise substantially.
- Despite adequate funding for Gutu District (which will be integrated into GF funded activities) there is overall a national funding shortfall for VL monitoring (2015 MoHCC goal was 21% coverage but actual figure was 5% - mainly attributable to lack of VL platform provision by other partners).
- TAT must be kept low to preserve effectiveness of VL as decision making.
- The health system needs national genotypic surveillance to function optimally (to guide decisions about optimal 1st and 2nd line regimens and switching rules).
- Transport of DBS specimens from Gutu District to NMRL/ Harare is currently done by MSF – alternatives are being trialed by MOHCC/ other partners in other districts. MSF should integrate transport in Gutu within one of those systems long before departure.
- MOHCC is investigating use of the national postal system, which could potentially connect health facilities directly with the NMRL.
- Private courier options (FedEx, Swift) exist and could be contracted with GF funding available for such costs.

Limitations/Weaknesses/ District Level

- Potential for increasing TDR related to increasing cohort of viremic patients failing 1st line ART with high levels of R.
- Potential for increasing acquired DR among patients with LLV.
- More use of 2nd line ART will increase ART costs.

CONCLUSIONS

1. The project strategy is appropriate in order to achieve the UVL objective providing there is emphasis on measuring the first VL at M3, since evidence suggests this is the optimal time for intervention if needed (Kerschberger, 2015).
2. Appropriate and timely adaptations were made principally in response to changes in the evolving environment of MOHCC and partners in Harare that have enhanced the operational capacity and the logistical and financial sustainability of VL monitoring nationally.
3. The UVL objective has been achieved to a moderately high degree across the project, with the proportion of the cohort with VL <1000 copies/ml ranging from 70-92% in 29 HF in Q1 of 2015, but these results need to be considered 'pilot project' results and can be expected to improve over time.
4. The related activities were carried out as originally planned, except insofar as VL measurement was temporarily outsourced to South Africa.
5. The reasons for achievement or non-achievement of the 90% UVL target are likely to relate to some health system issues and some patient-level issues:
 - a. Delayed measurement of VL1 or delayed response to HVL with VL1 contribute to virological failure
 - b. Low-level viremia (40-999 copies/ml) is likely to contribute to HVL if not addressed systematically
 - c. Patients who are LTFU and/or restart ART are more likely to have HVL (Luebbert, 2012), so retention in care is as important as viral suppression among those present
 - d. The most important threat to the UVL objective is poor adherence related to stigma and inability to accept and adapt to the reality of living with HIV, particularly among children, adolescents and young adults among whom major struggles related to autonomy, identity (including sexual identity), and self-worth and personality development are ongoing.
 - i. This demands a comprehensive psychosocial perspective and programmatic response which must necessarily be delegated largely to the community in which the PLWHA lives or PLHIV support organizations – for reasons of feasibility and cultural relevance, and to de-medicalize living with HIV as much as possible
 - ii. The primary counselor or others (nurses) engaging in adherence-related counseling need to work as members within a network of services which work along a spectrum from more psychological to more social services
 - iii. Counselors would benefit from training in group counseling techniques
6. The limitations inherent in the approach:
 - a. Enhanced adherence counseling may have limited benefit (Jobanputra, 2015; Peltzer, 2012), particularly if VL is very high or behavior change is delayed
 - b. Monitoring retention in care is as important as the proportion retained who have VL <1000; a major meta-analysis of virological outcomes of ART in low and middle income countries found that while 'On Treatment' proportions with virological suppression were >80% at 5 years, with 'Intention-to-Treat' analysis this proportion declined to 62% by 4 years (Boender, 2015)
7. The opportunities inherent in the approach:
 - a. SMS VL results delivery to patients is 'state-of-the-art' and every effort should be made to continue and expand it.
 - b. Involving community groups and individuals can enhance the social support that helps support adherence and simultaneously diminishes stigma – this is already occurring in CAGs.

- c. Try various alternative refill systems; not all people might opt for joining CAG but might prefer another easy refill system.
 - d. Advocate and support MOHCC in support for psychosocial programs aimed at enhanced adherence for high risk groups with the explicit rationale, from a health systems perspective, it holds the potential to reduce virological failure including the need for more costly 2nd line ART regimens, and the spectre of increased TDR which could threaten the effectiveness of the current 1st line regimens
8. This component of the intervention can be made more effective by addressing systematic issues such as the timing of VL1, rapid TAT for VL results, systematic switching for persistently HVL, and more comprehensive psychosocial support, particularly for young people.
 9. Some of the factors contributing to a high proportion of undetectable VL in the 'high performing' clinics be replicated in other clinics, including using flagging systems, registers, or visual reminders to ensure that a VL measurement is not missed.
 10. 'Low performing' clinics could learn from 'high performing' clinics within Gutu and in Zimbabwe generally through targeted site visits, mentorship by mentors from high-performing clinics and practical suggestions to help keep track of VL dates, and to correctly interpret and manage VL results.
 11. Low coverage of VL monitoring in the Gutu clinics appears often to result from frequent changes in personnel, busy, somewhat chaotic clinics, and lack of systematic reminders to perform VL testing.
 12. VL coverage could be increased by aiming for staff continuity, mentoring on organizational issues like the timeliness of VL measurement and ensuring that personnel (mainly nurses) understand the importance of VL results and how to act on them.
 13. VL monitoring has good prospects for sustainability after the departure of MSF if national funding for laboratory services is improved to match the volume of testing anticipated, and if independent transportation of specimens from Gutu HF is functional.
 14. Sustainability of VL monitoring can be improved with streamlining data entry in VL laboratories to avoid duplication of efforts and repetitive tasks. These factors will most strongly influence the sustainability of VL monitoring
 15. Certain types of training could improve the sustainability of VL monitoring:
 - a. Expansion of VL laboratory services to several locations in Zimbabwe Support the MOHCC & NMRL in the development of contingency plans in the event of TAT increases > 30 days, to prioritize the kinds of specimens based on risk of HVL (which categories of patient – e.g., age <20 years; which situations – e.g., restart after default or LTFU) that should be processed and resulted first
 - b. Establishment of consensus on ART switching rules and training on implementation of those
 16. MSF could support the activities above plus the development of more comprehensive psychosocial care systems at community level before the end of the project in Gutu to improve the sustainability of VL monitoring, and the efficacy of treatment.

RECOMMENDATIONS

- ⇒ Recommendation 1: Improve the systematic uptake of the M3 VL because it is crucial to early ART management and the avoidance of antiretroviral drug resistance. Health facilities can use visual (e.g., paper clip) or written prompts or VL register for M3 VL & subsequent VL; the In-Charge nurse at each facility can monitor M3 VL for the main cohort (not just 2nd line and Option B+ patients). If M3 VL missed then obtain it as soon as possible after M3; always specify date of next planned VL (adjust timing based on result but always with specific date) Consider exploring the use of VLIS (or future Laboratory Information Management System, LIMS) to generate automatic, facility-specific VL prompts for M3, M12, etc., and for FU 3 months after any HVL value reported (list of prompts could be delivered by SMS for small cohorts, or by email for larger HF with larger cohorts)
- ⇒ Recommendation 2: Advocate for an official MoHCC switch to M3 first VL nationally from M6 for optimal outcomes to 1st line ART, given additional system delays (up to several weeks) adding to TAT and higher likelihood of virological failure ; M3 VL to be emphasized and put on supervision visit template and routine monitoring dashboard
- ⇒ Recommendation 3: Avoid prolonged treatment on 1st line with sustained viremia – this is associated with double the risk of mortality than observed if ART is switched (Petersen, 2015). Switch to 2nd line unless there is convincing evidence that adherence is poor. Develop an algorithm & mentorship on management of HVL after first response (EAC x 2); clarify grounds for 2nd line ART and teach around interpretation of response to 2nd line ART. Switching rules could be systematically implemented and if this is done it can (and should be) readily be evaluated with follow-up VL data. This should be pursued in collaboration with MOHCC counterparts.
- ⇒ Recommendation 4: Manage low-level-viremia (between lower limit of assay and 1000 copies/ml) with EAC and early post EAC follow-up VL measurement.
- ⇒ Recommendations 5: Look for national and regional NGOs or community-based organizations involved with support for PLWHA, and seek expert advice on community psychosocial support development, particularly for children & adolescents, linking these to HF-based personnel such as primary counselors and nurses working in OI/ART clinic. Consider other feasible means of supporting ART adherence based on evidence relevant to SSA, including SMS adherence support; note that this is not only a reminder system, and not a surveillance system – it is a means of maintaining a therapeutic connection between health worker and patient (Lester, 2010); Treatment supporters: these have been shown to enhance adherence and could be complementary to the benefits of EAC and SMS adherence support (Mills, 2014; Chaiyachati, 2014); this could potentially be explored with Zimbabwean NGO partners as a form of peer support, particularly for adolescents or young adults

ANNEXES

ANNEX I: TERMS OF REFERENCE

OVERALL OBJECTIVE and PURPOSE

Conduct an evaluation of the viral load component of the Gutu District HIV/TB project to directly contribute to an immediate improvement of the project, as well as to understand the prospects for viral load monitoring sustainability after MSF departure.

SPECIFIC OBJECTIVES

1. Review the performance of the 29 MSF clinics (including staff and communities served by clinics) in Gutu Province in reaching the project goal of 90% HIV patients with undetectable viral load (UVL), with a view to understanding the related causal factors for success and limitations;
2. Identify learning that will enable capacity building of 'lower performing' clinics in Gutu Province;
3. Assess the sustainability of Viral Load monitoring for Gutu Province after MSF's scheduled departure in December 2016.

The specific objectives can be broken down using evaluation criteria as follows:

APPROPRIATENESS:

- *Is the strategy appropriate in order to achieve the UVL objective?*
- *Were appropriate and timely adaptations made in response to changes in the environment?*

EFFECTIVENESS:

- *To what extent has the UVL objective been achieved across the project?*
- *Were the related activities carried out as originally planned?*
- *What were reasons for achievement or non-achievement of the 90% UVL target?*
- *What are the limitations/opportunities inherent in the approach?*
- *What can be done to make this component of the intervention more effective?*
- *Can the factors contributing to a high proportion of undetectable VL in the 'high performing' clinics be replicated in other clinics? If so how?*
 - *How can 'low performing' clinics learn from 'high performing' clinics within Gutu and in Zimbabwe generally?*
- *What factors can be identified that contribute to a low coverage of VL monitoring in the Gutu clinics?*
- *What measures are needed to increase coverage of VL monitoring in places where it is a problem?*

CONNECTEDNESS & SUSTAINABILITY:

- *How sustainable will VL monitoring be for clinics after the departure of MSF?*
- *What factors will affect the sustainability of VL monitoring?*
- *What further training will be needed to improve the sustainability of VL monitoring?*
- *What else could MSF do before the end of the project in Gutu that will improve the sustainability of VL monitoring?*

EXPECTED RESULTS

- **Inception Report** upon initial review of the evaluation documentation (refer to SEU standard)
- **Participatory feedback** to the project team based on initial findings and observations
- **Intermediary Report**, containing summary of field visit, and first reflections shared with the field teams upon completion of the field visit (no SEU standard – to be discussed)
- **Final Report**, as per SEU standard, including:
 - o A clear indication of strengths and weaknesses of the clinics success in UVL objective
 - o Concrete recommendations on achieving the UVL objective in all clinics
 - o Minimum one example of ‘best practice’
- **A final presentation** including ppt (English Max 10 slides)

TOOLS AND METHODOLOGY PROPOSED

- Review and analysis of project documents
- Review of VL and clinic level data in patient files, electronic databases
- Meeting/discussion/interviews with key-team members at HQ and field levels
- Meeting/discussion/interviews with key-authorities in Gutu
- Meeting/discussion/interviews with clinic staff at selected clinics
- Meeting/discussion/interviews with community leaders at selected clinics
- Meeting/discussion/interviews/focus group discussions with patients in selected clinics
- Observation

RECOMMENDED DOCUMENTATION:

- *Copro, AAP, CPP, Project documents (narrative and logframe)*
- *Situation reports*
- *Trip reports (eg. Visit report from HIV advisors)*
- *Medical reports*
- *MSF report to DGD 2014*

ANNEX II: LIST OF INTERVIEWEES

Sandra Simons, Dr	MedCo MSF Harare
Zee Ndlovu, Dr	Op Res Epidemiologist MSF Harare
Newten Handireketi, Mr	Laboratory Team Leader MSF Harare
Purity Mupenda, Ms	Laboratory Data Entry MSF Harare
Oniwell Nyekete, Mr	Patient Support Mentor MSF Gutu
Tendai Chigurah, Ms	Nurse Mentor MSF Gutu
Chengerai Gumunyu, Mr	Polyvalent Data Team Leader Gutu
Munyaradzi Makari, Mr	Health Promotion Officer Gutu
RGN Dzikite	Nurse Mentoring Team/ Gutu MH
RGN Teerai	Nurse Mentoring Team/ Gutu MH
PC Chikoore	Counselor Mentoring Team/ Gutu MH
RGN Machingura	Nurse Chimombe HC
RGN Makumbende	Nurse Chinyika HC
RGN Dzikite	Nurse Mutero MH
RGN Chongoveza	Nurse Cheshuro HC
PCN Macheka	Nurse Cheshuro HC
PC Progress Chihabu	Primary Counselor Cheshuro HC
RGN Nyanzira	Nurse Chitando MH
RGN Magwira	Nurse Chitando MH
RGN Madheya	Nurse Chitando MH
RGN Mugudhura	Nurse Chitando MH
PCN Chaza	Nurse Matizha HC
PCN Chiwawa	Nurse Matizha HC
PCN Mangombe	Nurse Matizha HC
PC Stabile Mukute	Primary Counselor Matizha HC
RGN Mugauri Mupepe	Nurse Gutu RH
PCN Sibanda	Nurse Serima MH
PCN Gweme	Nurse Serima MH
PC Tongesai Majengwa	Primary Counselor Serima MH

ANNEX III: INFORMATION SOURCES

Principal documents reviewed:

3rd Quarterly Review Meeting 2015 (PowerPoint)

Field Visit PCS Zimbabwe 2013 Final

Log Frame OOD 2014 draft 4
MSF-B Annual Report 2014 draft 7
MSF Belgium 2013 Annual Activity Report
Narrative Report 2014 MSFB Final
OOD Log Frame 2015 Field Final Zim
OOD Project document 2015 Field Final Zim
OOD Project document 2014 draft 3
Q1 2015 Narrative OOD Final
Q2 2015 Narrative OOD draft 3
Q2 2015 Annex
SAMU Trip Report Gutu Project Zimbabwe (May 2015)
Zimbabwe Visit Helen Bygrave (Oct 2014)
Viral Load Cascade –Gutu District (Dec 2014)
Viral Load Toolkit (MSF/SAMU)
Patient OI ART booklet
Zimbabwe Operational & Service Delivery Manual (2014)
Zimbabwe HIV Viral Load Scale Up Plan (2015-2018)
VL per clinic in Gutu District (PowerPoint)
HVL Explanation (prepared by Gutu team)
Zimbabwe VLIS Database [extract prepared by Zee Ndlovu at my request]

Sites visited:

Virology Laboratory, NMRL, Harare Central Hospital (4 Nov 2015)
Serima Mission Hospital (10 & 17 Nov 2015)
Matizha Health Centre (10 & 17 Nov 2015)
Chitando Mission Hospital (11 Nov 2015)
Cheshuro Health Centre (11 & 17 Nov 2015)
Chimombe Health Centre (12 Nov 2015)
Chinyika Health Centre (12 Nov 2015)
Mutero Mission Hospital (12 Nov 2015)
Gutu Rural Hospital (13 Nov 2015)
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ANNEX IV: REFERENCES

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