MAKING VIRAL LOAD ROUTINE

Successes and challenges in the implementation of routine HIV viral load monitoring

PART 2: THE VIRAL LOAD LABORATORY

MEDECINS SANS FRONTIERES

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ABBREVIATIONS

ART	antiretroviral therapy
DBS	dried blood spot
EID	early infant diagnosis
EQAS	external quality assessment scheme
ERP-D	Expert Review Panel for Diagnostics
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
HCV	hepatitis C virus
HPV	human papilloma virus
HR	human resources
LIS	laboratory information system
MoH	Ministry of Health
POC	point of care
QA	quality assurance
QMS	quality management system
RAP	rental agreement plan
ROI	return on investment
SOP	standard operating procedure
SRA	stringent regulatory authority
TAT	turnaround time
TB	tuberculosis
TCO	total cost of ownership
UPS	uninterruptable power supply
VL	viral load
WHO-PQ	WHO pre-qualification
Abbott VL	**Abbott Molecular (Des Plaines, Illinois, USA):** Instruments: m2000sp and m2000rt; Assay: Abbott RealTime HIV-1
Biocentric VL	**Biocentric (Bandol, France):** Instruments: Nordiag Arrow and Fluorocycler (Bio-Rad realtime thermocycler CFX96); Assay: Generic HIV Charge Virale
BioMérieux VL	**BioMérieux (Marcy L'Étoile, France):** Instruments: NucliSENS EasyMAG and NucliSENS EasyQ; Assay: NucliSENS EasyQ HIV-1 V2.0
Roche VL	**Roche Molecular Diagnostics (Pleasanton, California, USA):** Instruments: COBAS AmpliPrep / COBAS Taqman System (CAP/CTM); Assay: CAP/CTM HIV-1 Test V2.0
SAMBA I	**Diagnostics for the Real World (Little Chesterford, UK):** Instruments: SAMBAprep and SAMBAamp; Assay: SAMBA HIV-1 Semi Q Test
Xpert HIV-1 VL	**Cepheid (Sunnyvale, California, USA):** Instrument: Genexpert IV; Assay: Xpert HIV-1 Viral Load

Isabel Corthier

FOREWORD

When I met Juliana, an activist for women living with HIV in East Africa, earlier this year she told me that despite being born HIV positive she was not diagnosed and put on treatment until she was 11. Now, at 23, she is happy and proud to be still receiving first-line treatment in full knowledge that it is working. Juliana knows this because a test shows her viral load – the amount of HIV in her blood – to be undetectable.

Viral load testing is the most important tool that we have to determine whether HIV treatment is having the desired effect. Not everyone is as fortunate as Juliana because this kind of testing is not widely available.

So how can countries today bring routine viral load testing to people on antiretroviral treatment? This is the question that this report seeks to address, based on lessons learned over the past four years in the course of a UNITAID-funded project implemented by Médecins sans Frontières (MSF). The project aimed to establish the feasibility of viral load testing in resource-limited and challenging environments and the extent to which its use can be decentralised.

For much of the last decade, healthcare workers have relied on measuring the CD4 cell count to monitor how people living with HIV respond to treatment. The CD4 cell count measures the blood cells that play an important part in the body's defences against infection and illness.

A patient's CD4 cell count decreases as HIV progresses but recovers when an HIV positive person is put on antiretroviral treatment. Although useful, this test does not quickly pick up what the virus is doing in the body. And as a monitoring tool it is not as effective as viral load testing at indicating treatment failure.

A viral load test quickly detects exactly how much HIV is in the blood. If treatment is not working, the virus will replicate. By monitoring how well antiretroviral therapy is controlling the virus, a viral load test can help prevent a treatment failure and avert a switch to more expensive and toxic second-line treatment regimens.

A Harvard University epidemiologist, Phyllis Kanki, presented the first study to show viral load testing was the only sure way to determine promptly if antiretroviral treatment was not working. Unveiled at a meeting of HIV specialists in 2009, the study prompted a call to make the tests available to all. Their adoption was initially held up by high costs and the challenge of deploying the tests in resource-limited locations.

In 2013, WHO guidelines recommended viral load testing over CD4 count in the monitoring of people on antiretroviral treatment (ART). UNAIDS' 90-90-90 targets call, among other things, for 90 percent of all people receiving antiretroviral therapy by 2020 to have viral suppression, meaning that they have no detectable HIV in the blood. UNAIDS estimated in June 2015 that more than 15.8 million people are accessing ART – but less than 30 per cent of them have ever had a viral load test.

In 2012, UNITAID funded its first grant with MSF to demonstrate the feasibility of monitoring HIV treatment using viral load testing. Almost four years on, this richly detailed report provides guidance on how we can make viral load testing routine for all those on antiretroviral therapy. The authors pull together lessons learned and make recommendations to support countries as they move to viral load testing. A key finding is that viral load diagnostic tools and approaches need to be adapted to the setting they will be used in. Also a key factor contributing to success is to work with clinicians, health workers and people living with HIV in order to create awareness and stimulate demand.

We have a long way to go if we want to reach global health targets. For this reason UNITAID has invested more than US$180 million in the last three years in a range of projects that address the diagnostic needs of countries, assess innovative and adapted solutions, and generate essential evidence to inform countries and global stakeholders on how to invest more effectively in this key area of the HIV response.

The recommendations in this report will prove invaluable for countries seeking to scale up use of this vital monitoring tool.

Lelio Marmora
Executive Director
UNITAID

EXECUTIVE SUMMARY

From 2013-2016 the UNITAID-funded MSF HIV viral load initiative has supported the programmatic and/or laboratory scale-up of viral load testing in seven countries (DRC, Lesotho, Malawi, Mozambique, Swaziland, Uganda and Zimbabwe) performing almost 320,000 viral load tests. The three years of implementation have seen both laboratory and programmatic strategies developed to enhance the uptake of routine viral load. Success withstanding, significant challenges still remain.

Based on a survey performed across ten MSF supported ART sites and seven viral load testing laboratories in February 2016, "Making viral load routine" aims to share practical lessons from the field with Ministries of Health and implementing partners. The report reflects both on the programmatic strategies required within the clinic (for clinicians, counsellors and patients) and the realities of both setting up and keeping a viral load testing laboratory functional in such settings. National viral load scale up plans must link both programmatic and laboratory planning if viral load tests are to be taken, processed and results utilised.

Part 1 of this report, ***Programmatic Strategies***, examines the outcome of the viral load cascade from coverage of routine viral load testing through to an appropriate switch to second line ART. Coverage of routine VL in the MSF supported sites ranged from 32-91% whilst the chance of having a second VL test following an initial high viral load was as low as 23% in Changara, Mozambique, and as high 71% in Chiradzulu, Malawi. In all sites more than half (50-78%) of patients who received a second VL had persistent viraemia > 1000 copies/ml. Although second line initiation rates have significantly increased with the introduction of viral load monitoring, the proportion of patients with persistent viraemia who were switched remained low. To address the leaks in the viral load cascade four essential programmatic investments were identified to make viral load routine: (1) Strengthening of health systems to identify those in need of viral load and enhanced adherence counselling (EAC) (2) ensuring a dedicated health care worker can provide psychosocial support for those with high viral load (3) creating demand for viral load testing through patient education and engagement of civil society, and (4) the decentralisation and task shifting of second line ART provision.

Part 2 of this report, ***The Viral Load Laboratory***, demonstrates that scale up of viral load testing was feasible in these settings. The choice of viral load platform must remain context specific and take into account the ability to prepare and transport specific sample types, the sample throughput and the clinical urgency of the test. Where polyvalent platforms exist, testing needs beyond HIV-VL should also be considered. Although plasma remains the gold standard, if it is to be used in decentralised settings significant investment in both sample transport or establishing the ability to centrifuge and store samples at peripheral clinics is needed. The use of dried blood spot samples (DBS) and near point-of-care technologies (POC) overcame the challenges of sample transport for plasma and significantly facilitated the scale up of viral load. In some settings either because of instability within the country or as an initial phase in the scale up of VL, testing was outsourced to established private laboratories. In some laboratories, prolonged turn-around time of results triggered outsourcing of viral load testing so as to maintain provision of the service for patients. When setting up a laboratory, the option to lease the viral load platform provided cost savings, flexibility and assured service and maintenance provision. Finally those responsible for scaling up viral load also have a responsibility to manage the waste that is produced, an area that still requires technical guidance, regulation and funding.

Our MSF field teams in collaboration with Ministries of Health have made great strides to begin the scale up of viral load testing, developing models of care that optimize the use and benefits of viral load. We hope that learning from the successes and failures documented in this report will result in more patients having access to viral load testing and have the test results acted upon. For the success of this scale up, sustainable funding must be assured, whilst Ministries of Health, donor agencies and implementing partners must develop a coordinated response. If they succeed we may truly make viral load monitoring routine.

Vicente Descalzo

When we started our HIV project last year we did not think that VL would be possible. But by sending DBS samples to a private laboratory in South Africa we have the results back in two weeks. We're now thinking whether it may be possible to use our GeneXpert machine to test for VL. If it's possible here it's possible anywhere.

Dr Vicente Descalzo Jorro, Medical Doctor. Yambio, South Sudan

INTRODUCTION

From 2013 to 2016, through an UNITAID-funded initiative, MSF has supported the development of in-country viral load (VL) testing capacity at seven sites in six countries (DRC, Malawi, Mozambique, Swaziland, Uganda, Zimbabwe).

The objective of the initiative was to generate and document field experience of scaling up VL testing using a range of available viral load platforms. Table 1 outlines the details of the laboratory platforms and sampling techniques used across the MSF-supported laboratories. This report draws on the field experience from these sites and the results of a survey performed in February 2016. In addition to the laboratories supported by MSF, this survey has also drawn on the experience of MSF HIV programmes outsourcing routine VL testing through national and private laboratories in Nairobi and in Durban, allowing further development of VL testing capacity in Kenya, Lesotho, South Sudan and Guinea.

The findings of this report are relevant for both high and low prevalence settings, illustrating that the choice of VL testing platform must be context specific. At the start of this project the only pre-qualified platform for performing VL testing on dried blood spots (DBS) was the BioMérieux VL platform. Now, three years later, improved techniques developed for DBS on other platforms and polyvalent near point-of-care (POC) technologies are becoming available, allowing further adaptations in how we deliver VL testing.

LESSONS LEARNED

- Scale up of HIV viral load testing is feasible in resource-limited settings
- The choice of platform must be context-specific. It should take into account the sample type, volume of samples expected, testing needs beyond HIV VL (e.g. EID, TB) and the clinical urgency of the test
- If plasma is used in decentralised settings, significant investment in sample transport and/or infrastructure to centrifuge and store samples at clinic level is needed. In settings where this is not possible, using DBS or near POC technologies (where throughput, human resources and infrastructure allow) significantly facilitated the scale up of viral load testing
- Near POC technologies allow task shifting to lower cadres to perform sample preparation and testing and provided same day results for 80% of patients
- Outsourcing VL testing to established private laboratories allows VL testing in challenging contexts where no in-country capacity existed, and is important for back-up planning
- Strengthening of laboratory data quality through laboratory information systems (LIS) coupled with innovative result delivery systems is key in scaling up HIV VL testing
- In country maintenance and servicing support must be improved to reduce down-time of testing. Rental agreement plans may facilitate improved provision of maintenance
- Backup planning (e.g. outsourcing testing to another laboratory) is essential and should be triggered by clear criteria (e.g. specified target intra-laboratory turnaround time exceeded)
- Leasing agreements allow flexibility, may encourage better maintenance and facilitate the future upgrading of platforms
- Solutions for waste management have not yet been addressed
- Pooling of procurement across countries supports price reductions. This should be coordinated by international donors

TABLE 1: MSF SUPPORTED VIRAL LOAD TESTING LABORATORIES (2013-2015)

SITE	SETTING OF VIRAL LOAD TESTING PLATFORM	VL PLATFORM	SAMPLE TYPE	VL PERFORMED 2013–2015
KINSHASA, DRC	Hospital Laboratory	Abbott RealTime HIV-1 assay (1 m2000sp, 1 m2000rt)	Plasma	2364*
CHIRADZULU, MALAWI	District Hospital Laboratory and 4 primary care clinics	Diagnostics for the Real World SAMBA HIV-1 Semi Q Test (1 SAMBAprep, 3 SAMBAamps)	Plasma	26,106
THYOLO, MALAWI	District Hospital Laboratory	BioMérieux NucliSENS easyQ HIV-1 assay (1 easyMAG and 1 easyQ)	DBS	39,796
MAPUTO, MOZAMBIQUE	National Laboratory	BioMérieux NucliSENS easyQ HIV-1 assay (2 easyMAGs and 1 easyQ)	DBS	46,080
SHISELWENI, SWAZILAND	District Hospital Laboratory	Biocentric Generic HIV Charge Virale (2 Nordiag Arrow, 2 Bio-Rad Fluorocycler CFX-96 (1 operational, 1 back-up)	Plasma	65,633
ARUA, UGANDA	District Hospital Laboratory	Diagnostics for the Real World SAMBA HIV-1 Semi Q Test (2 SAMBApreps, 5 SAMBAamps)	Plasma	15,391
HARARE, ZIMBABWE	National Laboratory	BioMérieux NucliSENS easyQ HIV-1 assay (2 easyMAGs and 1 easyQ)	DBS	99,180

* Viral load testing in Kinshasa, DRC commenced mid 2015

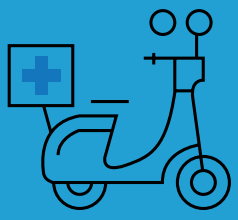
Plasma DBS

CHOOSING A SAMPLE TYPE AND VL PLATFORM

*

LESSONS LEARNED

- Using plasma samples and a centralised platform is feasible but requires substantial investment in sample transport and/or additional investment in infrastructure (cold chain) and human resources (HR) at clinic level to centrifuge and store samples.
- Sending plasma samples to centralised sites resulted in restricting the number of days patients could give blood, leading to patient dropout and reduced coverage of viral load testing.
- Use of near POC testing or DBS samples facilitates daily specimen collection from patients in the clinic and eases the burden of sample transport.
- Near POC technologies (SAMBA I and Xpert HIV-1 VL) use plasma samples, and thus require phlebotomy but – when positioned for patients on site – negate the need for sample transport. Both platforms are capable of providing same day results. In Chiradzulu, Malawi, 80% of patients tested with SAMBA I received their results on the same day. The remaining 20% were tested too late or the clinician was not available in the afternoon to give the result.
- Near POC technologies (SAMBA I and Xpert HIV-1 VL) allow task shifting of sample preparation and processing to non-laboratory technicians.
- Sample transport is under-resourced and efforts are fragmented. Sample transport should be coordinated at national level and planned for all specimen types (VL, EID, TB, haematology, biochemistry). Funding for sample transport is urgently needed.



SAMPLE TRANSPORT MUST BE COORDINATED AND FUNDED

SAMPLE TYPES

The gold standard sample type for HIV VL testing remains **plasma**, which is generated from whole blood through centrifugation. All high-throughput centralised platforms perform VL on plasma, and the two near POC technologies (SAMBA I and Xpert HIV-1 VL) use only plasma samples at present. In the near future SAMBA II VL will use capillary whole blood with plasma separated in the SAMBA II device. Phlebotomy is therefore required to collect an EDTA whole blood sample, and plasma generation requires centrifugation. Current guidance recommends that EDTA blood samples should reach the testing laboratory within 6 hours of collection otherwise plasma must be processed on site and reach the testing laboratory within 24 hours if no cold-chain is available. If cold-chain is available, plasma remains stable at 4°C for 5 days or for a year at -20°C.

Since the generation of plasma comes with challenges, particularly in settings where phlebotomy is not feasible and where sample transport is a challenge, **dry blood spots** (DBS) provide a solution. DBS samples, which can be safely transported and remain stable at ambient temperatures, even above 30°C, have been used as an alternative to plasma. Whole blood is spotted onto filter paper, filling 5 spots, either pipetted from EDTA blood collecting tubes or directly applied through finger-prick. Both these methods have been successfully task shifted to lay cadres (1). The cards are dried and packaged with desiccant bags and humidity indicator cards, which act as a humidity level quality control (QC) measure. Standard operating procedures (SOPs) for these procedures may be found in the viral load toolkit (2).

However, the use of DBS for HIV VL testing also presents some challenges:

1. Currently, only one assay is CE-marked and WHO prequalified for use of DBS – the BioMérieux (BM) NucliSENS easyQ HIV-1 assay. Abbott VL has recently been CE-marked for DBS and Roche is developing a new technique for VL measurement from DBS samples.
2. Sensitivity is decreased due to the lower volume of blood available (50-70 μl), whereas 1 ml of plasma is the norm.
3. Specificity is decreased due to pro-viral DNA (if extracted / amplified – this can depend on the assay) and cell-associated RNA, particularly at lower viral loads (affecting the reliability of the result at the critical WHO recommended 1000 copies/mL threshold for diagnosing virological failure).

The new technique to process DBS samples developed for the Abbott platform has very recently been CE marked but not yet WHO prequalified (with acceptable sensitivities and specificities at a threshold of 1000 copies/ml). The new DBS technique for the Roche platform awaits certification. Thirteen peer reviewed articles for Abbott and one for Roche have been published assessing the sensitivity and specificity of their DBS techniques. However, it should be noted that sample sizes were small across all studies. A systematic review published in 2016 presents this data for all available techniques (3).

THE SAMPLE TRANSPORT CHALLENGE

As specified above, where plasma is used as the VL sample type, strict guidelines must be followed regarding the timing between drawing blood, plasma separation, and how the blood or plasma sample is transported to the VL testing laboratory. These restrictions add additional complexity to an already challenging programmatic component.

In 10 of the 11 sites surveyed, MSF was either directly performing sample transport or funding another actor to do so. Lack of national coordination and a clear funding line for national sample transport systems are major barriers for future roll-out of VL testing. Lesotho has a national sample transport system, coordinated through the NGO Riders for Health, but funding is not assured. The majority of sites have developed national systems for EID specimen transport (using DBS specimens), but these are not coordinated with other sample types and have often been vertically funded.

Sample transport should not be provided independently for each sample type, but should be coordinated across all programmes (sputum, CD4, biochemistry, haematology, EID etc). Not only should sample types be coordinated under one system but this system should also interact with the delivery of consumables and commodities, facilitating the reduction of stock-outs, particularly where an emergency supply of drugs is needed.

The need to address this sample transport challenge is urgent and should be brought to the attention of donors. POC technologies are unlikely to reach every clinic for every sample type, and careful analysis and modelling of the costs of coordinated sample and commodity transport to "reach the last mile" should be performed.

CHOOSING A SAMPLE TYPE: WHAT DID WE LEARN?

- **VL TESTING PLATFORMS RESTRICTED TO PLASMA:** Where VL testing platforms already exist (often already in place for EID) the sample type for VL may be restricted to plasma due to lack of strict regulatory approval and/or WHO pre-qualification to perform VL DBS on the specified platform.

  In Lesotho the platform available at national level was the Roche COBAS AmpliPrep/COBAS Taqman, which currently cannot be used for DBS testing. Clinics in Lesotho are in very remote mountainous areas where sample transport is possible, but a challenge. Using plasma samples would restrict sample collection from the patient to once-weekly, making patients travel long distances to have their blood drawn. To overcome this challenge, a programmatic decision was made to use DBS samples sent to a private laboratory in South Africa for testing on a prequalified platform for DBS.

- **AVAILABILITY OF HUMAN RESOURCES TO PERFORM PHLEBOTOMY:**

  In Thyolo, Malawi, due to limited HR and policy limitations as to who is able to perform phlebotomy, it was not possible to scale up centralised VL testing without using a finger prick technique. In 2012, a study was performed to validate the use of fingerprick DBS prepared by lay workers to ensure adequate accuracy. The study showed similar sensitivity and specificity to when DBS samples were prepared by laboratory technicians (4).

- **AVAILABILITY OF SAMPLE TRANSPORT:** If plasma is to be used, sample transport to a laboratory that can perform centrifugation must be on the same day.

  In Kenya (where MSF sent viral load samples to the MoH VL testing laboratories), both in Nairobi and in rural Homa Bay, use of plasma samples posed challenges for uptake of VL testing. In Kibera, Nairobi, viral load samples were initially taken to the VL laboratory 2 days a week, with patients from three different sites having to attend the laboratory of the central clinic to have blood drawn. This resulted in many patients not attending. The clinic increased to taking samples five days a week, but this resulted in small numbers of samples being transported each day. To overcome this challenge, the clinic purchased a -20°C freezer to store plasma allowing sample transport to occur twice a week.

  In the MSF-supported project in Ndhiwa sub-county from January to June 2015, patients in the larger, centralised facilities had better access to VL testing (76%) than those in the smaller more remote sites (49%) due to the challenges of providing adequate sample transport for whole blood samples from remote sites.

  In Chiradzulu, Malawi sample transport is performed daily for specimens taken at sites where SAMBA I was not directly on site, and in Uganda it is performed twice weekly.

  In Swaziland, to reduce the frequency of sample transport, lay workers at each clinic were trained to perform phlebotomy and centrifugation. All clinics were able to refrigerate plasma samples, allowing samples to be drawn daily but transport to be reduced to twice weekly.

VIRAL LOAD PLATFORMS

Viral load platforms can be classified as: high throughput centralised machines (sophisticated machines requiring infrastructure and skilled HR, some accepting DBS samples, others only plasma); near POC machines (requiring less heavy infrastructure and HR skills but requiring plasma); and true POC testing platforms. Table 2 (centre) outlines the specifications of the platforms used in the MSF-supported laboratories. The SAMBA I system has been the only near POC platform used throughout the duration of the grant and, although recently CE-marked (March 2016), it remains without WHO pre-qualification. The near POC Xpert HIV-1 VL (CE-IVD and WHO prequalification approved), which became available for use at the end of 2015, has the advantage of being a polyvalent platform; it offers testing for TB, EID, HPV, HCV and is developing further testing capacity. True POC VL technologies are not yet on the market despite numerous products named in the pipeline since 2012. In addition to SAMBA II, which is being deployed in the second half of 2016, there are three true POC devices under development but with no clear date for launch and no WHO pre-qualification to date.

WHICH SAMPLE TYPE AND PLATFORM SHOULD I CHOOSE?

This decision will always be context specific. Criteria to consider include:

- Is **phlebotomy** feasible? If phlebotomy is not feasible, finger-prick DBS may be used and a platform accommodating DBS selected
- Is **sample transport for plasma** feasible, without making patients attend on additional days for sample collection (is increased transport frequency or clinic centrifugation and refrigeration possible?) If not, consider DBS or plasma with near POC
- **How many sites** send VL and what is their forecasted **weekly throughput by site and as a collective?** Which platforms or combination of platforms (knowing that more than one near POC machine can be aligned to increase throughput) may meet demand?
- Considering both centralised and near POC, what **infrastructure/space and HR** requirements will be needed to meet demand?
- What and how many **other sample types** are sent from the area served that may also be run on a given platform? For example, EID and TB samples
- Are all samples of equal **clinical priority?**
  - » *VL in a clinically well versus VL in a clinically failing patient – a near POC platform using plasma samples positioned at the hospital level may be the best choice for clinically unwell patients*
  - » *EID in a child whose mother has a suppressed VL versus EID in a child whose mother is not on ART – near POC technologies for EID use DBS samples, so a platform positioned at district level could serve for these priority samples*
  - » *A diagnostic test that will result in an immediate treatment decision (e.g TB diagnosis) versus a monitoring test*

At the start of this project, only one platform was approved for DBS samples (BioMérieux VL) and no near or true POC technologies were available on the commercial market. In Thyolo, Malawi, and all sites in Zimbabwe and Mozambique, collection of plasma samples from all sites was not feasible. Hence DBS was selected as the sample type, limiting the choice of VL platform to BioMérieux until the end of 2015.

In Chiradzulu, Malawi, and Arua, Uganda, SAMBA I was selected to demonstrate feasibility of this new VL near POC technology, tested with close cooperation with the manufacturers to demonstrate sensitivity, specificity and ease of use in field conditions. Biocentric was chosen in Swaziland because collection of plasma samples was feasible, the platform could be used at a district laboratory and it provided experience in using this “open source” platform.

Abbott has since developed an improved technique with better sensitivities and specificities around the 1000 copies/ml threshold for tests processed from DBS samples, and was recently CE marked. In 2016, with increasing choice of platforms, the strategic use of near POC and centralised high-throughput options requires further feasibility studies and may benefit from modelling analysis. However, context is key and each setting must assess the above elements. **One solution will not fit all.**

DIAGNOSTIC FOR THE REAL WORLD, SAMBA I

We designed a floor plan for a mini lab in each clinic that could be copied for all sites. We had enough room for one SAMBAprep and three SAMBAamps. After renovations were carried out, installation of the equipment just took half a day. Training lasted 3 days and most of the operators reported that they felt confident after processing 4–5 runs. What was great is that we managed to task shift using SAMBA I to lay workers recruited from the local village; it hopefully will help with staff retention, which is difficult with the highly trained laboratory technicians. The other good thing is that we managed to give 80% of the patients their result on the same day, and that most patients were willing to wait for their results.

Monique Gueguen, Laboratory referent for Chiradzulu, Malawi, and Arua, Uganda

Guilio Donini

VL PLATFORMS: USER EXPERIENCES

DIAGNOSTIC FOR THE REAL WORLD, SAMBA I

"We designed a floor plan for a mini lab in each clinic that could be copied for all sites. We had enough room for one SAMBAprep and three SAMBAamps. After renovations were carried out, installation of the equipment just took half a day. Training lasted 3 days and most of the operators reported that they felt confident after processing 4–5 runs. What was great is that we managed to task shift using SAMBA I to lay workers recruited from the local village; it hopefully will help with staff retention, which is difficult with the highly trained laboratory technicians. The other good thing is that we managed to give 80% of the patients their result on the same day, and that most patients were willing to wait for their results.

We did have some technical challenges along the way, which were addressed by the manufacturer (changing the shape of the adaptor to reduce interruptions in processing and the problem of cartridge sealing). At present there is also limited manufacturer capacity with an official lead time for equipment and test kits of 4 months (although this can be halved on occasions) and internal challenges for importation. However, ordering is very simple because all consumables are supplied with the kits, which can be stored up to 37°C.

At the end of the day though, the laboratory is very reliant on how well the patient flow is organised. If phlebotomy is done late or the clinician is absent in the afternoon and cannot release the results on the same day, the benefit of POC testing disappears."

(Laboratory referent for Chiradzulu, Malawi, and Arua, Uganda)

CEPHEID XPERT HIV-1 VL

"I found it very simple to perform and quick to learn the technique as we were used to using Xpert for TB and my microscopists can easily run the test. You get the result in 90 minutes and can run four samples independently (EID, TB, VL and HPV in our project). I wish we could use DBS samples as well though, as it would make things easier. Other good things are that there are in-built QC checks and the reagents don't need refrigeration, which is convenient at the peripheral clinics, but we still needed to set up air conditioning and there is no battery run option at the moment. They should change the label on the cartridge as VL cartridges are the same colour as the TB cartridges, so you have to check carefully. Also the way the viral load result is produced by the machine is in exponential format (e.g. 10 000 000 copies is written as 1.0E7 in the printout from Xpert), so we have to then convert it to avoid errors with the clinicians."

(Laboratory technician, Gutu mission hospital, Zimbabwe)

BIOMÉRIEUX, NUCLISENS EASYMAG & EASYQ

"BioMérieux NucliSENS was the first platform approved for DBS testing using a 1000 copies/ml threshold, so we have quite a lot of experience using this platform. Space wise, it requires a relatively small bench-top size and we did not need to have double doors fitted into the laboratories. With two easyMAGs and one easyQ, the throughput is higher than with the other platforms but could be better if the easyMAG could extract more than 24 samples. Also we can store the eluates longer (>24 hours), which is convenient. The QC system is also very convenient as each specimen has an internal control. However if the negative and/or positive control fail, the whole batch of tests must be repeated.

However, there are a lot of manual steps, meaning there is more workload for the laboratory staff. Also, there is no self-contained decontamination system; this would be really beneficial. One other thing that takes additional time is having to manually calculate the correction factor for the haematocrit; why can't this be built within the system?

The maintenance procedures for the user (daily, weekly, monthly) are also quite time consuming. Maintenance has been a challenge but has definitely improved over time as the local engineers have gained experience."

(Laboratory technician, National Medical Reference Laboratory, Harare, Zimbabwe)

BIOCENTRIC

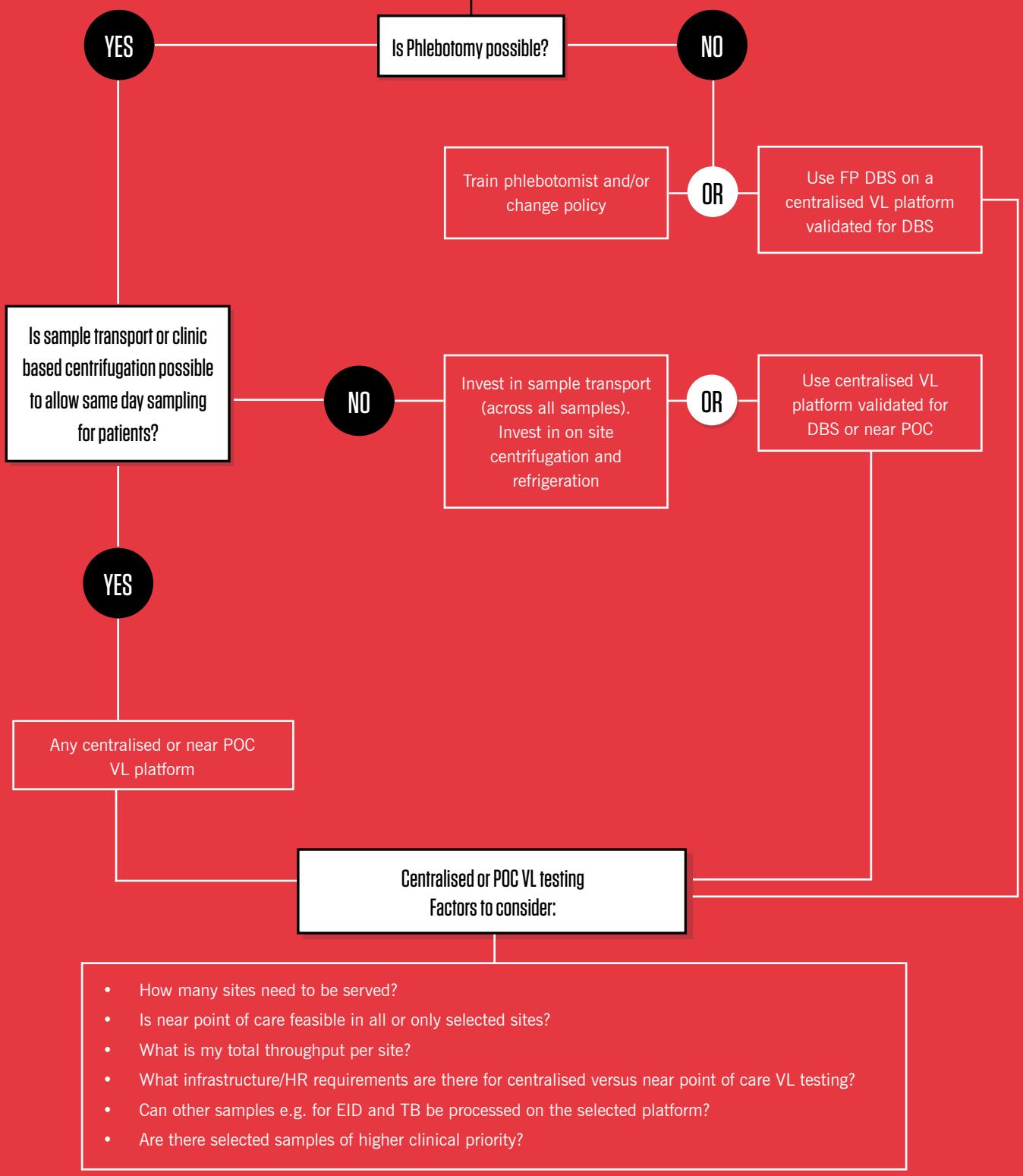
"Our success was that we managed to cover the whole Shiselweni district with a relatively cheap test and demonstrated that with good sample transport that this was feasible using plasma as a sample type in a setting serving 25 decentralised primary care clinics.

What I did not like was the very manual technique, which needs very well trained and experienced staff to perform. It's been really difficult to find and retain staff.

The technique itself does not consist of a "platform" but of several instruments not specifically designed for VL: the two critical ones being the Arrow nucleic acid extractors and thermocycler, the rest being simply centrifuges, sealers and micropipettes. All this makes it an "open" technique but we still needed one supplier (Biocentric) to program the instruments and to configure the reagents in pre-prepared kits. So it's only nominally an "open" platform. If it was really open, getting reagents from elsewhere, the technique would become too complex for routine use."

(Laboratory referent for Shiselweni, Swaziland)

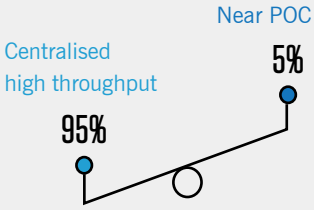
THE TUG OF WAR BETWEEN CENTRALISED AND NEAR POINT OF CARE VIRAL LOAD TESTING



- How many sites need to be served?
- Is near point of care feasible in all or only selected sites?
- What is my total throughput per site?
- What infrastructure/HR requirements are there for centralised versus near point of care VL testing?
- Can other samples e.g. for EID and TB be processed on the selected platform?
- Are there selected samples of higher clinical priority?

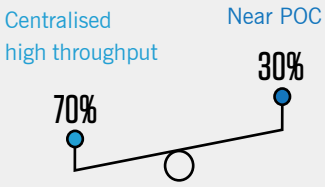
CASE SCENARIOS

SCENARIO 01



- District population 220,000, HIV prevalence 16%.
- Staff can perform phlebotomy.
- There are many sites in the district (25-30) with a high throughput (total: 1000 VL samples per month). Sample transport for plasma samples is not feasible. If near point of care platforms are positioned in " hubs" transport from sites would be limited to once a week. DBS samples are therefore selected as the sample type of choice.
- The existing near point of care care technology used for TB testing and positioned at the hospital has capacity to test priority patients (clinically failing inpatients and exposed babies whose mothers did not receive PMTCT).

SCENARIO 02

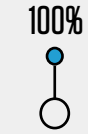


- District population 220,000, HIV prevalence 12%.
- ART cohort 14,000.
- Clinic staff cannot perform phlebotomy except at the hospital.
- There are 2 hospitals and 7 primary care clinics (PHC). 1 hospital and 1 PHC (total cohort 4000) are near to each other and have difficult transport access for three months of the year due to flooding. Daily VL requirements could be met for these two sites with a near point of care technology.
- Throughput at remaining sites is high, and there is no additional funding available to enhance sample transport to more than once per week. DBS will be used for routine viral load testing from the remaining sites.
- At the hospital a near point of care platform is available that could be used for VL testing for inpatients suspected of treatment failure.

SCENARIO 03

- District population 220,000, HIV prevalence 6%.
- Staff can perform phlebotomy.
- There are 6 sites in the district providing ART with a daily throughput of samples that could be met by a near point of care technology. Four sites are very close to each other and daily specimen collection is feasible by motorbike. The remaining two sites are one to two hours by car from the district hospital. Placing one near point of care at the hospital serves four clinics and one at each of the remaining clinics will meet demand.

SCENARIO 04



- This hospital ART clinic is in a low prevalence (2%) urban setting with an ART cohort of 2,100 patients.
- Staff can perform phlebotomy.
- Many complicated patients are referred to this site and the daily throughput required for VL testing is 8 VL tests per day. TB testing is also performed on site.
- Near POC is chosen due to the clinical urgency of testing for the majority of patients in this site. Further modules may be added if demand increases.

TABLE 2: MAKING VIRAL LOAD ROUTINE: EXPERIENCE FROM MSF-SUPPORTED LABORATORIES

Laboratory setting				Specifications of platform											Sample transport system		Setting up the laboratory								Quality assurance		Maintenance				Testing capacity and performance						
Site	Setting of viral load platform	Date established	Number of ART sites served	VL platform	Platform conformation in projects	Test	Regulatory approved sample type	Sample type used in project	Level of automation	Cadre able to perform the test	Size of the machine (WxHxD cm)	Maximum throughput: 8-hour day	Polyvalency	Training	Sample transport system	Frequency of sample transport	Approx time from platform order to functioning laboratory	New building or adaptation of existing laboratory space	Power supply	Water	Storage	HR	LIS	Result delivery format	Internal QC	External QC	In-country technical support available	Most common malfunction and its cause	Response time	Backup planning	Maximum capacity in 8-hour shift with current number of platforms	Annual capacity (240 working days)	Hours worked /day	Annual capacity in specified working hours	VL performed Yr 1-3	Capacity used in working hours 2015 (%)	Error rate (%) Yr 1-3
Uganda; Arua	Provincial hospital	Sep-13	Regional hospital and 2 nearby health centres	SAMBA 1	2 extraction + 5 amplification modules	SAMBA I HIV-1 SemiQ Plasma Test. Gives more/less than 1000 copies/ml	Plasma (WHO pre-qualification in process; Test CE-marked March 2016)	Plasma	Semi-automated	Minimal training for lab technicians; lay workers possible after 10 day training	SAMBAprep 60x60x50 SAMBAamp 40x32x14.5	Using 1 SAMBAprep and 3 SAMBAamps: 48 tests/day	VL semi-quantitative (1000 copies), EID	Training provided and included in initial equipment cost	MSF car/driver	Daily testing on site; twice weekly sample transport for peripheral clinics	6-12 mths	Adaptation of existing building	Generator as a back up for power cuts, plus dedicated UPS for each instrument	Water tank	All consumables are stored in a dedicated container in the hospital compound, plus stock in MSF Kampala pharmacy	2 Laboratory technicians, 1 laboratory clerk, 1 phlebotomist, 1 data entry clerk	Research Electronic Data Capture (REDCap University of Vanderbilt, USA): REDCap is a web-based open source software allowing minor modifcations by users. It has been used off-line in Uganda. REDCap is provided free but installation and maintenance require IT engineer. SAMBA is not integrated to REDCap with all data entered manually. 580 results are released per month in Uganda	Results are released as hard copies and REDCap can produce regular result summary lists. High VLs are manually flagged on the result form	DRW QC panels every 2 months. Continuous QC of 5% of samples tested with a conventional platform. Plasma storage: -80°C freezer. IC band checked with every test. Checks carried out: reagent expiry date, individual checking of cartridges for buffer levels and cartridge integrity. Dedicated QC manager and SOP for QC processes	CDC PT programme	DRW technician is Ugandan	Failure to reach temperature (1 SAMBAprep replaced after 2.5 years), electrical contact defect (1 SAMBAamp replaced after 2 years)	Online assistance within 24 hours (site visit 7-14 days)		80	19 200	7	16 800	2061; 6466; 6864	41%	1.99; 0.54; 0.44 higher error rate in Yr 1 related to sealing defect on cartridge
Malawi; Chiradzulu	District hospital and 4 primary care clinics in rural district	Sep-13	District hospital and 4 primary care clinics in rural district		District hospital and each clinic: 1 extraction with 3 amplification modules			Plasma							MSF car/driver	Daily for sample transport of targeted viral load samples from the peripheral clinics not equipped with SAMBA to the district laboratory	<6 mths in primary care clinics	Adaptation of existing clinic space	Frequent power cuts; Independant UPS 8 hours often not sufficient; plans to install UPS with capacity for 48 hours	Water tanks installed for all primary care clinics	Storage space limited at district hospital, capacity for 250 tests so regular restock from central pharmacy required	District hospital 2 lab techs and 1 clerk; Each PHC 1 lab tech and 1 clerk; none had experience			CDC PT programme	DRW technician is Ugandan	The high staff turnover significantly contributed to frequent SAMBAprep processing delays	Online assistance within 24 hours (site visit 7-14 days)	Sent to neighbouring clinic with SAMBA; only one breakdown in 2015	48 in 1 site	11 520	District hospital 8 hrs; PHC 1 5hrs: PHC 2 6hrs; PHC 3 6hrs; PHC 4 5.5hrs	District hospital 11520; PHC1 7200 PHC2 8640 PHC3 8640 PHC4 7920	District hospital: 1100; 5218; 6027 PHC 1: 491; 2040; 2884 PHC 2: 1478; 2782 PHC 3: 190; 1835 PHC 4: 124; 1937	District hospital: 52% PHC1: 40% PHC2: 32% PHC3: 21% PHC4: 25%	0.44; 0.21; 0.26
Congo; Kinshasha	Referral hospital in capital	Jun-15	MSF HIV cohort at central CHK Hospital in Kinshasa	Abbott VL	District hospital laboratory with one extractor device (Abbott m2000sp) and one amplification device (Abbott m2000rt)	Abbott realtime HIV-1	Plasma DBS: WHO pre-qualification in process; Test CE marked 2016	Plasma	Semi-automated	Laboratory technician	Sp 179x187x124; Rt 34x49x45	93	EID, HCV VL, HCV genotyping	Training provided in country by manufacturer	On site	Not applicable											Yes								2015: 2364	Low prevalence setting - device is used once/week for HIV VL and once/week for EID	
Malawi; Thyolo	Rural district hospital	Mid-2011	Thyolo district (28 sites); Nsanje District (14 sites)	BioMérieux VL (changed to Abbott VL end 2015)	1 easyMAG; 1 easyQ	NucliSENS easyQ HIV-1	Plasma and DBS	FP DBS	Semi-automated	Laboratory technician	EasyMAG 100x65x53; easyQ 42x42x22	1 EasyMAG and 1 EasyQ 140	HPV, respiratory panel, immunocompromised meningitis	Training provided	Motorcycle provided by Riders for Health	Once weekly	12-18 mths	Adaptation: BioMérieux VL machines are accommodated in a very small space	Frequent power cuts; end 2014 very bad due to heavy rainfall	Challenge during set up; power cuts affect water pump	Limited: additional storage is provided at MSF office	Staff redirected to VL testing: 3 trained for BM; a further 2 for Abbott; none with experience	Laboratory Information Management Systems (LIMS CHAI). VL results from the equipment are uploaded into LIMS using a USB port	1 data clerk is responsible for data entry. Results are issued only as hard copy. LIMS prints VL >1000 copies/ml in red but availability of colour cartridges has proved a challenge	Humidity checked for DBS based on the desiccants and the humidity indicator card. QA SOPs in place	CDC programme	Yes	Damage to amplifier cable (m2000rt)	2-3 days		140	33 600	8 hours (1 easyMAG: 1 easyQ)	33 600	9619; 15,416; 14,761	44%	
Mozambique; Maputo	National Laboratory Maputo	End 2013	MSF-supported clinics in Maputo (7) and Changara, Tete (10)	BioMérieux VL	2 easyMAGs; 1 easyQ			FP DBS							By MoH and an MSF driver, by road/car	Once weekly	6-12 mths	Adaptation	Frequent Power cuts		Can store cold-chain material at laboratory and 1 month dry stock; remainder at MSF Supply	3 Laboratory technicians; 2 data clerks	VLIS as below	Individual results are delivered by hard copy twice weekly from national laboratory to district sites. Individual results are automatically flagged using smiling or sad faces to indicate < or > 1000 copies/ml. Monthly summary result lists are generated in hard copy and can be emailed for each clinic highlighting high VL results	Samples rejected due to poor quality or sample identification or inadequately filled request forms. Humidity monitors are used to maintain humidity levels within the laboratory and humidity indicator cards accompany the DBS cards to monitor humidity levels of the samples. The laboratory manager acts as QC manager	CDC programme	Yes	Failed amplification due to power failure	2 days and service offered is of good quality and consistent	Send samples to private laboratory in South Africa	280	67 200	8 hours 2 easyMAGs: 1 easyQ	67 200	1595; 16,171; 28,314	42%	15; 2; 2
Zimbabwe; Harare	National Laboratory Harare	Sep-13	Routine VL Buhera district (28 clinics), Gutu district (19), Chikomba district (13); targeted VL Nyanga district (19), Harare central hospitals	BioMérieux VL for DBS samples and uses existing Roche platform for EID and plasma VL where feasible	2 easyMAGs; 1 easyQ			EDTA DBS							Environmental health technicians (motorbike, fuel paid by MSF) or Riders for Health from clinic to district; MSF car from district to capital; plan to transfer to DHL	Once weekly	6 mths	Adaptation	Occasional power cuts but UPS 8 hours insufficient	Challenge in initial set up; now constant	Limited: 2 weeks of reagents	6 Laboratory scientists; 4 data clerks	Viral Load Information System (VLIS), developed at cost to MSF but available free. VL equipment is not connected to VLIS. VLIS is matched identically to the format of the VL request form. Samples are identified using bar codes placed on specimens when DBS are spotted. VLIS requires Microsoft Access. Four data clerks are employed to encode (approx 4474 results/mth). In pilot site has been double data entry for research purposes	As for Mozambique, plus where consent is given (indicated on the VL request form) an SMS is sent to the patient with a message saying everything is fine or advising to attend the clinic as soon as possible. High VL results are SMSed to the clinic	Humidity levels are monitored within the laboratory and maintained using a hygrometer. NMRL aiming for ISO 15189 accreditation through SLIMPTA. There is a dedicated QC manager. EQA VL samples sent to CDC proficiency testing scheme	CDC programme	Yes, but need capacity building	Pump failure, liquid level sensor failure, lamp failure, calibration failure. Average 3 break-downs in 2015	Average response time from local representative 3 days; generally, local rep has no spare parts	Send samples to private laboratory in South Africa	280	67 200; 2 shifts run 134 400	8 or 16 hours according to demand (2 easyMAGs: 1 easyQ)	67 200 or 134 400	10,055; 35,439; 53,686 + 4577 (outsourced)	80% of one shift	9; 15; 3
Zimbabwe; Gutu	2 District hospitals and 1 rural clinic	Installed mid 2015; in-country validation phase completed; feasibility studies starting 2016	Routine VL in Gutu (1 district hospital, 1 rural hospital and 5 clinics)	Xpert HIV-1 VL	4 module device in each setting	Xpert HIV-1 Quantitative	Plasma (undergoing WHO pre-qualification; CE-marked)	Plasma	Manual sample preparation with automated testing. <5 mins hands-on time during sample prep	Minimal laboratory training (e.g. microscopist)	Four modular system 27.94 x 30.48 x 29.72	Four module device 24 (90 mins/test)	TB and rif resistance, EID, CT/NG, HCV, HPV	Training included in the price	On site	Not applicable	< 6 mths					No additional staff employed: existing microscopists perform tests			The district lab is enrolled in proficiency testing with the NMRL. Each Xpert HIV-1 Quant reagent cartridge is a self-contained test device with internal controls and PCR reagents						The GeneXpert GX4 has an average optimal daily capacity of 16 samples in an 8-hour day with results accessible within 90 minutes						Feasiblity phase started early 2016	
Swaziland ,Shiselweni	Nhlangano rural District Hospital	2012	Shiselweni district (25 sites)	Biocentric VL		Generic HIV charge virale	Plasma	Plasma	Manual method. Only automated process is RNA extraction	Laboratory technician	40x45x46	40	HIV-2VL, TB, HBV VL.	On-site training offered	MSF-facilitated transportation/car from the clinic to the laboratory	Twice weekly		Adaptation				At hospital: 4 laboratory technologists, 2 phlebotomists, 1 data clerk; at each PHC: lay-worker to perform phlebotomy and centrifugation	Biocentric Database. VL platform is not directly connected	Individual hard copy results are generated with no flagging system. Monthly summary reports can be generated for each site. 3000 results are released monthly with 1 data clerk	IQC added during the extraction and amplification phases. The standards and controls supplied by the manufacturer are extracted and amplified in each run. Regular calibration of the equipment. Annual revision of SOPs. Frequent training. Annual maintenance certificates are provided by the manufacturer and external companies for smaller devices. The project has an assigned QC manager	CDC programme	Not available locally	Failures in standard and controls during extraction. Arrows extractors failing			150	36 000	8	36 000	17,179; 21,487; 26,967	75%	

TABLE 2: MAKING VIRAL LOAD ROUTINE: PROJECTS PERFORMING ROUTINE VL USING NON-MSF-SUPPORTED LABORATORIES

Laboratory setting				Specifications of platform		Sample transport system	
Site	Setting of project	Number of ART sites served	VL laboratory used	VL platform	Sample type used in project	Sample transport system	Frequency of sample transport
Mumbai, India	Urban	1 Clinic	Private laboratory	Roche VL	Plasma	Independent collection by the private laboratory, from the clinic by car/land transportation	Twice daily
Nairobi, Kenya	Urban	2 Primary care clinics	MoH VL programme			MSF car/driver	Twice weekly
Ndwiwa, Kenya	Rural	32 clinics	MoH VL programme	Abbott VL	Plasma	MSF motorcycle system from collection site to plasma separation site; EGPAF transports the frozen plasma samples from the separation site to the referral laboratory	Daily
Roma, Lesotho	Rural	10 Clinics	Samples sent to: Global Clinical and Viral Laboratory, Durban South Africa	BioMérieux VL	EDTA DBS	Motorbike courier provided by Riders for Health once or twice weekly (MSF funded); DHL to laboratory in South Africa	Once/twice weekly
Yambio, South Sudan	Rural	Mobile outreach approach	Samples sent to: Global Clinical and Viral Laboratory, Durban South Africa	BioMérieux VL	EDTA DBS	MSF plane to Juba. DHL to laboratory in South Africa	Every 2 weeks

SETTING UP A VIRAL LOAD TESTING LABORATORY

LESSONS LEARNED

DO I NEED TO SET UP A VIRAL LOAD TESTING LABORATORY?

- Outsourcing VL testing was a successful alternative:
  - » Where there was no possibility or need to set up in country VL testing in the near/medium term
  - » To support phased implementation of VL, focusing on programmatic issues before setting up in-country laboratory capacity
  - » To act as back-up testing, allowing response to increasing demand, breakdowns and stock outs

SHOULD I PURCHASE OR LEASE MY VIRAL LOAD PLATFORM?

- Leasing controls costs and allows flexibility to change platforms as technologies develop
- Leasing is only feasible where throughput is high
- Leasing may incentivise local distributors to provide timely service and maintenance
- Leasing allows for the inclusion of maintenance costs within the leasing fees, ensuring that maintenance is paid for, which is not guaranteed when platforms are purchased or donated

INFRASTRUCTURE REQUIREMENTS

- All sites required adaptations taking 6–12 months to place the selected VL platform
- Near POC technologies were easier to install but still required infrastructure investment for power, air-conditioning and water supply
- Finding sufficient space (and for some platforms the need for separation between extraction and amplification) was a major challenge and limited the number and choice of devices that could be installed
- Power cuts were a problem in all sites. Uninterruptable power supply (UPS) systems with longer backup or positioning two UPS in series should be recommended to avoid down time related to power cuts
- Providing sufficient storage space for consumables was a challenge

HUMAN RESOURCES

- Availability and retention of trained laboratory technicians is a challenge for VL testing
- Near POC technologies allow task shifting to lower cadres
- Data clerks must be budgeted for and adequately trained to ensure sample and result flow is efficient

LABORATORY INFORMATION SYSTEMS (LIS)

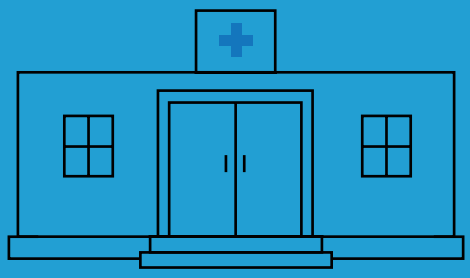
- Ideally LIS for VL should be incorporated into a LIS for the whole laboratory. This has not been possible in our sites due to funding limitations and time constraints
- Direct connectivity of results from the platforms to the LIS is recommended to reduce transcription errors
- LISs should be programmed to produce outputs that are useful for laboratory and clinical management
  - » Monthly reports for laboratory use: samples performed, turnaround time etc
  - » Flagging of high VL results
  - » Monthly lists by clinic – flagging high VL results
  - » User-friendly search functions for result queries

QUALITY ASSURANCE

- Transparency on the timing and duration of the quality assurance processes has had a significant impact on the decisions to place platforms in specific settings

WASTE MANAGEMENT

- Waste management demands more attention as VL testing is scaled up
- Compounds generated by VL testing include guanidine thiocyanate, a compound defined as acute toxic level 4.
- It is estimated that 10 mg of cyanide – coming from guanidine thiocyanate – will be present in every kg of waste from the Roche, BioMérieux and Abbott VL platforms
- Clear SOPs for adequate incineration processes should be urgently developed and funded



6 - 12 MONTHS

is the time all sites took to complete the infrastructure requirements to place the selected VL platform

DO I NEED TO SET UP A VIRAL LOAD LABORATORY?

> *"In South Sudan access to viral load testing is extremely limited and very costly. Sending DBS samples to a private laboratory in South Africa allowed us to monitor our patients. Patients felt proud to have an undetectable VL and we could give additional support to those failing. We get the results quicker than some of my colleagues in Malawi who send their tests to their own laboratory."*
>
> **(Cecilia Ferreyra, HIV advisor, MSF Spain)**

Many low- and middle-income countries have strong ambitions to expand HIV VL testing but face financial and implementation challenges. Factors to consider when deciding to set up or strengthen VL testing capacity in a given setting include:

- An accurate and reliable forecasting of the number of tests required. This should be taken from national estimates of ART cohorts in conjunction with estimates of coverage during the first phases of VL implementation (see programmatic report)
- The contextual factors that may influence the efficient running of a VL laboratory network including:
  - *economic and political stability of a setting,*
  - *readiness for manufacturers to offer the desired procurement and maintenance schemes to their systems, and*
  - *availability of trained HR to perform VL testing*
- Mapping of the existing VL laboratory network:
  - *How much of the demand could already be met through maximising the use of existing polyvalent platforms that may be in place for other programmes such as EID and TB?*
  - *Do existing platforms allow the use of a feasible sample type and transport system to support VL scale-up?*
- Are there options to use private laboratory testing capacity in country or out of country? If yes, are the VL testing platforms available certified to process the chosen sample type?
- What are the costs associated with laboratory upgrades and acquisition of equipment and reagents? How sustainable is the set-up compared with costs of referral testing and sample transport?

MSF HAS USED OUTSOURCING OF VL TESTING IN FOUR SCENARIOS:

SCENARIO 01: DBS NOT AN OPTION IN COUNTRY

As the primary strategy for routine VL testing where existing platforms were not validated for DBS and there was no short- to medium-term solution to introduce new platforms (e.g. Lesotho).

In Lesotho, existing VL testing platforms (Roche VL) were not validated for DBS samples. To scale up access to VL testing in some of the very remote mountainous sites, DBS sampling was felt to be more appropriate to allow everyday sampling and simplify sample transport. Therefore, DBS samples were outsourced to a high throughput private laboratory with a validated platform (BioMérieux) for DBS in South Africa. Results were received by email within 2-3 weeks, with the local team printing results for distribution. Tests were charged at US$13/test plus a courier (DHL) charge of $4/batch, a price comparable to that of in-country testing.

SCENARIO 02: UNSTABLE CONTEXTS

In conflict settings where there is no in-country testing capacity and barriers to establishing VL testing laboratories are too high (South Sudan). In other unstable settings (Eastern DRC and Central Africa Republic), near POC technologies are now being considered.

In Yambio, a rural district in South Sudan recently affected by increasing conflict, mobile outreach teams are providing ART to the population. Through an outsourcing approach, VL monitoring has also been provided. EDTA DBS samples are prepared by nurses in the field and sent via MSF transport to Juba. Samples are then sent by courier (DHL) in batches of approximately 50 samples to a private laboratory in South Africa with results being received by email within 2-3 weeks. Tests are charged at $13/test plus a courier charge of $15 per batch.

SCENARIO 03: TO BUILD PROGRAMMATIC CAPACITY

As the first step of a phased implementation plan for national VL scale up (Zimbabwe).

In Zimbabwe, VL testing was initiated by outsourcing testing to a private laboratory in South Africa in 2011. This allowed time to build capacity and create demand at clinic level and establish sample transport whilst the infrastructure requirements for in-country VL testing were made. Once in-country laboratory capacity was established at the national reference laboratory, a phased shift of samples was made to in-house testing. (Fig 1). The option for outsourcing remained as a backup.

VL TESTING IN ZIMBABWE

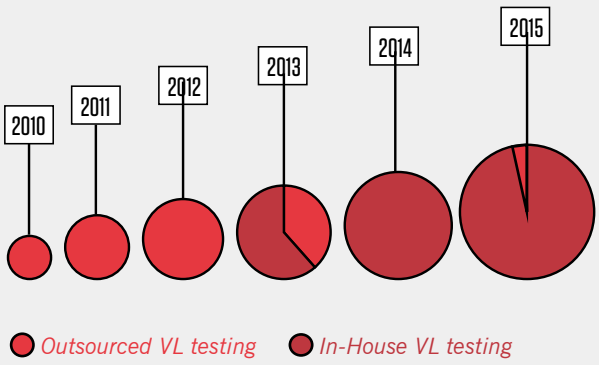


Fig 1: In country and outsourced VL testing in Zimbabwe

SCENARIO 04: BREAKDOWNS OR STOCKOUTS

As a backup when there are machine breakdowns or reagent stock-outs (Zimbabwe, Malawi and Mozambique (see page 29).

SHOULD I PURCHASE OR LEASE MY VIRAL LOAD PLATFORM?

During the project, VL testing platforms were procured through three modalities: direct purchase through the headquarters of the manufacturer; direct purchase through a regional subsidiary (with maintenance contracts at HQ or local level); and through a rental agreement with the local distributor (but negotiated with the manufacturer). During the direct purchase process, costs such as transport, import taxes, distributor margin and ongoing maintenance were not included in the purchase price but added considerable extra cost, approximately 20% in addition to the purchase price. At the same time, the majority of sites reported that local distributors were poorly motivated to service the VL platforms and lacked knowledge and access to spare parts in country.

The leasing option was considered when the laboratories in Malawi and Mozambique were switching from BioMérieux to Abbott platforms to align with national scale-up plans. Table 3 summarises the pros and cons experienced during the set-up of the lease agreement.

PROS OF LEASING	CONS OF LEASING
No equipment acquisition, reducing up-front investment	Service and maintenance contract has to be set up with the owner of the equipment and the distribution network service
Provides flexibility to swap instruments after the initial installation (in case of technological upgrade, or change of standards and recommendations)	This contract cannot bypass the local distributor margin. Over the duration of the contract, this results in slightly higher costs than purchasing the machine up front because of financing costs
A rental agreement gives a global price per unit (test, rental cost, service and maintenance included). This total cost of ownership (TCO) approach, allows better cost control and more accurate budgeting, and may facilitate negotiation with donors to cover the totality of TCO expenses and not limit grants to provision of reagents only	A volume commitment is required, because the manufacturer and distributor want to ensure return on investment (ROI). This commitment may, however, be renegotiated downwards as time passes, as more direct competitors enter the market
This all-inclusive approach also ensures that the local distributor is well incentivised to have the machine working (they are responsible for the maintenance, and any downtime means less tests sold)	Linked to the ROI, currently the leasing option is only offered (by the manufacturers) in high HIV prevalence countries/sites with large ART cohorts. In the low prevalence country where a leasing contract was discussed, throughput was too low to make a leasing deal feasible either for MSF or at country level

Table 3: Pros and cons of leasing a Viral Load platform

HOW TO LEASE?

The lease "bundled" price is negotiated based on:

- The base price, which is the purchase price per test including reagents and consumables
- The leasing cost including service and maintenance costs. This cost is based on the volume commitment to guarantee the ROI. However, a clause may be set that a fixed fee is paid if the minimum threshold is not met
- Delivery Duty Paid incoterm (shipment to final destination, clearance paid and delivery to site)
- Distributor commission. This can be difficult to negotiate and evaluate. This is key to ensuring that the local distributor is incentivised to provide quality maintenance service, but it should not be overinflated. Including the manufacturer in the negotiation facilitated setting this cost.

CASE STUDY: PLACING ABBOTT PLATFORMS IN MALAWI, MOZAMBIQUE AND DRC

The laboratories in Thyolo, Malawi, and Maputo, Mozambique, were initially set up using a BioMérieux platform as the only prequalified system able to process DBS samples. In 2015, with the introduction of the new technique for DBS on the Abbott platform and the national programmes' choice to use Abbott technology, MSF decided to change to an Abbott platform in order to be able to integrate the MSF-purchased devices into the national plans and to allow supply of reagents from the government. In Kinshasa, DRC, the VL laboratory was only established in 2015 and an Abbott platform was selected to align with the platform selected at national level.

A target price for leasing was set for $15 per test plus $1.2 for the rental and maintenance.

Annual tests performed in each site were estimated as follows: DRC 8,000; Malawi 30,000; Mozambique 25,000

Due to the low testing volumes in DRC, a rental agreement plan (RAP) was not considered feasible by the manufacturer. A discounted price was negotiated and a separate maintenance agreement was signed with Abbott.

In Malawi and Mozambique, a RAP was negotiated. The price included:

1. Reagents
2. Consumables
3. Instrument leasing
4. Service and maintenance
5. Shipment to the country
6. Distributor commission
7. Custom clearance paid
8. DBS reagents for the open mode protocol
9. Delivery and installation to the MSF laboratory

INFRASTRUCTURE REQUIREMENTS

Scaling up VL testing in resource-limited settings has the potential to overwhelm public health laboratory services, some of which are already aging and have inadequate infrastructure and human resources. Apart from the laboratory in Arua, Uganda, all of the VL platforms were installed by adapting existing space in established district or national laboratories. Where SAMBA 1 was installed at the four primary care centres, complete rehabilitation of an empty room was carried out with a standard floor plan designed for all sites. Efficient ventilation was also ensured along with reinforced roof insulation to maintain the temperature below 35°C. SAMBA 1 does not require the installation of air conditioning like the centralised platforms or Xpert HIV-1 VL.

All sites required investment in water supply during initial set-up and most experienced frequent power cuts. UPS systems installed were reported as often inadequate to ensure continuous processing of samples across all sites. Storage for reagents and consumables was also raised as an issue with the cold chain storage area needing full rehabilitation in some sites such as Zimbabwe. Where VL testing is further decentralised, storage volume capacity for cartridges and other consumables should be considered. Table 2 describes the infrastructure investments made at each site.

HUMAN RESOURCES

With the introduction of VL testing, each site must allocate sufficient human resources to ensure throughput. Additional human resources for data entry have also been essential to ensure efficient flow of samples and results. All sites had difficulties identifying and retaining qualified laboratory staff. Infrastructure challenges such as frequent power cuts and stock-outs of consumables also contributed to staff demotivation. Centralised platforms with increasing levels of automation reduce the staffing requirements, but where DBS is used the elution processes still must be performed by skilled laboratory technicians.

Near POC technologies have allowed task shifting of VL testing as demonstrated in Chiradzulu, Malawi. Community workers received a 2-week structured training on SAMBA I operation. Samples were tested in parallel by a laboratory technician and the trained community worker and outcomes compared. Overall agreement between community workers and laboratory technician test results was 98.3% (CI 95%:

95.2-99.7). No invalid SAMBA results were obtained (5). Xpert HIV-1 VL has also been performed by non-laboratory technicians previously trained as microscopists. Salaries for these additional human resources have been provided through the MSF-UNITAID VL initiative, and the need for ongoing funding for additional personnel must be recognised. Table 2 summarises the additional staff recruited to set up the VL testing laboratories supported by MSF.

LABORATORY INFORMATION SYSTEMS (LIS)

Clerical errors at the pre-analytic and post-analytic stages of VL testing form the bulk of errors in laboratories. Different electronic LIS were implemented in the MSF sites conducting VL testing. One was developed specifically by MSF (VLIS), one by Clinton Health Access Initiative (LIMS) and one by Vanderbilt University (RedCAP). The LIS were used for patient specimen registration, result entry, searching existing patient records and regular reports. Table 2 outlines further details of the LIS used. There is a need for future investments into LIS which can be integrated with other laboratory services, and for direct input of tests results from the platforms to LIS. Challenges include high cost of LIS solutions, high maintenance costs, service expenses and lack of trained IT professionals.

Two features developed in VLIS and in LIMS that were reported positively by the clinical teams were the ability to have automatic flagging systems for high VL results (smiling/sad faces or VL results >1000 copies/ml in red) and the production of automatic lists for each clinic highlighting those patients who had high VL that could be used for tracing, clinical management and supervision.

In Zimbabwe automatic exports from VLIS were used to send SMS results to both patients and clinics. Content of the message for patients with VL <1000 copies/ml indicated that the patient was doing well and if VL was >1000 copies/ml to visit the clinic as soon as possible. No reference to "viral load" itself was included in the message. A study to assess the impact of SMS of results on the viral load cascade is ongoing.

QUALITY ASSURANCE (QA) FOR VL TESTING DEVICES

Several regulatory bodies exist for assessing *in vitro* diagnostics. These include WHO pre-qualification, the US Food and Drug Administration (FDA), and notified Bodies for CE marking in the European Union. Furthermore donor procurement policies, including GFATM, require strict regulatory approval from one of the founding members of the Global Harmonisation Task Force and/or WHO PQ.

However, many of these processes are very lengthy and do not have time-bound deadlines. To address these delays and accelerate the availability of products urgently needed for patient management, the Expert Review Panel for Diagnostics (ERP-D), led by GFATM and UNITAID, was established in 2014 to assess the potential risks/benefits associated with the procurement of diagnostic products that may have a high public health impact but have not yet undergone a stringent assessment, either by WHO pre-qualification or by a stringent regulatory authority (SRA). ERP-D risk/benefit assessment does not replace WHO-PQ/SRA assessment, but should be seen as a step towards a WHO-PQ full regulatory review. After review, products are classified according to risk-benefit analysis, and categorised into four sections:

Risk category 1 and 2 = Approved for time-limited procurement

Risk category 3 = Approved for time-limited procurement only if there is no other option and the benefit of diagnosis for clinical management is higher than the risk of using the product

Risk category 4 = No procurement may occur under any circumstances

GFATM/UNITAID request that WHO organise a ERP-D round for selected diagnostic technologies. The ERP-D is hosted by WHO and advises GFATM, UNITAID and other partners, as relevant, on the use of grant funds for procurement of such diagnostic products for a time-limited period. To date, all the centralised devices discussed in this report are WHO prequalified for official diagnostic use with plasma, with only one for DBS – BioMérieux. Abbott VL is now CE marked for DBS but awaits WHO-PQ. SAMBA I is CE-marked and Xpert HIV-1 VL is CE-marked and WHO prequalified. During the period of the grant, the decision to select a particular platform has therefore been driven by the regulatory approvals to use a specific sample type on a specific VL platform. With the exception of ERP-D, where an outcome is given 4 months after an application is made, one of the greatest challenges has been to obtain a transparent and reliable estimate of the timing of these processes, which has resulted in significant delays in implementation, particularly when trying to align with national VL scale-up plans.

WASTE MANAGEMENT

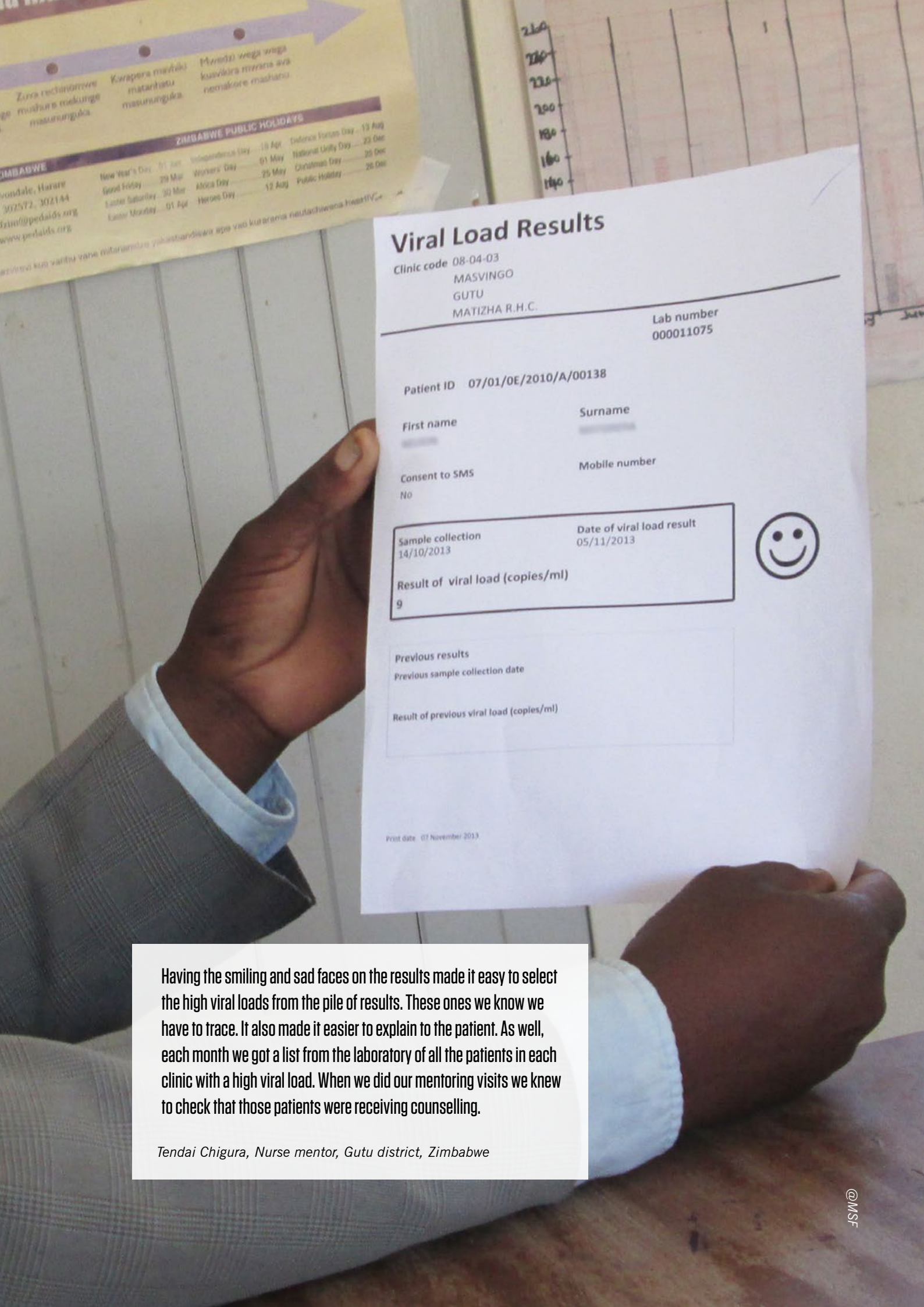
Waste management includes the collection, transport, treatment and safe disposal of waste in conjunction with monitoring and regulation of the process. Waste from the process of VL testing, if not managed correctly, poses a significant threat to the laboratory staff, environment and local inhabitants. According to the SOPs provided by the manufacturers, all waste generated by a VL laboratory should be considered as hazardous. However, no exact plan of disposal is issued, except a disclaimer to the effect of "follow hazardous chemical waste management according to the health and safety legislation of the country in which testing is being performed." Furthermore, since these technologies are still new, consideration of specialised waste management has not yet been formally included in testing policy.

Reagents to run VL testing include guanidine thiocyanate, Triton X-100 and 2-amino-2-(hydroxymethyl) propane-1,3-diol hydrochloride. Guanidine thiocyanate is present in the chemical waste generated by the Biomerieux VL, Abbott VL, Biocentric VL, Roche VL and Xpert HIV-1 VL, with the exception of the SAMBA I. Guanidine thiocyanate is a chemical compound used as a general protein denaturant, most commonly used in molecular biology for the extraction of DNA and RNA. Contact with acids and chlorine liberates a highly toxic gas. Further analysis of the chemical waste generated by HIV VL testing performed by a waste management company, revealed the presence of high levels of cyanide (10,000.00 ppm). It is estimated that around 10g of cyanide – coming from guanidine thiocyanate – will be present in every kg of waste from the Roche, BioMérieux, Biocentric and Abbott VL platforms.

Of the MSF supported sites, Zimbabwe is one of the few countries that provide a national regulatory framework on the issue of laboratory waste disposal. The Environmental Management Agency of Zimbabwe is the government department that oversees the provision and assurance of the implementation of hazardous waste management, established as an official regulation in 2007. MSF subcontracts a local, in-country waste management company to ensure that waste is being disposed of correctly.

VL waste must be incinerated at a temperature of at least 850°C within the second combustion chamber with a retention time of 2 seconds. An important parameter to respect is to not include more than 6% V/V of hazardous chemical waste per incineration cycle to avoid unexpected temperature collapses. Compliance with such regulations poses a significant challenge in resource-poor settings. For example, ensuring that adequate incineration temperatures are met already poses significant challenges. Advocacy and technical guidance towards governments to improve their incineration capacity or liaise with private industries that have such capacity (e.g. cement industries) must be taken into consideration when establishing VL testing capacity.

> *"Since 2011 up until today the waste from the molecular laboratory was disposed of by diluting it with water and then pouring it into the drain on the laboratory premises. This is acceptable as an immediate solution, and greatly reduced the risks of contamination, but is unacceptable in the long term. We need to look for safe options when disposing of the laboratory waste, and as we plan to further support viral load monitoring, we should look to build experience in successful and responsible management of this waste."*
>
> **(MSF medical coordinator, Malawi)**



Having the smiling and sad faces on the results made it easy to select the high viral loads from the pile of results. These ones we know we have to trace. It also made it easier to explain to the patient. As well, each month we got a list from the laboratory of all the patients in each clinic with a high viral load. When we did our mentoring visits we knew to check that those patients were receiving counselling.

Tendai Chigura, Nurse mentor, Gutu district, Zimbabwe

@MSF

KEEPING A VIRAL LOAD TESTING LABORATORY RUNNING

LESSONS LEARNED

POWER CUTS

- A realistic assessment of likely power outages is essential to decide on the type and duration of UPS required

MAINTENANCE

- Local contractors need ongoing training and assured access to spare parts
- Manufacturers should have spare parts in the region/ country to reduce downtime
- Rental agreements may provide motivation for provision of efficient servicing

PROCUREMENT

- Quarterly rather than biannual ordering may prevent both stock-outs and expiry, and be more compatible with storage volume constraints
- Better linkage with ART cohort and VL cascade data is required to estimate needs

BACKUP PLANNING

- There should be a clear SOP which triggers the backup testing plan
- Backup may be within an in-country VL testing network or where DBS is sent out of the country. Options within the government and the private sector should be considered to ensure ongoing testing capacity

STRATEGIES FOR INCREASING THROUGHPUT

- All platforms (with the exception of Zimbabwe) were under utilised
- Increased investment in programmatic aspects of VL to increase coverage of testing is urgently needed
- To increase throughput consider:
  - » *Funding for HR to run additional shifts (2 x 8 hours shifts)*
  - » *Staff incentives for reaching targets*
  - » *Creating space for additional modules (near point-of-care) or extraction components (e.g. 2 easyMAGs for 1 easyQ)*

In 2015, our newly installed VL testing platform in DRC was working 72 days out of 191 (37.7% of the time).

Our VL testing platform arrived in June 2015. Already in July the VL activities were put on hold, first due to lack of consumables and later due to a technical problem (little bolt broken), which was only resolved in October. The VL analyses restarted in October but were then put on stand-by again, this time because of a cold-chain rupture resulting in the reagents being put in quarantine. By the end of December, the quarantine was lifted and VL analyses could restart.

EXCERPT FROM DRC LABORATORY REPORT DEC 2015

Maintaining continuous VL testing capacity has been a challenge, particularly at centralised high throughput sites. Down time of SAMBA I was significantly lower than any other system, with only one breakdown during 2015. In addition, both near POC technologies allow modular repairs to be carried out whilst remaining modules continue to run. This chapter highlights the main challenges faced in keeping the VL laboratory running. Further details may be found in Table 2.

DOWNTIME DUE TO POWER OUTAGES

All sites quoted this as a major problem, with UPS backups felt to be inadequate in a number of sites.

REPAIRS AND MAINTENANCE

To have an overview of machine performance and maintenance response, laboratories should keep an updated routine equipment maintenance QC log, together with records of all service or breakdowns with detailed downtimes. A record of all errors should also be shared with the local distributor/manufacturer when they visit the site.

Inadequate repair and delayed maintenance provision caused significant disruption to VL testing. The most common problems are listed in Table 2. Local contractors often lacked technical skills to perform repairs and did not have timely access to the necessary spare parts. In order to cope with lack of capacity from the local technicians, MSF has requested that laboratory technicians be trained to perform minimal repairs, but this has not been agreed by manufacturers. Rental agreements have the potential to improve maintenance as down time will reduce testing volume and hence reduce profit.

PROCURING CONSUMABLES

Procurement and forecasting depends on reliable consumption and ART programme data. The links between the laboratory and real-time ART cohort and VL cascade data (See Part 1) must be strengthened to improve forecasting both to avoid stock-outs and wastage. Each reagent should be recorded in terms of the number of tests that can be performed rather than quantities of reagents.

The number of staff adequately trained to carry out orders or conduct stock counts was also noted as a weakness (a minimum of two should be fully trained) along with availability of storage capacity acting as a rate-limiting factor. Storage space should also be considered in the infrastructure plan for scale-up of viral load. When possible, porta cabins or prefabricated cabin buildings could be used to store reagents that do not need cold-chain. Finally, the short shelf-life of some reagents necessitated quarterly rather than biannual orders.

BACKUP PLANNING

A standard operating procedure for backup testing should be in place. A threshold (e.g. turnaround time exceeded by 1.5-2 times, or 40-50% of monthly samples are still pending) should be set to trigger the backup plan. Clear communication between in-country VL testing laboratories should be established to allow potential loaning of reagents or outsourcing of testing within a country's VL testing network or to a private provider in or out of country. Zimbabwe, Malawi and Mozambique MSF projects have all used a private VL laboratory in South Africa for backup when in-country laboratory capacity was not meeting the demand. Ensuring that the laboratory selected for outsourcing uses a WHO prequalified platform for the sample type and can ensure an acceptable turnaround time are prerequisites for laboratory selection.

MAXIMISING CAPACITY

All sites ran below the capacity of the platform. Availability of skilled HR was reported as a major challenge to optimising the use of the machines up to the theoretical maximal throughput, while limited request for VL tests from clinics explained suboptimal requests for tests compared with the machine's capacity. Hence, understanding the capabilities of the device and ensuring that sample flow strategies maximise the effective use of hands-on laboratory HR is essential. Strategies that should be considered include:

- Increase the available equipment

In Mozambique and Zimbabwe, two easyMAG extraction devices were used with one easyQ amplifier doubling the number of samples run in an 8-hour shift. This was not possible in Thyolo, Malawi, due to space limitations. With near POC technologies, additional modules can be added where space allows. Space again was a limitation for adding modules in Chiradzulu district hospital.

- Increase the hours the machine is running by introduction of a shift system

In Zimbabwe, two shifts were introduced: morning shift (08h00-16h30) and evening shift (14h00-22h00). The number of staff required per shift depends mainly on the 'hands-on' stages of VL testing; for example, at NMRL in Zimbabwe, VL is enumerated on BioMerieux VL from DBS samples and each shift has three staff members. Each shift is expected to release a minimum of 144 VL results.

- Introduce incentives for overtime and weekend shifts

Overtime availability is triggered in Zimbabwe when weekly sample volumes reach target but a backlog remains. This system prevented underperformance of staff. Failure to reach normal targets even with overtime incentives would trigger outsourcing of HIV VL testing.

- Consider viral load pooling

VL testing using a pooling technique was started operationally in February 2014 in a rural district laboratory in Malawi (Thyolo district) on the BioMérieux VL platform. The pooling technique was validated on both DBS and plasma specimens; details of the technique and outcomes have been published elsewhere.

Pooling resulted in a reduction of 29% in HIV VL tests performed, to cover the same number of samples tested, translating to significant cost savings ($47,110/year)(6).

Pooling does, however, involve additional hands-on workload, and with decreasing costs of testing and increasing automation of devices there is debate as to whether this approach will be efficient in the future. Efficiency will also depend on the prevalence of virological failure as each positive pool requires re-testing of individual samples.

Figure 2 (number of HIV tests performed in the VL laboratory in Zimbabwe) illustrates three points:

1. The importance of having a **monthly target** for VL testing
2. The impact of introducing a **second shift** as demand increased
3. The ability to **trigger outsourcing** when, due to downtime related to machine breakdowns, the monthly target was not met

REDUCING ERRORS

Clinical laboratory errors affect patient care and directly lead to increased healthcare costs and decreased patient and clinician satisfaction. Thus pre-analytic, analytic and post-analytic stages of laboratory testing must be error-free as far as possible. Even with the considerable advances in automation, laboratory instrumentation and information technologies, the pre-analytical phase remains the most error-prone stage in testing.

The following components improve specimen identification and verification:

- Adequate training and continuous competency evaluations of the specimen management team
- Clear protocols for streamlining the lab workflow
- Use of automated bar-coding system where possible

Testing accuracy is improved with:

- Selection of testing devices that have been validated (see QA of laboratory equipment section) and shown to have good sensitivity and specificity
- Strict adherence to manufacturers' instructions and laboratory testing SOPs
- Equipment maintenance and regular stock audits (expiries)
- Regular proficiency assessment of personnel with continuous revisions of laboratory workflow
- Use of appropriate controls (internal and external)

The laboratory should keep a record of all errors and document the corrective actions taken. Fig 3 illustrates error rates for the VL platforms in Mozambique, Zimbabwe and the two SAMBA 1 sites. Most errors in Zimbabwe (BioMérieux VL) occurred during a period of delayed scheduled platform maintenance. The lamp in the platform had ceased functioning and was replaced by a used lamp, whereas in Mozambique (BioMérieux VL), the high error rate was due to power cuts. Error rates for SAMBA 1 were low, including when performed by lay workers. Xpert HIV-1 VL testing has so far been conducted during a diagnostic performance evaluation of the index instrument under ideal laboratory conditions and had a total of error rate of 4.3%. However, field performance evaluation in district laboratories is ongoing.

MONTHLY HIV VL TESTS PERFORMED

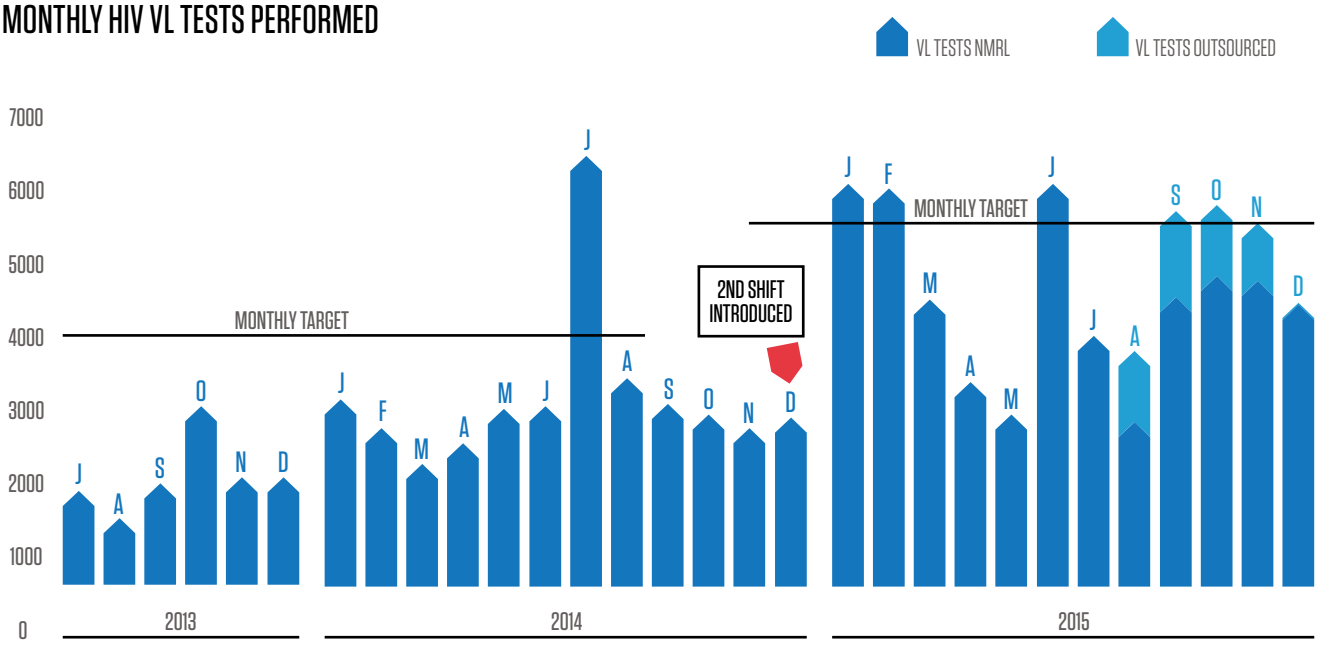


Figure 2: Monthly VL tests performed at NMRL Zimbabwe demonstrating introduction of shift system and outsourcing

ERROR RATE IN HIV VL TESTING

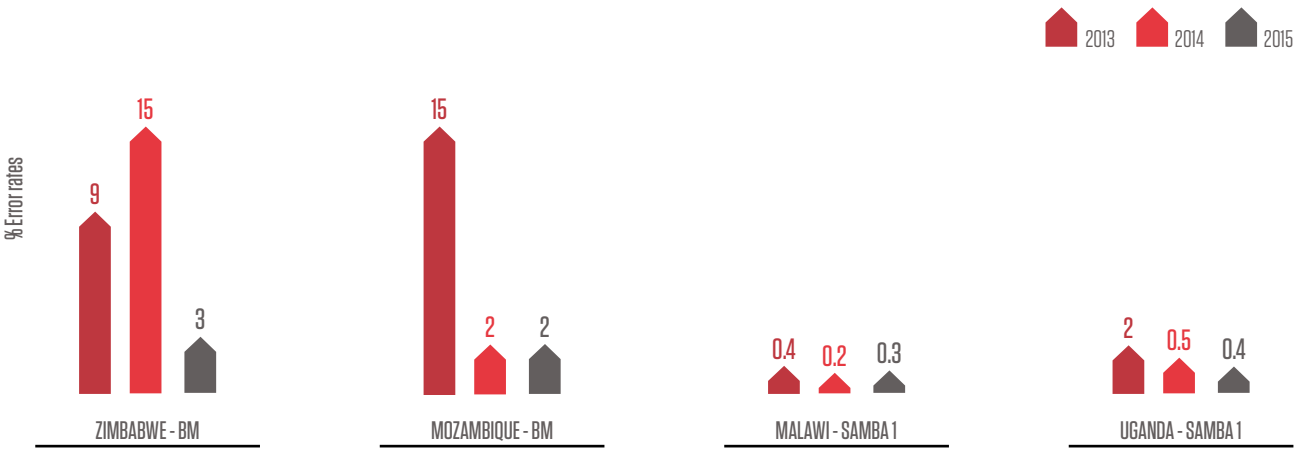


Figure 3: Percentage error rates in HIV VL testing

TURNAROUND TIME

Turnaround time (TAT) for results is a key performance indicator of any laboratory. TAT is composed of three important variables: time from collection of the sample from the patient to its arrival at the laboratory; intra-laboratory TAT, defined as the time it takes from receiving the sample to the result being released back to the clinic (calculated as date of result dispatch minus date of sample arrival); and TAT for delivery of the result to the patient, which heavily depends on elements related to the organisation of the clinic and the patient's appointment schedules. Although results of less than 1000 copies/ml must be communicated to the patient and may be used to differentiate ART delivery (See part 1), clinics should ensure that systems are in place to trace those with high VL results.

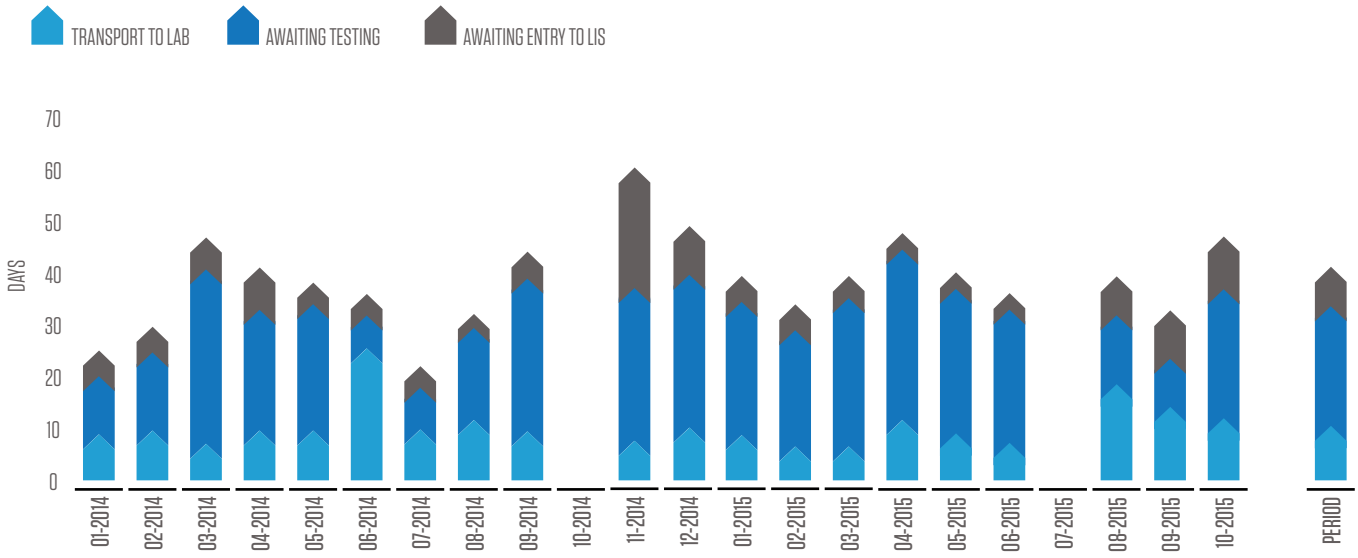
With POC and near POC, these three components are very closely related, as delivery of the results to the patient may be almost immediate, allowing a global reduction of TAT and potentially improvement of quality of care; especially when immediate results are required for clinical reasons. In Chiradzulu, Malawi and Arua, Uganda, where SAMBA I was implemented within the health facilities, 80% of patients received their result the same day. Peripheral clinics, where SAMBA 1 was not installed, sent samples to the district site where they were processed using SAMBA 1. Results were delivered to the clinic within 3 days and patients received the result within 1 week.

Figure 4 i, ii and iii demonstrate the time from sample taken to arrival in the laboratory and the intra-laboratory TAT for the laboratories in Zimbabwe, Mozambique and Swaziland. Swaziland had twice-weekly specimen collection from all sites to the local district hospital. The increase in TAT in Swaziland from August 2015 onwards was due to a reagent supply problem from the manufacturer. In Zimbabwe, samples are collected weekly from 25-30 sites in each district and brought weekly to the capital 3-4 hours away. Maputo is an urban setting with sample transport from the clinics to the VL testing laboratory once a week.

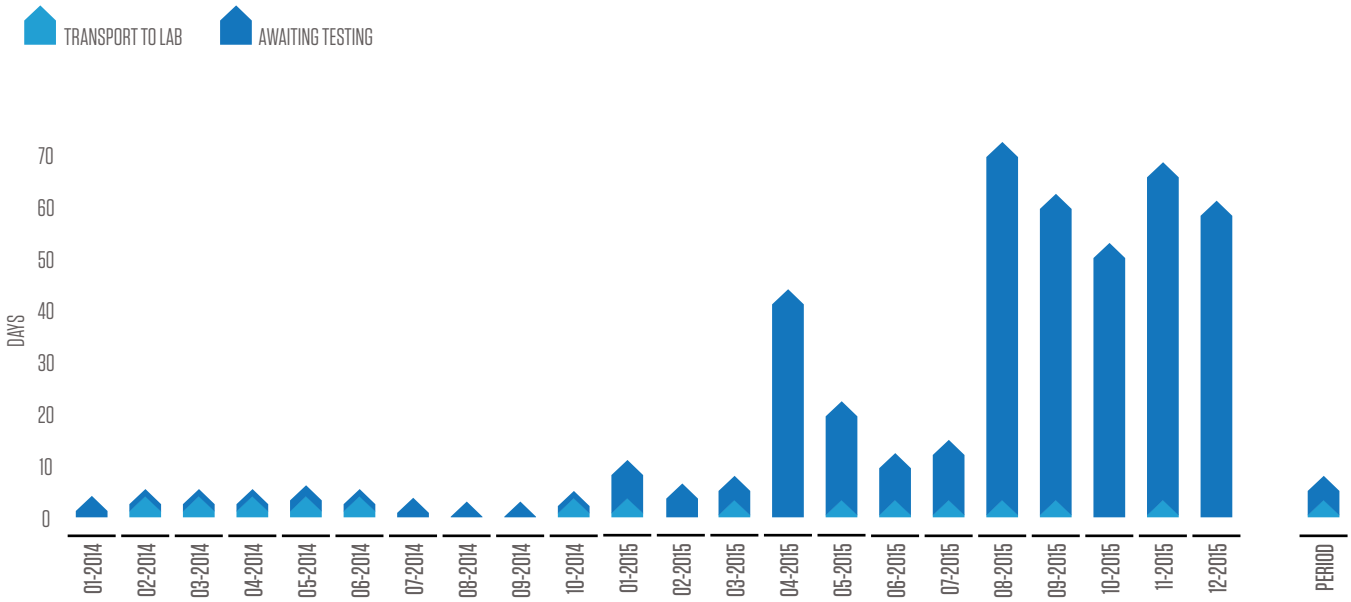
Each laboratory should set an intra-laboratory threshold for TAT which, when breached, should trigger a response and possible outsourcing. Zimbabwe's target intra-laboratory TAT at NMRL for 2016 is 10 days or less.

FIG 4: TURNAROUND TIME FOR VIRAL LOAD TESTING

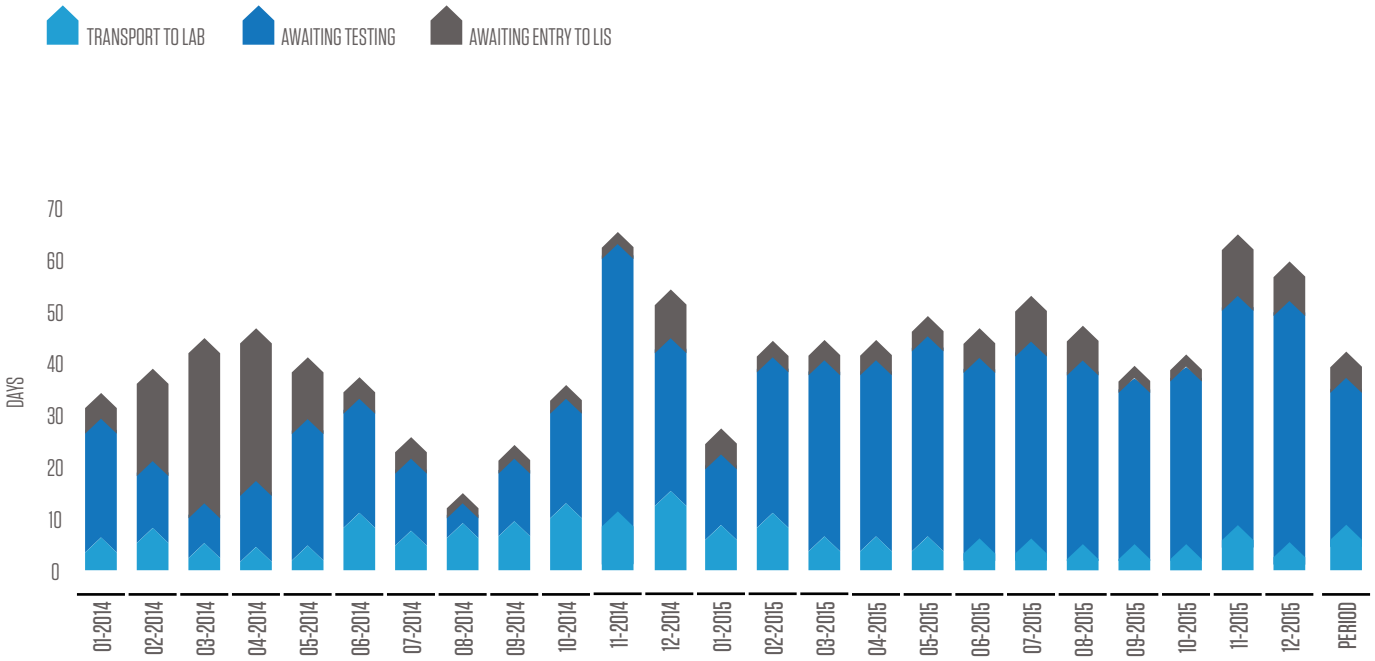
i: NMRL HARARE, ZIMBABWE



ii: SHISELWENI, SWAZILAND



iii: MAPUTO, MOZAMBIQUE



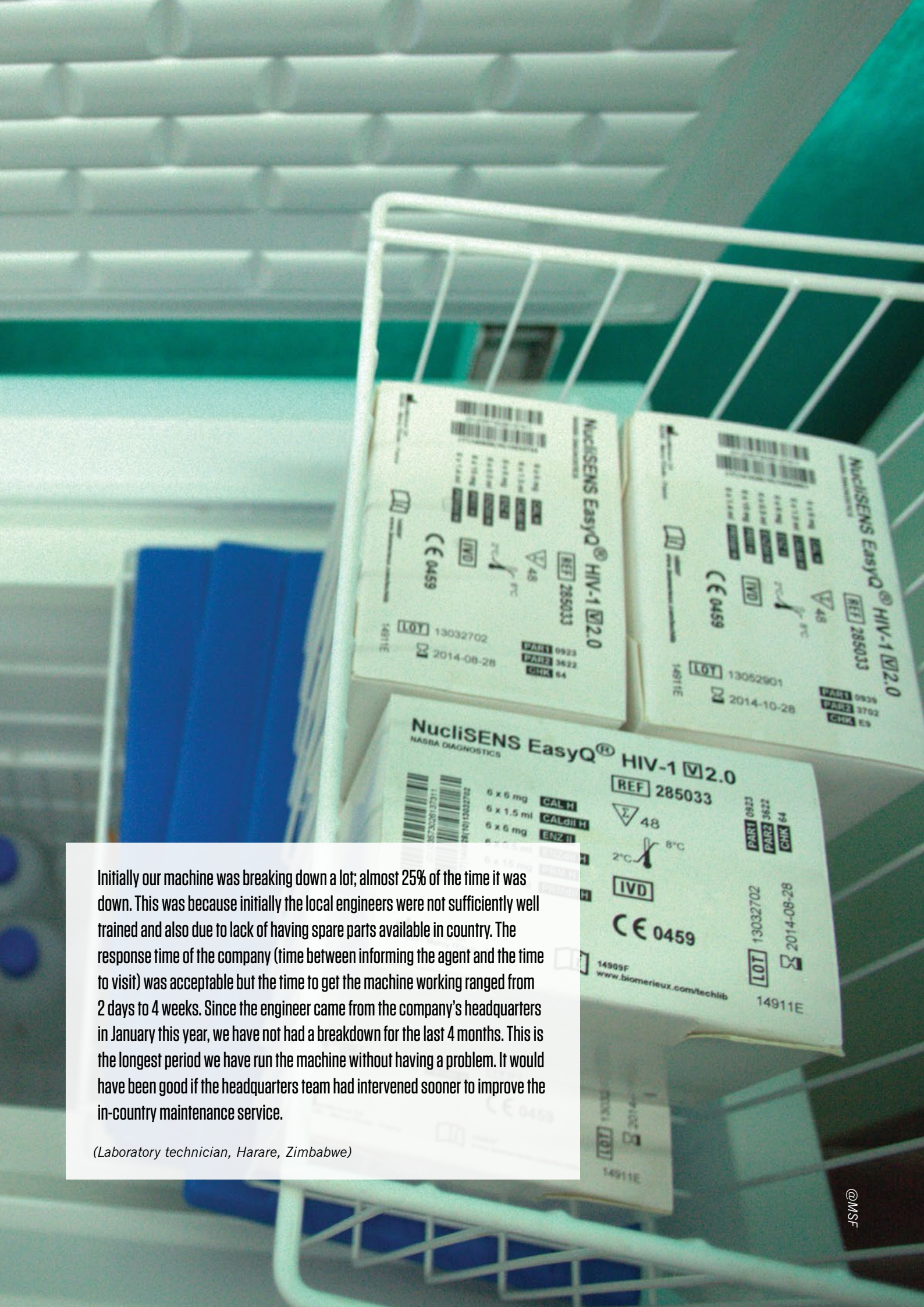
FACTORS AFFECTING INTRA-LABORATORY TAT IN NMRL, ZIMBABWE

- Increasing volume of samples received each month
- Machine breakdown with prolonged downtime, especially when spare parts are not locally available in the country
- Reagents stock-out
- Competing priorities for HIV VL testing laboratory technicians. Laboratory managers should be able to determine the 'man hours' that each laboratory technician should spend per day processing HIV VL samples
- Organisational and behavioural culture within the laboratory
- Highly manual transcription/writing/calculations which could be done by LIS

ENSURING QUALITY

The maintenance of a quality management system (QMS) is crucial for any laboratory. Important elements of a QMS include documentation, standard operating procedures (SOPs) and QC samples. Table 2 outlines the QC measures undertaken across the sites. Part of the QA for a laboratory lies not only in the accuracy of the test result, but also in the intra-laboratory turnaround time of the result, from the time the laboratory receives the sample to when the result becomes available for clinical dispatch to the clinician/clinic. A budget for internal and external quality assurance programmes must be assured as part of the laboratory scale-up plan. An on-site dedicated QC manager was found to impact the correct implementation of QC processes positively.

An external quality assessment scheme (EQAS) is a programme in which the accuracy of testing within a laboratory is ensured through external review. A blinded testing panel is sent to the laboratory, the panel is run on the device and the test results are submitted to the external provider. The external provider compares the results and generates an accuracy report for the laboratory. The laboratory uses this process to ensure a high quality of testing on an ongoing basis. This process is commonly known as 'proficiency testing'. Funding for EQAS must be included in budgets and is required if laboratories wish to obtain any form of accreditation.



Initially our machine was breaking down a lot; almost 25% of the time it was down. This was because initially the local engineers were not sufficiently well trained and also due to lack of having spare parts available in country. The response time of the company (time between informing the agent and the time to visit) was acceptable but the time to get the machine working ranged from 2 days to 4 weeks. Since the engineer came from the company's headquarters in January this year, we have not had a breakdown for the last 4 months. This is the longest period we have run the machine without having a problem. It would have been good if the headquarters team had intervened sooner to improve the in-country maintenance service.

(Laboratory technician, Harare, Zimbabwe)

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THE WAY FORWARD

Viral load testing is recognised by the major donors as one of the essential programmatic components to reach the third "90" target. Although there is technical agreement to scale-up VL testing, allocating funds to VL testing over other priorities requires ongoing advocacy.

Within a 3-year period, VL testing capacity for MSF-supported ART cohorts has been significantly increased, hence demonstrating that VL testing is feasible in such contexts. However, this experience has demonstrated the significant resources that were invested to reach where we are today. Basic infrastructure challenges (power and water supplies) continue to affect the ability of laboratories to maintain targets and retain motivated staff.

WHAT DO WE NEED TO FOCUS ON GOING FORWARD?

Due to the delayed availability of near and true POC VL devices, operational strategies to assess **how best to combine POC technologies** with high-throughput platforms have not been tested. Although placement of platforms will be context-specific, development of a decision framework that can be used to guide Ministries of Health on how best to use these technologies is urgently needed.

As it is unlikely that POC technologies will be available for all tests at all sites how do we advocate for a **coordinated approach to sample transport within a national VL testing scale up plan?**

Ensuring adequate in **country maintenance** and a systematic approach to **back up planning** must be a priority to ensure uninterrupted VL testing services.

What about **the waste**? This has not been adequately considered, and in the absence of government regulatory frameworks potentially may be left unaddressed. Advocacy is needed towards both manufacturers and donors to ensure that information and funding are provided to develop improved technological solutions to mitigate the health risks posed to both laboratory staff and the neighbouring populations.

Finally, we must recognise that no one solution will fit all settings. Patient's needs and the realities faced at health centres providing ART must be central to any VL testing scale-up plan. These needs should encourage us to call for further adaptations to VL testing devices in order to truly make VL routine in such contexts.

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ANNEXES: AVAILABLE ONLINE OR ON USB

Annex 1: Activist Toolkit: Campaigning for routine VL monitoring
Annex 2: Monitoring and Evaluation of the Viral Load Cascade
Annex 3: MSF Viral Load Toolkit
Annex 4: MSF VL publications and conference abstracts

Viral load testing is feasible in resource poor settings, but we have to change our way of working if we are to respond to the increase in demand. Effective collaboration is possible and necessary to combine strengths and experiences of private and public sectors; this will be critical for initiating a sustainable change. Patient's care depends on it, we have to get this right.

Zee Ndlovu, MSF Laboratory Advisor

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www.msfaccess.org/makingviralloadroutine