ISSUE BRIEF

MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN

ACHIEVING UNDETECTABLE:
WHAT QUESTIONS REMAIN IN SCALING-UP HIV VIROLOGIC TREATMENT MONITORING?

MSF UNDETECTABLE | VOLUME 6

With the 2013 WHO consolidated HIV treatment guidelines, and further evidence from operational and cost-effectiveness research supporting the use of viral load monitoring in low- and middle-income countries (LMICs), there is a need to rapidly scale-up this important technology to strengthen the provision of quality and effective HIV treatment and care.

A number of barriers may be hindering scale-up, including the price of viral load testing, logistical and implementation barriers, and even potential costs incurred from the higher price of second-line antiretrovirals (ARVs) as more patients failing first-line treatment are identified.

When addressing the task of introduction and use of routine virological monitoring, national HIV programmes and other implementers are faced with competing priorities, limited resources and logistical barriers. In this briefing document, Médecins Sans Frontières (MSF) Access Campaign presents further evidence from a five-country study of viral load implementation and MSF's own operational experience, to help respond to questions and concerns countries may face when planning viral load scale-up.

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ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

MSF Access Campaign
Médecins Sans Frontières, Rue de Lausanne 78, CP 116, CH-1211 Geneva 21, Switzerland
Tel: + 41 (0) 22 849 84 05 Fax: + 41 (0) 22 849 84 04 Email: access@msf.org

www.msfaccess.org facebook.com/MSFaccess twitter.com/MSF_access

1. WHAT ARE THE CURRENT RECOMMENDATIONS AND TARGETS FOR VIRAL LOAD?

The World Health Organization (WHO) strongly recommends routine viral load monitoring (six and twelve months following treatment initiation and annually thereafter) for all people living with HIV/AIDS (PLWHA) who are taking antiretroviral therapy (ART).[1] For those found to be virologically failing (defined as a viral load above 1,000 copies/mL), WHO recommends enhanced adherence counselling, followed by an additional viral load test to identify either re-suppression or confirmation of treatment failure, requiring a regimen switch. In a recent guideline supplement, WHO also acknowledged a shift in the role of CD4 testing. Evidence shows that, while CD4 values are still important to inform the need for ART initiation and risk of opportunistic infections (including screening for tuberculosis and cryptococcal meningitis at very low CD4 counts), people who are stable on ART, with an undetectable viral load, do not require additional CD4 monitoring because their CD4 counts remain high as long as their viral replication remains controlled.[2] This means that resource-limited countries can confidently prioritise resources towards scaling-up viral load testing for treatment monitoring, while saving resources on drastically reduced CD4 monitoring. Indeed, some already have.[3] For example, South Africa has dropped CD4 monitoring of virally suppressed people on ART, save for one test 12 months after ART initiation (to confirm immune reconstitution). Following this, only those who become viraemic receive further CD4 testing until viral suppression and immune reconstitution are once again achieved.

Critically, reducing CD4 testing has a major cost-saving advantage for countries. Using the new algorithm in South Africa has reduced CD4 testing cost estimates by 51% (from 2013 to 2017), with a saving of US$68 million over these five years.[4] This has also been a consideration in wealthy countries. For example, decreasing testing from biannually to yearly, for virologically suppressed people on ART in the USA, and for all people on ART in Australia, could save about $18 million and $1.4 million annually, respectively.[5,6] These opportunity costs related to redundant CD4 testing could allow for more efficient use of this money for improving HIV care.

UNAIDS has set ambitious diagnostic and treatment targets for 2020. Known as the 90:90:90 targets, these include 90% of people knowing their status; 90% of people diagnosed with HIV receiving ART; and 90% of people on ART having durable viral suppression by 2020.[7] These targets assume that the entire population of PLWHA - currently 34 million - will be eligible for treatment.

Critically, diagnostic and monitoring tools are essential to achieve these targets as both the initial HIV diagnosis, and measurement of viral suppression, are based on access to serological and virological tests, respectively.

To achieve the 90:90:90 targets, routine viral load monitoring must be greatly expanded. In 2013, only 23% of the viral load testing need was met, with an expansion to 47% access to routine viral load coverage anticipated by 2019.[8] Equally important to routine viral load testing scale-up are access to adherence support, and second- and third-line drugs, for those with elevated viral loads. In order to achieve a viral load undetectable status in 90% of people on ART, the remaining obstacles to viral load testing scale-up must be identified and overcome.

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2. HOW CAN ROUTINE VIRAL LOAD TESTING HELP IMPROVE HIV CARE?

Achieving an undetectable viral load – where HIV levels fall below the limit of detection of the test – means that ART is working effectively to block viral replication, maximising the health of those on ART[9] and also limiting transmission.[10] Viral load monitoring provides people with critical information regarding the level of HIV in their blood. If someone on treatment has an elevated viral load (classified by WHO as a level >1,000 copies/mL), they are more likely to develop drug resistance and experience treatment failure. Providing viral load information regularly enables early identification of people struggling with treatment adherence, or experiencing treatment failure that requires a change of drug regimen. A high viral load provides an early warning to someone who occasionally forgets his or her pills that this is allowing the virus to replicate. This in itself can help improve adherence and recognition of inadequate adherence by a person on ART.

During the implementation of viral load testing in countries, it will be important to concentrate on the entire viral load cascade, including the training of laboratory staff, clinicians and adherence counsellors, and the education of PLWHA to understand what their viral load result means and when they should be asking for a viral load test. The training of counsellors is particularly important as viral load can be used as a powerful tool to reinforce adherence.

Viral load testing identifies potential treatment failure far earlier than CD4 testing, allowing for a more prompt intervention, with less risk of developing drug resistance and, consequently, conserving first-line drug regimens.[11] A meta-analysis found that 70% of people achieved virological resuppression following enhanced adherence support, depending on how long they'd been on ART.[12] This is important as most countries only offer two regimens in the public health sector, and access to salvage therapy is therefore poor. Additionally, on average, the cost of second-line ART is over twice that of first-line, and third-line is nearly 15 times more expensive.[13] However, MSF has also shown that, after two years of routine viral load testing in Kenya, Malawi and Zimbabwe (restricting the analysis to those with a first-ever viral load test), over half of patients had a significantly elevated viral load after enhanced adherence counselling.[14] This highlights the need for diagnostic algorithms that will address the significant proportion of patients who may not re-suppress after adherence counselling. However, there appear to be delays and barriers to following guidance on changing these patients to second-line. In a programme in rural South Africa, of those patients with persistent viraemia who were referred to a clinician, less than half were switched to second-line, and, even when they were, it was a year after the first elevated viral load.[15] Thus, in real world situations, the advantages of viral load testing are not being realised.

Another critical benefit of viral load testing is to ensure prompt and correct switching to alternative drug regimens (high sensitivity), and preventing unnecessary switching (high specificity). With regards to sensitivity, a systematic review of the WHO 2010 guidelines for predicting virological failure, using clinical and immunological criteria, revealed very poor accuracy in adults and children. Immunological failure criteria in adults was only 55% sensitive in predicting virological failure, with a positive predictive value (PPV) no more than 39%; in children, the sensitivity was worse, at no more than 7%. Clinical criteria fared even worse, with only 11% sensitivity to predict virological failure in adults.[16] Thus use of clinical and immunological criteria may miss patients who are in need of adherence counselling or regimen change. With regards to specificity, use of clinical and immunologic criteria also causes over-switching of ART for people who do not yet present with virological failure. A multi-country study conducted by MSF found that 70% of people with clinical symptoms suggesting treatment failure did not have an elevated viral load[17]. Similar results were found in Malawi.[18]

Finally, viral load monitoring helps to meet prevention goals. Achieving virological suppression also reduces transmission. In a meta-analysis of 5,298 sero-discordant couples over 2,846 person years, with the HIV positive partner virologically suppressed, HIV transmission was recorded in only four instances – all of which were cases where virological suppression was unconfirmed.[19] In a recent modelling exercise, Estill *et al.*[20] found that routine viral load monitoring in Malawi could prevent hundreds of thousands of new HIV infections by helping to ensure peoples' viral replication is suppressed, starting with 357,000 infections prevented by scaling-up viral load testing under current ART coverage.

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3. ARE WE GETTING THERE: HOW IS VIRAL LOAD MONITORING BEING SCALED-UP AT NATIONAL LEVEL?

The latest UN report has highlighted the poor access to diagnostic tools and the lack of funding from countries to support their laboratory services[8]. In 2012, the share of the laboratory portfolio as a proportion of total spending on HIV treatment ranged from 15% in South Africa to 4% in Malawi. This is reiterated by a 2013 survey by WHO that highlights the poor access to HIV diagnostic and monitoring services in general across low- and middle-income countries.[21] Many viral load-testing instruments were under-utilised and 10% were not in operation due to lack of installation, repair or staff training. Furthermore, sample transport systems were not sufficiently robust to meet the needs of rolling out routine virologic monitoring. Fortunately, there is a positive trend, with eight viral load tests performed per instrument per day in 2013, up from five in 2012 (although testing at least 90 samples per day is possible using high throughput machines).

GUIDELINES AND IMPLEMENTATION GLOBALLY

While many LMICs recommend routine viral load monitoring for people on ART (39 of 52 countries), in line with WHO recommendations, in reality only a minority of those who need it have access to this service (Figure 1a). Routine viral load testing is only widely available in a handful of countries, while some countries still do not recommend viral load testing at all (3 of 52 countries), or recommend it only in the case of suspected treatment failure (10 of 52 countries). Where viral load testing does occur, the systems and clinical capacity to act promptly on the findings (e.g. to switch to second- or third-line ART) is rarely in place. Thus, while many countries have updated their guidelines on virological monitoring, implementation still lags far behind.

FIGURE 1A: GUIDELINES ON THE USE OF ROUTINE VIRAL LOAD MONITORING ACROSS 55 LOW- AND MIDDLE-INCOME COUNTRIES, AND THE LEVEL OF IMPLEMENTATION.

Source: UNAIDS database. For more information please see supplementary material (www.msfaccess.org/achieving-undetectable).

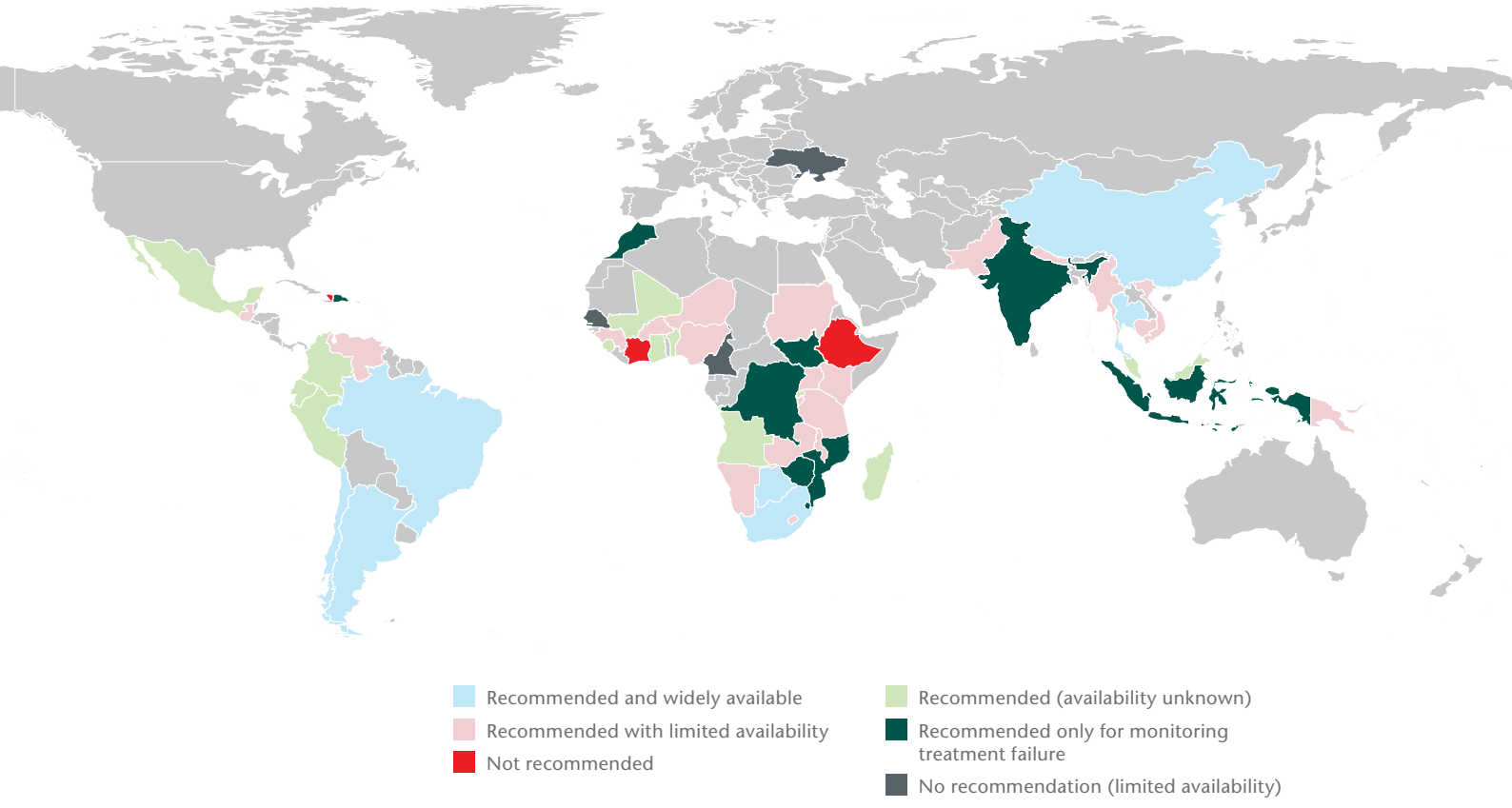
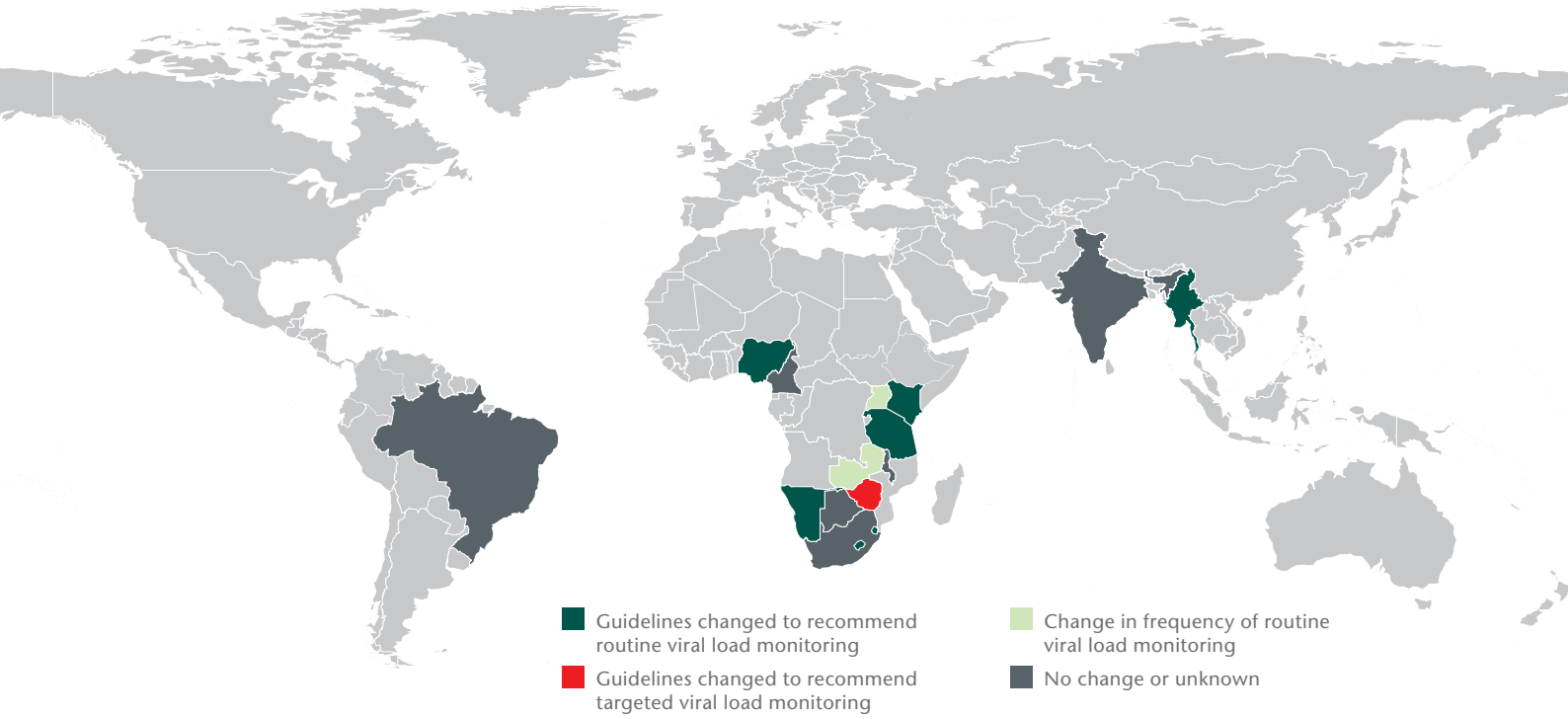


FIGURE 1B: CHANGES IN THE RECOMMENDATION ON THE USE OF VIRAL LOAD FOR MONITORING OF PEOPLE ON ART IN 15 HIGH-BURDEN COUNTRIES.

Source: UNAIDS database. For more information please see supplementary material (www.msfaccess.org/achieving-undetectable).



Guidelines from four of the 15 countries (Kenya, Malawi, Namibia and Uganda), released after the 2013 WHO guidelines, no longer recommend CD4 testing for routine monitoring of ART response. Routine CD4 monitoring is recommended in these countries only if viral load testing is not available. South Africa, which recommended CD4 monitoring at 6 months, 12 months and yearly thereafter, revised its guidelines to recommend one CD4 test at 12 months to assess the immunological status of those on treatment. Cameroon and Zambia have changed the frequency of CD4 monitoring to every six months and are consistent with the WHO recommendation. Most countries have not updated their guidelines over the past few years, since 2007. CD4 guidelines for ART monitoring have been updated to six-monthly for Brazil (although Brazil plan to discontinue routine CD4 testing for ART monitoring from 2015[3]), Cameroon and Zambia; discontinued for Malawi, Uganda, Kenya and South Africa (save for a test at 12 months post ART initiation in South Africa); and used only in cases of virological failure to assess immunological status and inform clinical management in Namibia. Brazil, Kenya, Lesotho, Myanmar, Namibia, Nigeria, Uganda, and Zambia have all updated their guidelines to recommend routine viral load ART monitoring. Zimbabwe has moved from not recommending viral load monitoring to targeted testing (Figure 1b and supplementary material). In addition, the United Kingdom and the United States of America have both moved to reduce the frequency of CD4 testing for treatment monitoring[22,23].

In a five-country survey conducted by MSF[3], three of the countries (Kenya, Malawi and South Africa) recommend routine viral load monitoring, however, only in South Africa is viral load testing widely available. India does not recommend routine viral load testing and, while Zimbabwe does, they have a phased implementation plan, and both countries have limited viral load testing capacity, even for targeted testing. In Zimbabwe, access to viral load testing reached only 7% of the ART cohort in 2013. Both India and Zimbabwe will likely continue with a policy of targeting only those suspected of virological failure for viral load testing. While there is strong political will for rollout in Zimbabwe, with a plan to reach universal access by the end of 2016, the country does not have the resources to scale-up testing without additional financial and implementation support. Whilst Malawi has prioritised routine virologic monitoring, resource constraints were a key factor behind a decision to set a goal of offering each patient a viral load test every two years, rather than yearly, as in the WHO recommendations. Current indications are that even less-ambitious goals might be difficult to achieve in the short- or medium-term due to challenges associated with implementation as well as financing. In Kenya, recently revised guidelines recommend routine viral load monitoring and access has risen sharply over the past year. Given the overall huge demand, however, it is too early to judge the success of implementation.

Given the gap between country guidelines and the extent of access to viral load testing, it is clear that countries require the political will, and financial and implementation support, to successfully scale-up viral load testing.

HOW VIRAL LOAD PLATFORMS ARE SELECTED

Selection of viral load platforms depends on many different factors, including cost, technical capabilities, service contracts, polyvalency, level of automation, throughput needs and level of decentralisation preferred.

In the MSF five-country survey, a country's platform selection depended on which parameters were most highly valued. In some cases, platforms were selected based upon donor preferences or manufacturer proactivity. Donors are encouraged to recommend and support the best platform for country-specific contexts. Country platforms selected are detailed in Table 1, which includes descriptions of country experiences with these platforms.

TABLE 1: VIRAL LOAD EQUIPMENT SELECTION AND IMPLEMENTATION EXPERIENCE ACROSS FIVE COUNTRIES*

Country	Public sector/MSF platform
India	The Roche-provided platform has, in the past, been preferred by the National AIDS Control Organisation (NACO), as Roche were most proactive in terms of technical support and follow-up. However, NACO has recently been disappointed with the quality of service from Roche, due to frequent equipment breakdowns and poor service quality. To promote competition, four Abbott-provided platforms have recently been purchased, and the performance of the Cavidi-provided platform has been evaluated, with favourable results.[24]
Kenya	Abbott- and Roche-provided platforms have been selected, with variation in composition across the country, presumably because they both offered a competitive price of $10.50 per test. A bioMérieux-provided platform is used for research purposes and was recently placed in Homa Bay.
Malawi	Abbott-based platforms were selected nationally, for uniformity and simplicity. Additionally, MSF use a bioMérieux-provided platform in Thyolo, chosen for the superior performance with dried blood spot samples, and the SAMBA I in Chiradzulu.
South Africa	Abbott- and Roche-provided platforms were selected as part of a competitive three-year tender process. In the previous tender they were given a 50/50 test split, however, considering that Roche offered the lower test price of $7.30 (ZAR80.58) in the most recent tender, compared to the Abbott test price of $7.90 (ZAR87.00), South Africa have increased the number of Roche-provided tests to 70%, and decreased Abbott-provided tests to 30%[25], likely changing the instrument ratio.
Zimbabwe	Roche-provided platforms are currently in place for infant diagnostic testing. MSF have provided a platform from bioMérieux, chosen for the superior performance with dried blood spot samples. Additionally, SAMBA I is being validated by the National Microbiology Reference Laboratory (NMRL).

* Although not included in the five-country survey, information gathered from Mozambique reveals that the country has chosen the Abbott-provided platform for national laboratory-based viral load testing, using dried blood spots as the main sample type. Mozambique has plans to scale-up to routine viral load testing by 2017, increasing the number of platforms from four to about 17. Additionally, there are four Roche-provided platforms for early infant diagnosis.

4. HOW LOW CAN WE GO: WHAT IS THE PRICE OF VIRAL LOAD TESTING NOW AND IN THE NEAR FUTURE?

Viral load test prices are rapidly dropping as volumes and competition increase, and negotiations improve. In September 2014, Roche announced a global ceiling price of $9.40 per test for 83 LMIC countries.[26] This ceiling price is expected to drop significantly with increased volume demand. For example, South Africa, as a result of high volumes (two million tests annually, with anticipated scale-up to over four million tests annually over the next three years), was able to successfully complete a competitive tender process for a "total HIV viral load solution" that achieved even more impressive price reductions, down to under $8 per test – $7.30 (ZAR80.58) from Roche and $7.90 (ZAR87.00) from Abbott – an impressive decrease from $20 in 2004.[25,27] A critical difference between the prices offered by Roche is that the global ceiling price includes only reagents, controls and proprietary consumables (and is likely an ex-works price only, rather than an in-country price). By contrast, the South African price of <$8 is an in-country price all inclusive of reagents, consumables, service, maintenance and instrumentation – everything except for labour and other operational costs including, for example, sample transportation, pre-analytical processing, the laboratory information system, quality assessment and results delivery.[45] However, the South African example demonstrates that with sufficient volumes and robust forecasts, improvements in prices, and instrument, service and maintenance packages, should be expected.

As many other countries will not have the same volumes as South Africa, pooling of demand or procurement can result in stronger negotiating power and lower prices. The Global Fund's Pooled Procurement Mechanism (PPM), or other strategies to pool demand, may help to achieve lower prices for all countries.

Countries, such as South Africa and Brazil, also demonstrate that lower prices can be obtained through a competitive tendering process. While it may not be feasible to contract with more than one manufacturer to provide viral load products to a given country, programmes may still benefit from the price-lowering benefits of competition by holding open tendering processes. Viral load pricing is also, in part, driven by the cost of the reagents and consumables needed to run the test. An MSF study across six countries, that aimed to enumerate the disaggregated, fully-loaded viral load testing costs, found that reagents and consumables occupy 63% of overall costs towards performing a viral load test, followed by sample transport, at 9.6% of costs.[28] Hence, the greatest impact in lowering viral load costs will likely come from price declines for reagents and consumables.

Improved transparency of costs paid for viral load tests, according to standardised Incoterms (a set of rules which define the responsibilities of sellers and buyers for the delivery of goods under sales contracts, which are published by the International Chamber of Commerce and are widely used in commercial transactions), will also help to lower prices and improve the negotiating position of countries and other implementers. Countries can contribute to price transparency by making their own procurement costs transparent and publicly available. Table 2 shows pricing data compiled as part of the MSF five-country survey, outlining the components included in the total cost, and across various sectors. Of note, prices differ significantly between countries and across service providers. Although the data is limited by the fact that many prices could not be verified, taken together, it highlights the differences, sometimes by an order of magnitude, depending on private versus public pricing, volumes and negotiating power.

> *Prices of viral load testing in South Africa demonstrates that – with sufficient volumes and robust forecasts – improvements in prices, and instrument, service and maintenance packages, should be expected.*

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TABLE 2. THE PRICES OF VIRAL LOAD TESTS ACROSS DIFFERENT SERVICE PROVIDERS IN FIVE COUNTRIES

The data has limitations for the following reasons: i) private sector costs are unconfirmed and may not be nationally representative; ii) comprehensive costs in the private sector include profit and, in the public sector, sample collection and transport costs are not always included in the comprehensive cost; iii) in both South Africa and Malawi (the latter regarding the low price negotiated for PEPFAR-funded procurement), the price for reagents and consumables includes instrumentation, service and maintenance; and iv) the new Roche ceiling price (likely ex-works) includes only reagents, proprietary consumables, and controls.

Facility type	Cost in USD (range)	Cost (local currency) - where known	Reagents	Consumables	Maintenance	Instrument	Lab HR	Sample transport	Blood collection
India viral load									
Private labs	$96.33 (65.13 - 130.25)	INR 5,916 (4750 - 8000)	x	x	x	x	x	x	x
For an NGO	$41.56 (29.31 - 57.99)	INR 2,552 (1,800 - 3,562)	x	x	x	x	x	x	x
Government lab	$22.79	INR 1,400	x	x	x				
NGO lab	$24.69	INR 1,350	x	x	x				
South Africa viral load									
Private labs	$105.40 (90 - 126.21)		x	x	x	x	x	x	x
For an NGO	$18.09	ZAR 200	x	x	x	x	x	x	x
NHLS to health departments	$27.58	ZAR 305	x	x	x	x	x	x	
NHLS contract with test suppliers	$7.58	ZAR 82.51	x	x	x	x			
Zimbabwe viral load									
For an NGO	$35		x	x	x	x	x	x	x
Private labs	$70 - $90		x	x	x	x	x	x	x
Public sector	$14.50		x	x					
Malawi viral load									
Public sector	$20.76 (20 - 41.28)		x	x	x	x	x	x	x
Public sector	$14.25		x	x					
Kenya viral load									
Private labs	$79.62 (40.90 - 100)		x	x	x	x	x	x	x
Public sector	$46.82 (40 - 51.64)		x	x	x	x	x	x	x
CHAI-negotiated price (public sector)	$10.50		x	x	x	x			
India CD4									
Private lab	$24.42		x	x	x	x	x	x	x
NGO lab	$19.05		x	x	x	x	x	x	x
Government lab	$2.93		x	x					

Costs for reagents and consumables procured under the Global Fund's PPM are detailed (not adjusted for inflation), by platform and country, in Figures 2a and 2b. Depending on country context, such as volumes ordered and negotiating power, prices varied substantially, although were approximated at $10-$40 (Figure 2a). Given the new global ceiling price of $9.40, and the <$8 price that South Africa has achieved, there is substantial room for improvement. As countries move to scale-up routine viral load testing, dropping routine CD4 monitoring can free up funds for viral load testing. Depending on viral load costs, two CD4 tests per year can equal one viral load test, thus being cost neutral if one viral load test replaces two CD4 tests per year (Figure 2b).

While in-country prices are not always directly comparable, given that reported prices can vary in terms of costs included in the final price, this transparent reporting allows for the analysis of trends and facilitates more informed negotiating power for countries. Going forward, it would be useful for the Global Fund, and other price reporting agencies, to ensure costs are reported in a disaggregated and standardised way, to allow for "like for like" comparisons, both within and between products.

FIGURE 2A: PRICES OF CD4 AND VIRAL LOAD TESTS PER COMPANY

Sources: (i) Global Fund's Price Reference Report, (ii) South African tender, (iii) Roche announcement on global ceiling price.

Values indicate the mean cost by company for Global Fund-supported countries. Purchase orders range from August 2011 - May 2014. When not provided, sample preparation costs for viral load were imputed as 22.8% of amplification and detection costs (this value was extrapolated from available sample preparation costs). Incoterms varied across products, therefore handling, insurance, and freight costs were included, as provided. The South African viral load price includes reagents, proprietary consumables, instrumentation, and service and maintenance costs, as reflected inthe 2014 tender (exchange rate October 2014). The lowest global ceiling price reflects the September 2014 reagent and proprietary consumable price announcement by Roche for 83 countries, and is likely an ex-works price. Products included (number of different country orders): Alere (n=11), Partec (n=9), BD (n=24), Beckman Coulter (n=1), Millipore (n=2), Roche lowest global ceiling price (n=83 offered), Abbott (n=8), Biocentric (n=1), bioMérieux (n=3), Cavidi (n=1), Roche (n=3).

CD4 AND VIRAL LOAD COSTS BY COMPANY

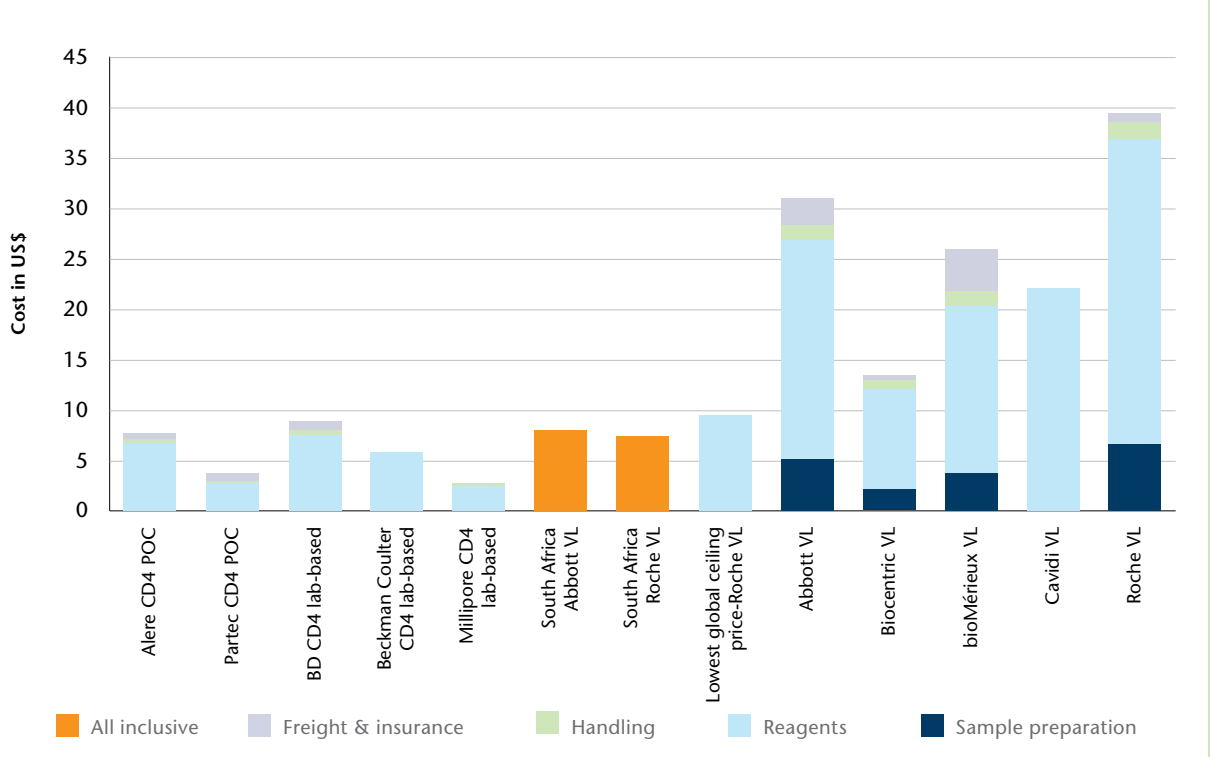
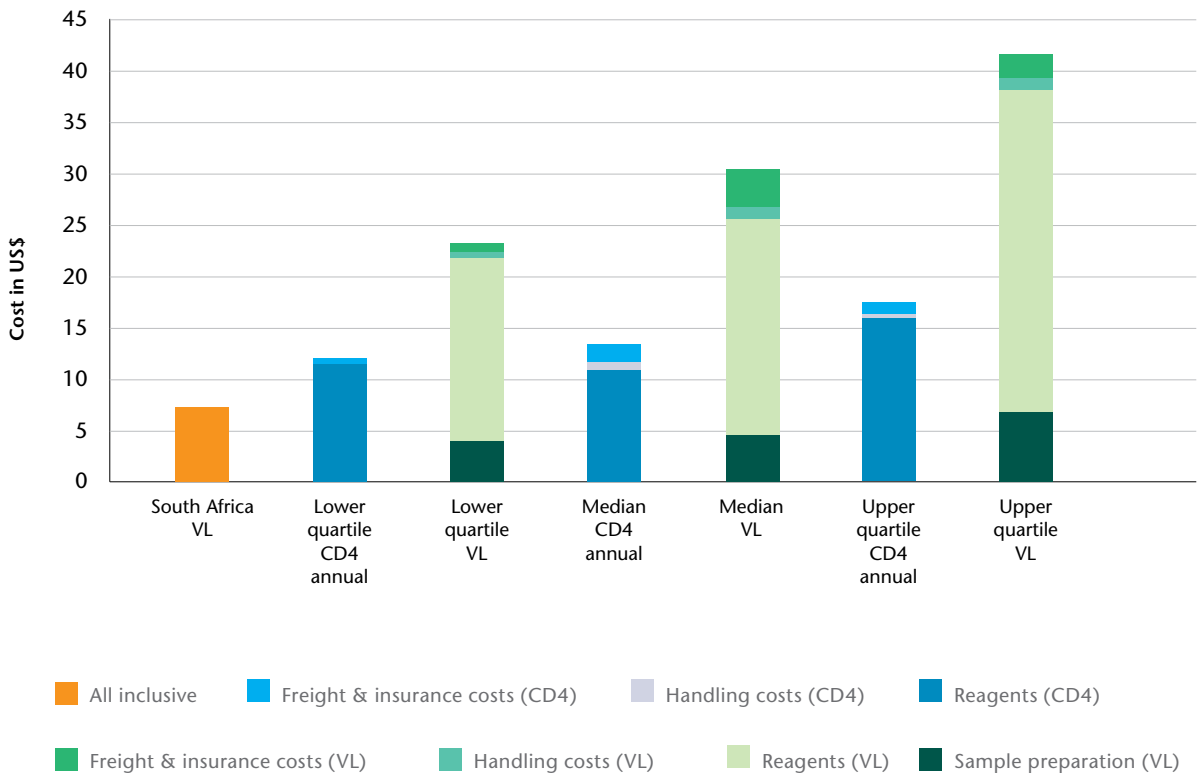


FIGURE 2B: PRICES OF CD4 AND VIRAL LOAD TESTS PER COUNTRY

Sources: (i) Global Fund's Price Reference Report, (ii) South African tender (10 October 2014), (iii) Roche announcement on global ceiling price.

Quartiles were calculated based on costs for countries supported by the Global Fund (n=13) as well as the South African viral load tender. Annual costs were calculated assuming two CD4 tests per year and one viral load test (as per the majority of current country guidelines for routine treatment monitoring). Purchase orders ranged from August 2011 - May 2014. When not provided, sample preparation costs for viral load were imputed as 22.8% of amplification and detection costs (this value was extrapolated from available sample preparation costs from Abbott). Incoterms varied across products; therefore handling, insurance, and freight costs were included, as provided. The South African viral load price includes reagents, proprietary consumables, instrumentation, and service and maintenance costs, as reflected in the 2014 tender (exchange rate, October 2014).

CD4 AND VIRAL LOAD ANNUAL COSTS BY QUARTILE



5. GETTING THE BEST DEAL: IS THERE ROOM FOR MORE EFFICIENCY IN CONTRACTING AND UTILISATION OF VIRAL LOAD MACHINES?

PURCHASE OPTIONS

Countries may have options in purchasing equipment outright, leasing equipment or having reagent rental contracts, where instrumentation (along with repairs, parts and labour, maintenance, replacement of equipment and training of laboratory personnel) is typically included. The latter requires known and accurate volume commitments for the length of the contract. Countries, such as South Africa and Brazil, who have a competitive tender process, usually opt for reagent rental contracts, otherwise known as reagent agreement plans (RAPs). In the MSF five-country survey, respondents noted the importance of RAPs, with several expressing dissatisfaction that they had been required to purchase particular machines due to company policies. RAPs place the responsibility for instrument provision and maintenance on the manufacturer and ensures that the platform is replaced when needed. Importantly, this also obviates the need for initial equipment purchase, which can be in region of $200,000 for large, high-throughput, laboratory-based platforms[29], thus avoiding large upfront costs and allowing for flexibility in changing platforms and suppliers, should better products enter the market (particularly as, to justify the large investment, laboratories usually want to use the machine for the extent of its lifetime).

The MSF five-country survey revealed that most countries are still purchasing instruments. In Zimbabwe, machines have been purchased, and viral load expansion will likely rely upon continued purchases, financed by donors. Malawi has also purchased six Abbott m2000 platforms with donor funds, with two additional ones planned. Abbott does not charge service and maintenance fees on the platform, but instead includes a top-up cost of $0.15 on each test. MSF has purchased the bioMérieux platform in Malawi, as it is validated for dried blood spots, and bioMérieux did not offer a reagent rental option. By contrast, in Kenya, companies place machines as part of an East African pricing agreement brokered by CHAI; as such, neither the government nor contracted laboratories purchase instrumentation, nor PEPFAR, as the donor who pays for the tests.

OPTIMISING THROUGHPUT OF MACHINES

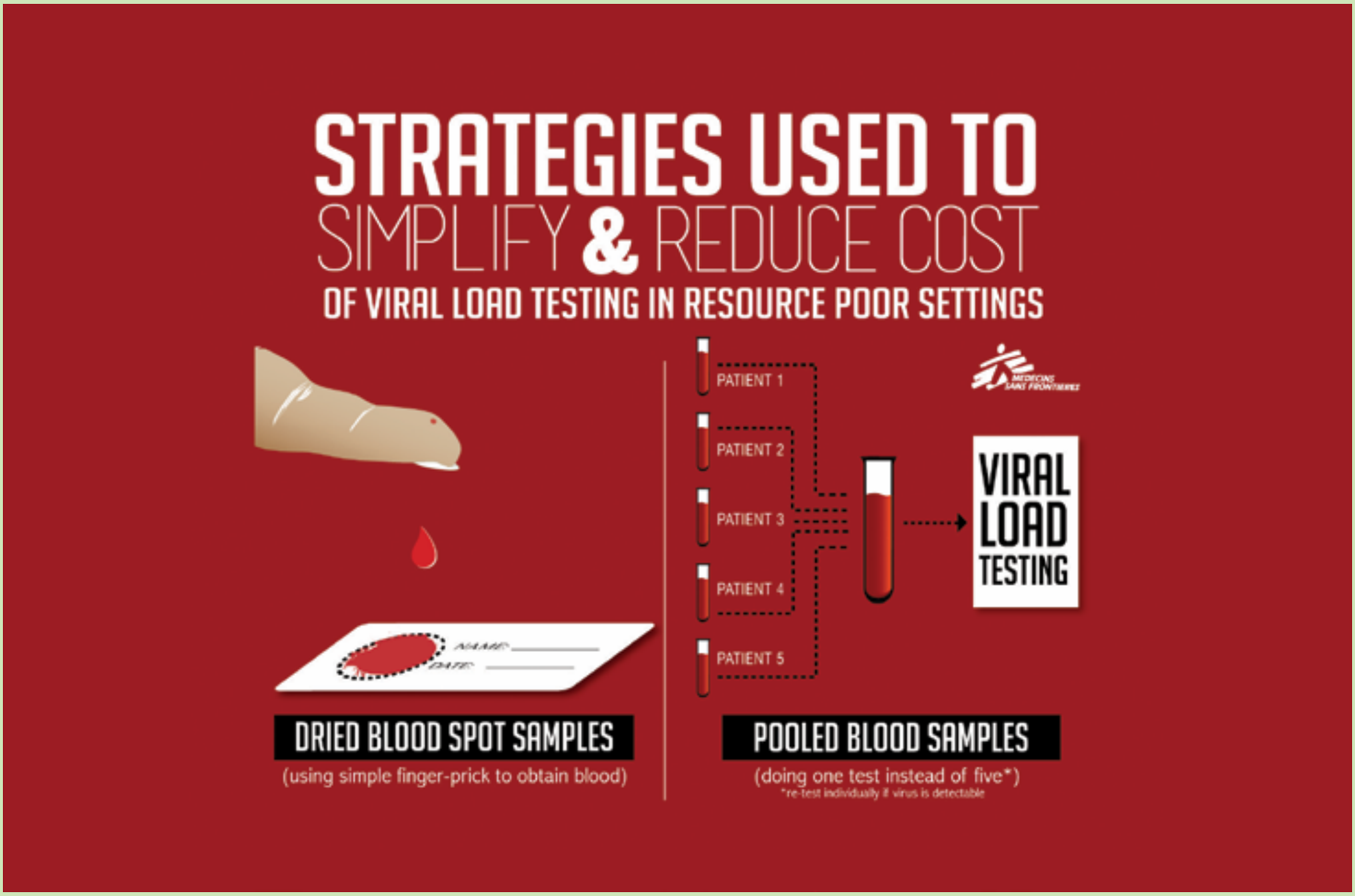
Cost savings are also possible through laboratory-based improvements in efficiency, where instruments are used as close to maximal capacity as possible[28]. For example, the Rio de Janeiro state laboratory service of Brazil, which is already operating a very efficient viral load laboratory system, demonstrated that an additional 20% cost-savings was achievable through sample flow improvements and consolidation of viral load monitoring laboratories.[30]

As countries consider which platforms to select, polyvalency – the capacity to run assays for other diseases on the same platform – also needs to be considered.[29] Investing in platforms with polyvalency enables expansions in laboratory capacity for other diseases, accelerating diagnostic access overall and general health systems strengthening. For those countries that have purchased instrumentation, it also reduces overall large upfront costs, as a different machine does not need to be purchased for each different disease, and – for simplicity's sake – allows for standardised human resource training, service and maintenance, and procurement.

SAMPLE POOLING

One method of decreasing the price of viral load testing is through a method known as sample pooling. Long utilised in blood banks, pooling has recently been introduced as way to save money and human resources in viral load testing. Although plasma can also be pooled, in resource-limited settings pooling of samples based on dried blood spots (DBS) is preferred, as DBS is an easier-to-implement sampling method for viral load testing. The DBS pooling method is based on combining DBS tests, one each from five different people, into one single sample. If the pooled result is undetectable then no further testing is required. However, if the result exceeds the virological failure threshold, then each sample must be retested separately to find out which people are viraemic. Considering that only approximately 20% of adults will have a viral load above 1,000 copies/mL[31], the efficiency of pooling can be quite high (reducing the number of tests required by around 30%, using a virological failure threshold of 1,000 copies/mL[32]). MSF have completed a comprehensive pilot of DBS pooling for viral load testing in Malawi, including preparation of DBS from fingerprick blood and pooling five samples, with good results.[31] In Malawi, using a cost of $30 per test, DBS pooling would reduce the number of tests performed by 30%, saving $207,000 per year.[32]

However, hesitation remains in taking DBS pooling to scale, with concerns around an increased complexity in both running the test and interpreting the result. In addition, as prices for viral load reagents and consumables continue to drop, particularly with an increase in volumes, the cost effectiveness of pooling may decline. Sample pooling may also be less of a priority while laboratory efficiencies are still low. Scaling-up viral load testing volumes should alleviate this problem.



MARKET UNCERTAINTY: KEY POINTS FROM A GLOBAL FUND CONSULTATION WITH MANUFACTURERS, DONORS AND IMPLEMENTERS

In September and October 2014, the Global Fund held a consultation both with manufacturers of HIV diagnostics products[33] and with implementers[34], respectively, in the lead up to issuing a tender for viral load tests in Q4 2014. They are developing a strategy to acquire and use HIV diagnostic products better and are intending to develop a range of different contracting models, including purchase, reagent rental and turnkey agreements.

The Global Fund has forecast a total spending of $90 million specifically for HIV diagnostics for 2014. This includes 500,000 viral load tests (cost $14 million; 16% of total GF 2014 HIV diagnostics spending), a significant increase. As of October 2014, the overall reported spend on HIV diagnostics for both 2013 and 2014 equated to $119 million. Procurement by the Partnership for Supply Chain Management, who procure commodities for PEPFAR programmes, has also increased its diagnostics purchasing steadily since 2007, with laboratory and clinical tests across diseases now amounting to 17% ($23,732,629) of non-pharmaceutical purchases.

With significant purchasing and market shaping power, the Global Fund and PEPFAR may help address available funded market uncertainties in viral load. This is a key moment in the journey of many of the new products to finally gain market entry into countries. Manufacturers are now in the so-called "valley of death" phase – named for the risk of inability to continue financially – which includes the expensive phases of pre-market validation, scale-up of manufacturing and commercial release and marketing of a product expected to be innovative, robust and of good quality but, at the same, affordable. The Global Fund engagement with manufacturers highlighted some key points, including (but not limited to): i) manufacturers are faced with complex and expensive regulatory requirements in countries and welcome the regulatory harmonisation work; ii) there is ambiguity surrounding how countries select products and whether DBS will be used for viral load testing; iii) there is concern around market saturation with existing products, with no room for new, perhaps more innovative, technologies in the future; iv) a large concern, which also limited manufacturers' ability to ensure production scale-up and price decreases, was a lack of realistic forecasting from countries (bottom-up forecasting) to gauge the true market size, rather than just a top-down estimate of the entire market potential (manufacturers would preferably need 12-18 month rolling forecasts to plan manufacturing needs); v) another large concern, from small manufacturers particularly, was having to absorb all of the financial risk, for example, when large orders are placed but not picked up and/or not paid for.

6. HOW CAN WE GET THE RIGHT RESULTS TO THE PATIENT ON TIME?

IMPROVING SAMPLE TRANSPORTATION

The MSF five-country survey revealed that efficient sample transport systems are one of the key constraints to scaling-up viral load testing. To overcome these challenges, countries can choose to invest in 1) better and quicker sample transport systems, so that fresh blood samples can be transported to the laboratory in time; 2) switching to using DBS as a sample type, which is stable at ambient temperature for weeks; or 3) decentralising viral load testing through point-of-care devices. A combination of these strategies, even within the same country, is also possible, based on the proximity of the clinic to the laboratory and the transport resources available.

South Africa has invested extensively in sample transport systems in conjunction with the National Health Laboratory Service (NHLS), a parastatal performing all laboratory tests for the public healthcare system, and this functions for the most part effectively. Data gathered in the MSF five-country survey indicated that the NHLS has refined its sample transport system, outsourcing sample collection to private couriers. These couriers are not province-specific, and so deliver the samples to the nearest facility by proximity, rather than by province. Currency fluctuations also put a strain on the services that the NHLS offer, because prices are often fixed in US dollars; in addition, inflation pushes the costs of these imported reagents and consumables ever higher.

Kenya has also invested in sample transport improvements and has hired a private courier to pick up samples from town level. Sample transport from facility level by private couriers has not been found to be cost-effective, and thus couriers are generally only employed for district-level collection. This creates transport gaps from the district to the clinic, the "last mile" of the transport system, causing delays and contributing to limiting access to viral load testing. This highlights that general sample transport needs to be improved as part of health systems strengthening. Countries that have already established efficient systems for DBS transport used for infant diagnosis can leverage this existing system for viral load testing.

India has not focused on improving sample transport for viral load. Instead, they require that people come to the State AIDS Clinical Research Panel to see if they qualify to have a viral load test, and then to have blood samples collected and receive the results, sometimes travelling 100km each way.

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One constraining factor in transporting fresh blood is the extremely conservative manufacturer recommendations that EDTA blood tubes must reach the laboratory within six hours at room temperature – this is impossible for most places, especially outside of central urban areas. However, sample transport guidelines both for EDTA whole blood and processed plasma may be revisited in light of evidence on the extended stability of viral RNA, which suggests that whole blood samples can be stored at 25°C in EDTA tubes for at least 72 hours.[35] Current recommendations require that plasma is transported within 24 hours at 25°C in EDTA tubes, or within five days at 4°C for EDTA or plasma preparation tubes, after centrifugation. If there is no access to centrifugation, whole blood in EDTA or plasma preparation tubes cannot be stored for more than six hours at 25°C. The logistical constraints, coupled with overall expense, make this option challenging to implement in resource-limited settings. In order to definitively amend current recommendations, further RNA stability testing is needed, particularly in field conditions. Manufacturers are encouraged to perform these tests as a matter of urgency so as to allow countries more flexibility in transporting blood samples and, in so doing, enabling more people to access the gold standard, plasma-based, viral load testing.

DRIED BLOOD SPOTS

DBS are a convenient form of blood sample, traditionally used for early infant diagnosis but also, increasingly, for viral load testing. DBS are stable at ambient temperature and are easy to transport. The use of DBS is often

the only option for resource-limited countries to expand viral load testing outside of urban areas. While the small sample volume limits sensitivity, and the cell-associated virus can diminish specificity compared to plasma, use of DBS is critical to ensure universal access to testing, and platforms can be found that offer adequate accuracy compared to the preferred alternative where limitations on using whole blood exist.[36]

DBS testing enables sample transport challenges to be overcome with lightweight, heat-stable drops of blood collected onto filter paper and shipped to national laboratories. As venous blood collection requires trained phlebotomists, the validation of DBS preparation from capillary whole blood, collected by fingerprick, including by lower-tier ART clinic staff in Malawi, has found that fingerprick DBS works well compared to both venous DBS and plasma. Additionally, lower cadre health workers are capable of providing high quality DBS specimens.[31,37,38] In Malawi and Zimbabwe, fingerprick DBS has also been validated on the bioMerieux-provided platform, with good correlation to plasma, despite the slightly higher rates of elevated viral load testing detected by DBS.[37,39]

The MSF five-country survey revealed that both Malawi and Zimbabwe have chosen to prioritise DBS to expand access to viral testing by overcoming sample transport challenges. With courier systems viewed as unreliable, and with limited diagnostics infrastructure, DBS is seen as the most pragmatic solution. DBS is also being scaled-up in Kenya, although there appears to be reluctance among key laboratory leaders on how much DBS implementation is actually desirable compared to plasma-based testing. Despite these hesitations, 32% of viral load tests in Kenya are being done with DBS.

The reason why DBS has been met with hesitation in several areas is due to validation gaps in some platforms, and potentially different thresholds for determining virological failure than the gold standard plasma. While commonly used viral load tests have yet to receive WHO prequalification for use with DBS, research studies suggest reasonable performance.[36] A Kenyan validation study showed that DBS prepared both from fingerprick and venous whole blood compared well to gold standard plasma testing, under normal field conditions, across 1,000, 3,000, and 5,000 copies/mL thresholds, using the Abbott m2000 platform.[40] Evidence from Rwanda also found that venous DBS – and to a lesser extent dried plasma spots (DPS) – have a high correlation with gold standard plasma viral load testing using the Roche CAP/CTM platform, although specificity was poor using DBS.[41] However, with their new cell-free elution method, the specificity of the Roche-provided assay has improved substantially.[36,42]

The potential for DPS to overcome the specificity problems associated with DBS may prove useful if plasma can be prepared from capillary blood using plasma separation devices. Although this method has yet to be field validated, there are some prototypes available, including a plasma separator currently used with the LYNX HIV p24 Antigen Test (Northwestern Global Health Foundation). Crucially, for these separators to be user-friendly, they must have an efficient filtration to maximise the volume of plasma obtained from a fingerprick sample, have a short filtration time, and be very affordable.

At present, as DBS testing yields somewhat reduced sensitivity and specificity, the acceptable misclassification rates need to be defined by the international community. Based on a meta-analysis and expert input, WHO issued interim guidance on DBS viral load testing: DBS should be used in areas where plasma cannot be accessed, with plasma confirmation preferred for treatment switch.[36]
No consensus was developed on DBS thresholds. At the 1,000 copies/mL threshold, sensitivity ranged from 81.02% (Roche Molecular Systems: COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 [free virus elution protocol]) to 95.24% (Abbott RealTime HIV-1) and specificity from 55.16% (Biocentric Generic HIV viral load assay) to 96.74% (Roche Molecular Systems: COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 [free virus elution protocol]).[36]
It is anticipated that further guidance from WHO will include acceptable misclassification thresholds, or guidance on how countries can perform a risk/benefit analysis based on the expected misclassification rates of using DBS. Often DBS will be the only solution available for expanding viral load testing, thus the best platforms for this purpose should be selected.

ELECTRONIC/MOBILE TECHNOLOGIES USED TO RELAY RESULTS

Relaying the results of viral load tests in a timely manner remains challenging. The MSF five-country survey showed that results delivery is primarily provided on paper, with high potential for human error and a perceived lack of urgency for delivering these routine test results. For example, even with heat-stable and lightweight DBS, sample transport remains challenging. To address these limitations, Malawi and Zimbabwe have piloted several innovations to improve both sample delivery (Riders for Health) and relaying results (by SMS, SMS printer, or a password-protected website). Several electronic options have been piloted within countries, though almost none have been used at scale. SMS printers, installed at many clinics, are not ideal for areas that lack access to electricity and may often be out of service, although have clear benefits for prompt results delivery, especially if they are bi-directional with the laboratory.
A direct SMS to the patient offers the most rapid response.

POINT-OF-CARE TESTING

While the use of DBS can overcome transport barriers, test turn-around time can still be an issue, particularly when mobile health and electronic solutions have not been employed for

faster result delivery. In five district hospital ART clinics in Malawi, only 68% of people received their viral load results within 3 months.[38] Furthermore, if sample transport cannot be done daily, people may have to return another day for a blood draw, which could reduce uptake, and transport challenges can be difficult to overcome in remote, hard to reach, areas. In early infant diagnosis, an immediate result is critical to ensuring good outcomes. Furthermore, for patients in virological failure, quick return of results is critical for timely reinforcement of adherence or timely treatment switch. For all those reasons listed, there is an interest in point-of-care testing. The MSF five-country survey revealed that, although there doesn't seem to be a broad utility of point-of-care viral load testing, it would be beneficial in certain contexts, such as for people living in very remote areas, and for those with important adherence challenges, such as children and adolescents. Countries noted interest in two types of point-of-care tests, along with their ideal profiles:

True viral load point-of-care test: which requires no electricity, operates via fingerprick whole blood (i.e. not requiring phlebotomy or plasma), requires no cold chain, is battery operated, requires simple training, can be operated by a community health worker, and with a comparable cost of testing compared to laboratory-based tests.

Near-point-of-care test: which may require electricity but would be placed at district/town level, with throughput between 50-100 tests per day (for example), with connectivity, includes an easy way to fix problems, has polyvalent options, and delivers reliable results.

Many respondents stressed, for both true and near point-of-care tests, the urgency of better and more regular training of health care personnel at local clinics who would administer point-of-care tests. Adequately and regularly trained staff are needed to ensure that tests are done correctly and that results are recorded and disseminated.

Point-of-care viral load test prices may not reach the low prices for reagents and consumables used in high-throughput laboratory-based systems. Typically, integrated cartridges, which automate all the complexity of laboratory-based testing and provide robust, heat-stable reagents and other innovative technologies (such as microfluidics), are more expensive to manufacture than laboratory-based assays[28]. However, once other costs – such as laboratory and human resource costs, quality control and sample transport costs – have been added, cost comparisons may change, especially when taking into account the programmatic benefits of point-of-care viral load testing.

The MSF five-country survey revealed that Malawi is seeking to expand numbers of laboratory technicians to support point-of-care testing. However, training and expansion relies on donor support, which has not yet been sought. MSF has been doing a task-shifting trial to train lower-level lay workers to do basic things that laboratory technicians might otherwise be required to do (such as take samples correctly and record results). One goal is to clearly show that it is not necessary to use laboratory technicians to perform a point-of-care viral load test that MSF has implemented in Malawi – the SAMBA test[43] – and, potentially, other new technologies for viral load that might eventually be used. In Zimbabwe, there is acceptability concerning the concept of point-of-care testing, and the SAMBA I test is in the process of being validated there (although is not yet included in national roll-out plans). Community respondents also noted the benefits of same-day test results.

For point-of-care testing, there is also the suggestion to develop a new level of lay worker that can be trained to perform these tests, and be responsible for the quality and reporting aspects needed. For example, in Swaziland, MSF have set-up so-called "mini-labs" with lay workers trained as phlebotomists who are responsible for the performance of all available point-of-care testing (including CD4, creatinine, haemoglobin, rapid diagnostic tests, etc.); for quality control and assurance; and for reporting of results. They have a dedicated room at the clinic for this, and the clear division of labour is helpful for the clinic in general.

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7. THE VIRAL LOAD TESTING CASCADE – HOW CAN WE MAKE EVERY TEST COUNT?

The MSF five-country survey revealed that, for the most part, overall patient-tracking remains extremely limited. Most countries do not have unique patient identity (ID) numbers, which is one of the main barriers towards tracking patients between clinics, and providing a reference to the results if an electronic database is used. Better patient and sample tracking is needed and there are opportunities to improve this. For example, CHAI and EGPAF are in the process of supporting the development of central database systems for countries.

While providing viral load testing remains critical, the viral load test itself is merely a tool that, on its own, cannot improve patient care. Particularly for those with a viral load above 1,000 copies/mL, intervention is critical, to reinforce adherence or to switch drug regimen, if needed. As most countries are now introducing viral load testing, training of clinicians and counsellors, both in the clinic and the laboratory, along with patient education, will be critical if we are to maximise the benefits of viral load testing.

The new algorithm (Figure 3) that MSF is using in Zimbabwe includes routine viral load with triggered CD4 testing only for viraemic patients, to inform the need for cotrimoxizole prophylaxis and to screen for opportunistic infections. In addition, when the first viral load test is above 1,000 copies/mL, this should trigger the need for enhanced adherence counselling, with a switch to second-line therapy should the person not re-suppress.

The importance of supportive adherence counselling cannot be over-emphasised, as many patients can re-suppress after an adherence intervention, thus preserving their first-line regimen[12]. However, adherence support must happen early on, and be prompted by routine viral load testing, if development of drug resistance is to be prevented.

Since human resources are often lacking for performing counselling tasks, it is clear that this important level of healthcare workers needs additional support and resources, and the need for this level of lay workers should be factored into viral load testing implementation.

BUDGETING FOR VIRAL LOAD SCALE-UP

As suggested by the WHO supplement to the 2013 guidelines[2], the 2015 guidelines are likely to include a strong recommendation on routine viral load for treatment monitoring as the preferred test, without parallel CD4 testing, once immune reconstitution has been achieved and the patient has reached virological suppression. Respondents in the MSF five-country survey were largely supportive of this decision, and, indeed, South Africa has already dropped routine CD4 testing after 12 months on ART. Other countries that have not yet scaled-up viral load testing face a more complex decision. Many respondents were concerned about the country's ability to manage the phase-in of viral load alongside the phase-out of CD4, to ensure sufficient CD4 capacity just for pre-ART and baseline testing, while ensuring that as many people on ART as possible receive at least some kind of laboratory-based ART monitoring during the transition period. As universal access to viral load monitoring has not yet been achieved outside of South Africa, the continuation of relying on CD4 testing for ART monitoring in other countries continues.

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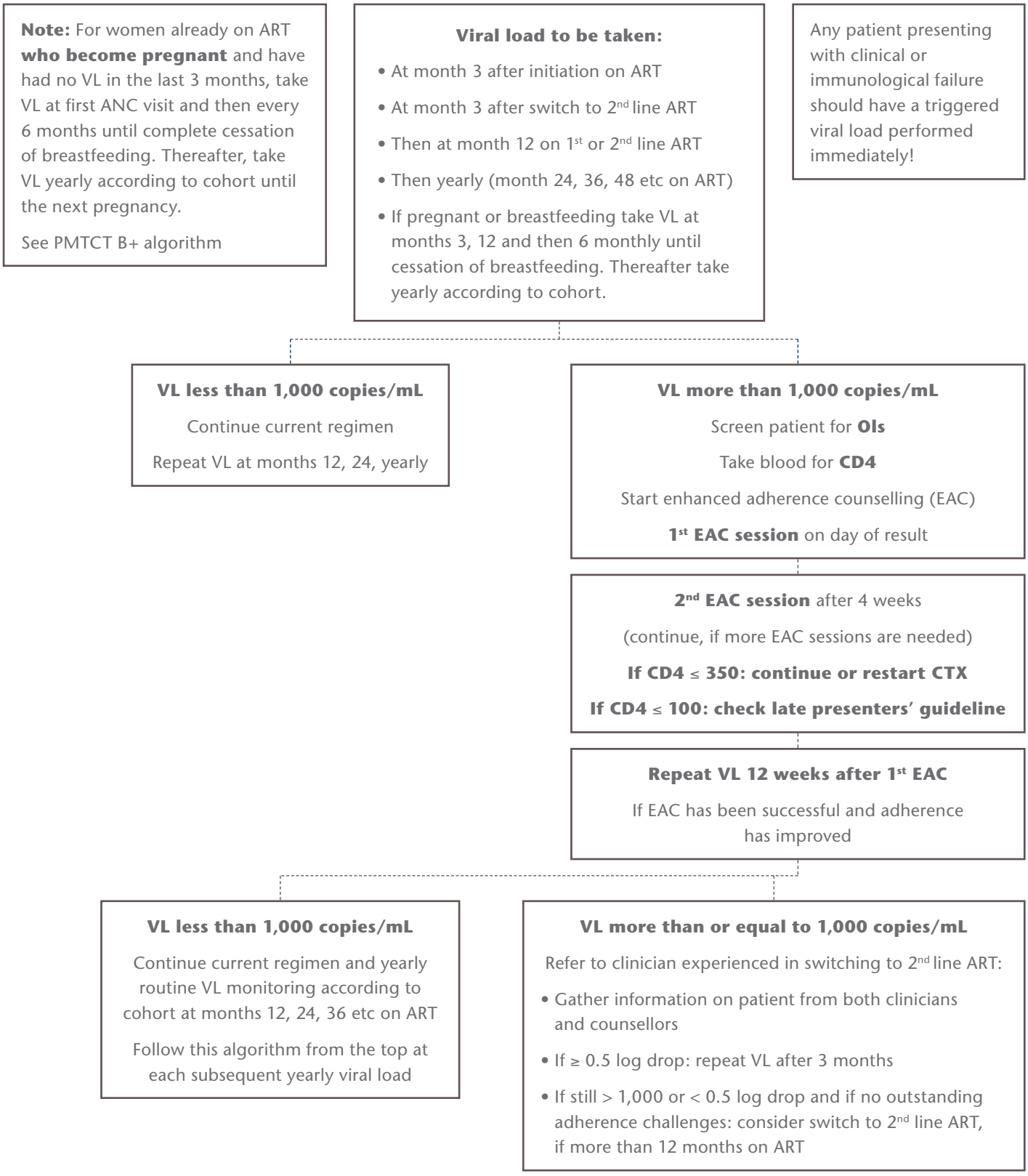
Figure 3: Algorithm for Routine Viral Load



SWAZILAND CASE STUDY

In 2012, MSF began viral load monitoring in Swaziland as a pilot project. The aim of the pilot was to demonstrate feasibility of viral load testing in the rural district of Shiselweni[44]. The number of monthly viral load tests performed increased from 500 in May 2012 (the beginning of the project) to more than 2,500 in June 2014. This corresponds to estimated viral load coverage of more than 85%.

While successful, this pilot study also revealed several programmatic challenges with the implementation of routine viral load testing, targeted adherence support and treatment decision-making along the "viral load cascade" (uptake for first viral load testing, return of viral load results, follow-up with enhanced adherence counselling, uptake for repeat viral load test, timely decision making on treatment switch, etc.), which other implementers, including country programmes, may face. There were several lessons learnt from this rollout.

Equipment selection had to meet both the cost and space requirements. MSF selected the open, multi-manufacturer, generic platform supplied by Biocentric, as it was the least expensive option at the time, and had a small laboratory footprint (ideal for the small space they had refurbished at the health centre for a viral load testing laboratory). They were able to hire well trained laboratory technicians, who would be able to perform the more manual process compared to the more fully automated, larger, central laboratory platforms. The current arrangement includes the purchase of the platform, reagents and other materials by MSF, along with payment for the annual maintenance and proficiency testing.

In the 22 primary care clinics served by MSF in the Shiselweni region, MSF also provides the sample collection. This was limited to the two days per week that transport cars could be made available. To reduce the need to only twice weekly pick-ups, MSF installed centrifuges in all 22 health centres so that plasma could be processed and stored in the refrigerator. This helped to improve access to daily sample collection for patients. This sampling process was task-shifted to trained lay worker phlebotomists - who already have experience operating "mini-labs" at the health centres – to allow for sample collection flexibility of up to five days. Sending plasma to the laboratory – located in the same district – made sample transport much easier and reduced the workloads on the laboratory staff, who no longer had to centrifuge the blood tubes themselves. Results are currently transmitted by paper every week, with a median time to result of 16 days.

Due to the success of the project by MSF, the Ministry of Health will scale-up routine viral load testing in all of the country in 2015, and has sought advice from MSF and the Clinton Health Access Initiative on how to implement this in the Swaziland context.

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CONCLUSIONS

Over the last two years, and since the release of the WHO 2013 guidelines, there has been a rapid acceleration in normative and country policies supporting routine use of viral load, but implementation continues to be slowed by a number of barriers. However, examples of best practices in price negotiation, sample type and transport, and task shifting already suggest that scale-up of viral load monitoring is realistic in LMICs. Countries can also now take advantage of price reductions for high throughput viral load testing. During this period of optimising implementation, continued national and international support will be needed – both in terms of finance and implementation support – to allow countries to rapidly scale-up viral load testing, to provide both optimal monitoring for patients and to allow countries to move away from CD4 ART monitoring. Transparency on prices paid for viral load tests, as well as on best practices and lessons learnt, is of the utmost importance during this time. Countries and other actors should coordinate this information and ensure that it is widely and publicly disseminated.

ADDITIONAL INFORMATION

More detailed information is available online in supplementary material, which may be accessed at www.msfaccess.org/achieving-undetectable. This includes: 1) the full UNAIDS guideline database analysis; and 2) additional information from the Global Fund's PQR tool pricing analysis.

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Previous MSF Undetectable publications (including training and implementation tools)

Volume 1 - Undetectable

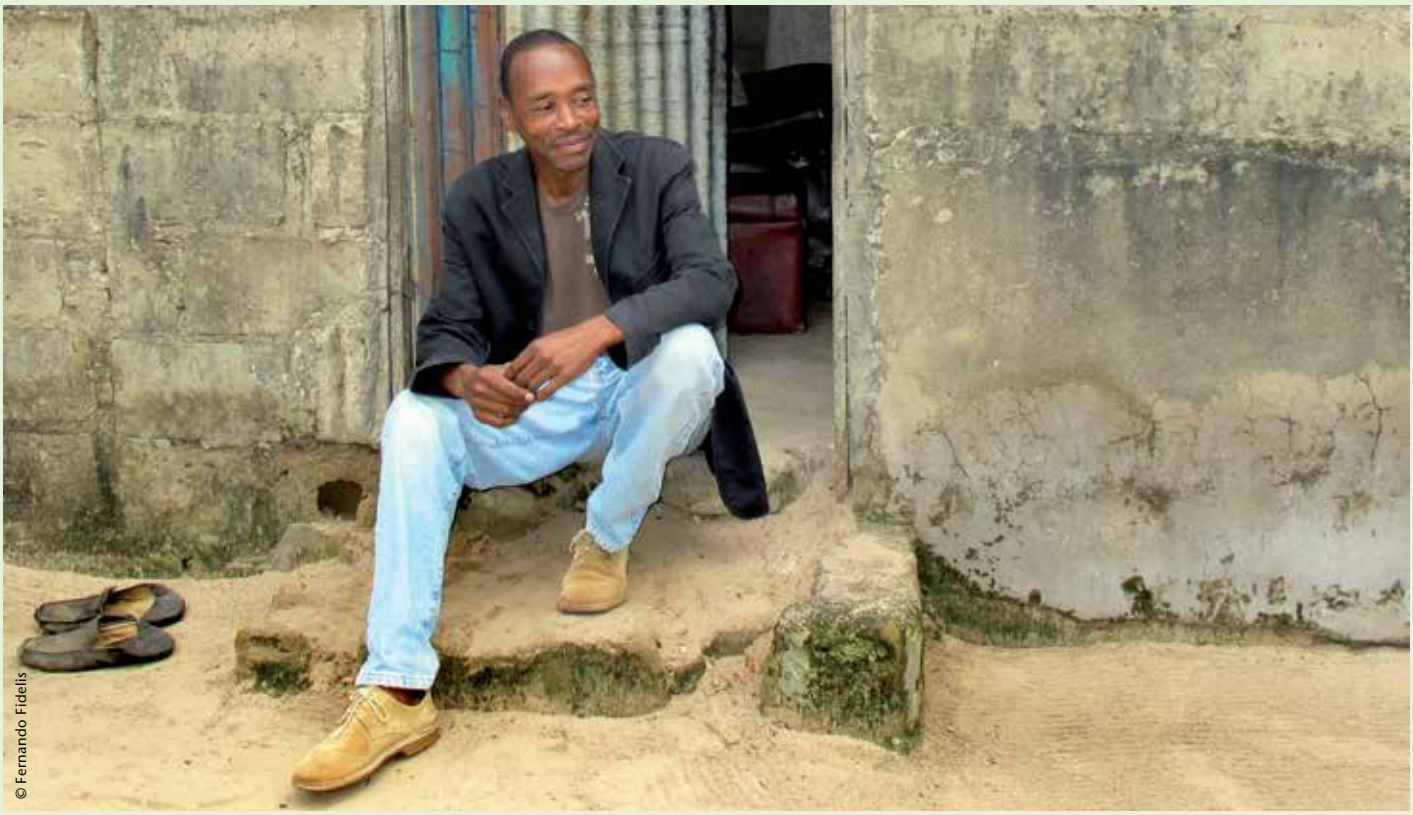
Volume 2 - Putting HIV Treatment to the Test

Volume 3 - How Low Can We Go?

Volume 4 - HIV Status? Undetectable

Voume 5 - Getting to Undetectable

Available at: www.msfaccess.org/undetectable



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ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

MSF Access Campaign
Médecins Sans Frontières, Rue de Lausanne 78, CP 116, CH-1211 Geneva 21, Switzerland
Tel: + 41 (0) 22 849 84 05 Fax: + 41 (0) 22 849 84 04 Email: access@msf.org
www.msfaccess.org facebook.com/MSFaccess twitter.com/MSF_access