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## Influence of evolving HIV treatment guidance on CD4 counts and viral load monitoring: A mixed-methods study in three African countries

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### Abstract

Little is known about how CD4 and viral load testing have evolved following implementation of universal test and treat (UTT) in African settings. We reviewed World Health Organization (WHO) guidance from 2013 to 2018, and compared it against national HIV policies in Malawi,

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Tanzania and South Africa. Three surveys rounds were conducted in 2013, 2016 and 2017–2018 in 33 health facilities across the three settings to assess implementation of national policies on the use of biological markers. Qualitative interviews were conducted with 26 HIV policymakers or programme managers, 21 providers and 66 people living with HIV to explore understandings and experiences of these tests. Various factors influenced adoption and implementation of WHO guidance, including historical policies on CD4 counts, governance issues, supply chain challenges and funding mechanisms. Facility-level practices relating to the use of these tests often diverged from national policies. Patients and providers valued both tests, but did not always understand their roles. In addition to continued support for scaling-up viral load testing, renewed focus should be placed on the ongoing value of point-of-care CD4 tests in the UTT era, including its role in assessing disease progression and informing clinical management of cases to reduce HIV-related mortality.

## Keywords

HIV; CD4 counts; viral load monitoring; sub Saharan Africa

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## Introduction

The past two decades have seen a rapid expansion in coverage with HIV treatment services for people living with HIV in sub-Saharan Africa, facilitated by national and international initiatives and resources (UNAIDS, 2014). Until recently, in most sub-Saharan African countries, CD4 cell counts represented the mainstay for assessing the immunological status of HIV patients, guiding decisions about eligibility for initiating HIV treatment, and for transitioning patients with poor immunological response to first-line treatment antiretroviral therapy (ART) regimens onto second-line drugs (World Health Organisation, 2010). In 2015, the World Health Organization (WHO) recommended that patients diagnosed with HIV should initiate ART at any CD4 cell count (World Health Organisation, 2015), a strategy known as ‘universal test and treat’ (UTT). The wide-spread adoption of UTT in sub-Saharan Africa has been recognised as a critical step in moving towards targets to eliminate AIDS by 2030 (Nsanzimana et al., 2015; United States Agency International Development, 2014).

While CD4 cell counts (hereafter referred to as CD4) provide an indication of the strength of the immune system, it does not report viral activity, which is best measured through a viral load test. However, compared with CD4 testing, viral load testing is expensive and more technically complex, reasons which were widely cited as inhibiting its wide-scale use in most sub-Saharan countries during the first decade of ART scale up. As evidence on the benefits of viral load monitoring to preserve the lifespan of first-line regimens and improve patient outcomes has become established, the WHO recommended viral load (VL) monitoring as part of routine care for monitoring adherence and treatment failure among people taking ART in all settings (World Health Organization, 2017; World Health Organization, 2016).

Frontline access to CD4 remains essential for assessing disease progression (World Health Organization, 2017), identifying people diagnosed late with HIV (as indicated by a CD4 <

350 cells/ $\mu$ L) (Fomundam et al., 2017), informing differentiated care models (World Health Organization, 2017) and, more broadly, providing healthcare workers with an objective measure of a patients' health (Ford et al., 2017). However, there are several factors that have undermined their use including the growing availability of VL testing and recent guidance on its use, adoption of UTT, and a decrease in donor support for CD4 testing (Medecins sans Frontières, 2017; PEPFAR, 2019). As a result, several sub-Saharan African countries have drastically reduced CD4 monitoring in favour of increased VL testing (United States Agency International Development, 2016), and CD4 tests performed in some low- or middle-income countries are not been optimally utilised to inform clinical management (Haas et al., 2015). These concerns are exacerbated by suggestions that coverage of VL monitoring remains limited in sub-Saharan Africa settings (Ford et al., 2014), and even where the scale-up of VL testing is underway, the test results are used sub-optimally for informing clinical decisions (Ehrenkranz et al., 2019).

Recognising the ongoing value of conducting both VL and CD4 testing, we investigated the extent to which national policies on the use of each biological marker reflect WHO guidance, and the degree to which national directives on their use are implemented at the facility level in rural Tanzania, Malawi and South Africa. We also explore the challenges to their implementation from the perspectives of in-country stakeholders, and experiences with their use among patients and providers.

## Methods

This study draws on data from the 'Strengthening health systems for the application of universal test and treat' (SHAPE UTT) study. The SHAPE UTT study is a multi-country health systems research project investigating the policy implementation and health systems impacts of HIV test and treat policies in these three countries. This study uses survey data from health facilities serving the populations of three health and demographic surveillance sites in Tanzania (Ifakara), Malawi (Karonga) and South Africa (uMkhanyakude) to assess the extent to which national policies on VL and CD4 testing are implemented in practice. We also draw on data from key informant interviews to contextualise the policy content and national implementation strategies, and from qualitative interviews with service providers and service users to explore how tests are experienced and understood in everyday clinical practice (see Table 1 for study site and participant characteristics).

## Policy review

A review of national HIV policies from 2013 to 2017 was conducted to describe adoption of policies regarding CD4 and VL measures within each of the three countries (Table 2). WHO guidance was also reviewed for the same time period and compared against national policies. The methods for the policy review have been described elsewhere (Ambia et al., 2017; Church et al., 2015; Jones et al., 2019), but in brief, involved a consultation with HIV researchers and practitioners, and a review of the published literature to define key policy indicators related to the delivery of HIV care and treatment services. For the purposes of this analysis, details of policies directing the implementation of CD4 and VL testing were

extracted into an Excel spreadsheet which captured the key policy content, policy document name and publication date for comparison across countries.

### Facility survey

Three rounds of health facility surveys were conducted in 2015, 2016 and 2017/2018 in health facilities in Karonga, Malawi (n=5), Ifakara, Tanzania (n=11) and uMkhanyakude, South Africa (n=17). The development and details of the questionnaire have been described previously (Church et al., 2017). The questionnaire was administered in English with the staff member in charge of each facility and covered all components of HIV service delivery. For this analysis, responses to two questions relating to implementation of CD4 testing, and six to VL testing, were extracted from the database. Descriptive statistics were used to report the implementation of CD4 and VL testing by site.

### Qualitative data collection

**Key informant interviews**—Between April and June 2019, we conducted 26 key informant (KI) interviews with policy makers, donors and programme managers including regional/provincial implementing partners in Malawi (n=10), Tanzania (n=11) and South Africa (n=5). The overarching aim of the in-depth interviews was to explore how policy processes, context and various actors influenced the adoption and implementation of UTT and the subsequent impacts on the health system. Questions were asked to understand influences on policy development and adoption processes in each country and the timeline for Option B+ and UTT formulation, adoption and implementation. We explored factors that were perceived to have facilitated or inhibited the adoption and implementation of UTT, with specific probes pertaining to relevant health systems components, including *the workforce* (training, cadre, numbers) *service delivery* (coverage, access, quality), *access to essential medicines and technologies* (including CD4 and VL testing), *health information systems* and *health systems financing*. The interviews were conducted in English by experienced local researchers in Malawi and Tanzania and by the senior study investigator in South Africa, and were digitally recorded.

### In-depth interviews with health workers and people living with HIV

In-depth interviews (IDIs) were conducted with women receiving prevention of mother-to-child transmission (PMTCT) services during their antenatal care (ANC) and post-pregnancy, and health workers providing these services (Table 1). In each of the sites, health facilities were stratified by type (hospital verses smaller facility) and location (district centre verses remote). One hospital, one remote and one district centre facility were then randomly selected.

IDIs were conducted by trained fieldworkers in the local vernacular and lasted approximately 45–90 min. We chose to use IDIs over focus group discussions in order to avoid significant disruptions in service provision, and because the common power dynamics between different cadre of health workers may have led to a few dominant voices giving more opinions, or lower cadre staff feeling unwilling to express themselves in front of their superiors, particularly to dissent. IDIs were conducted in a private location and were audio-recorded with permission. Among health workers, topics included provision of HIV services

and changes since the introduction of UTT, familiarity with guidelines and how they were implemented, and perceived health systems impacts of implementing UTT policies. Probes focused on the same health systems components which guided the KI interviews. Amongst service users, topics covered a woman's experiences of their first ANC visit and HIV testing process. For women living with HIV, experiences of treatment initiation, longer term care provision (including their experiences with and understanding of CD4 and VL tests) and, where appropriate, reasons for care disengagement were also explored. Interviews began by asking women living with HIV how they perceived their health to be, and how they knew how their body was responding to ART. Probes were then used to explore more specifically what they knew about CD4 and VL tests, where they had garnered this information, their understanding of why they were used and what the results meant, and their experiences of ever having their VL and CD4 tested. Debriefings were held after each interview between field workers and the study coordinator, with weekly joint teleconferences between the lead researchers to discuss similarities and differences in the emerging findings across the three sites. Interview summaries were written in English by interviewers and shared with other researchers to guide the weekly discussions.

### Qualitative data analysis

Interviews were transcribed and those with service providers and users were translated into English. Data were coded with the aid of Nvivo 11 (Ifakara, Karonga) and manually (uMkhanyakude), according to thematic areas covered in the topic guides to ensure comparability. Transcription and broad coding were undertaken by the study coordinators in each country. The lead researcher in each site kept detailed analytical memos during the coding and analysis process, and regular meetings were held with the researchers in the different sites. All data related to biological markers were extracted and broadly coded deductively under nodes corresponding to the topic guide, and then the lead authors further inductively analysed to identify common and refutable thematic areas across the sites and the different groups and focused on the themes relating to VL and CD4 testing

### Ethical approval

Ethical approval was obtained from the Internal Review Boards of the Ifakara Health Institute (14-2017) and National Institute for Medical Research for Tanzania (#2579), National Health Science Research Committee for Malawi (#1861), the Biomedical Research Ethics Committee for South Africa (BREC REF: BE400/14) and from the London School of Hygiene and Tropical Medicine (#13536-1).

## Results

### Review of CD4 and viral load testing policies

Since 2017, WHO has recommended VL testing as the preferred approach to diagnose and confirm treatment failure, with testing to be conducted at six and twelve months after ART initiation and every twelve months thereafter. The guidelines also state that where VL testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (World Health Organization, 2017). In addition, the guidance recognises

that CD4 remains the best predictor for disease status and immediate risk of death, and indicates that all patients entering or re-entering care should receive a CD4 test at treatment baseline and as clinically indicated for patients who are unstable or with advanced HIV disease (World Health Organization, 2017).

All three countries revised their national policies on the use of CD4 and VL tests for HIV care and treatment during the study period (Table 2). In Tanzania, CD4 counts were indicated for determining eligibility for ART, and every six months thereafter to monitor immunologic response to ART and aid decision-making for transitioning patients with poor immunological response to second-line regimens (National AIDS Control Programme, 2015). In the 6th National Guidelines for the Management of HIV and AIDS, CD4 counts were no longer required to determine ART eligibility under UTT policies, but were still indicated for detecting opportunistic infections (Ministry of Health, Community Development, Gender, Elderly and Children & The United Republic of Tanzania, 2017) and broadly align to the WHO guidance. The use of VL testing was adopted in 2015 in Tanzania for all patients after six months on ART, with CD4 counts to be conducted if VL testing is not available (Ministry of Health and Social Welfare & National AIDS Control Programme, 2015; National AIDS Control Programme, 2015).

In Malawi, throughout the study period routine CD4 testing was not required for ART initiation nor for monitoring patients on ART (The Ministry of Health Malawi, 2013). The policy was refined in 2016, such that ‘targeted CD4 counts may be requested by specialist clinicians for complicated cases’ (The Ministry of Health Malawi, 2016). Viral load monitoring was introduced into treatment guidelines in 2011 to monitor treatment failure, and was first included as part of routine care in 2016, at 6 months after ART initiation and then every 2 years thereafter (The Ministry of Health & Malawi, 2016).

In contrast, policy in South Africa increasingly included a role for CD4 testing over the study period. In 2013 and 2015, national policies specified CD4 testing at baseline and annually. In 2017, policy aligned with WHO recommendation to increase the testing frequency to every six months until a patient achieved viral suppression (National Department of Health. South Africa, 2017). Routine VL testing to assess virological failure was first included in policy in 2015 with scheduling aligning to the WHO recommendation (National Department of Health. South Africa., 2015).

### **Implementation of CD4 and VL testing at the facility level: facility survey findings**

**General availability of CD4 and VL tests**—In uMkhanyakude (South Africa), the availability of facility-based CD4 testing increased from 0% to 82% (14/17) of facilities between rounds 1 and 3, and turnaround times for CD4 test results reduced slightly from an average of 3 days to 2.6 days (table 4). In Ifakara (Tanzania), average turnaround times for CD4 tests also improved from 3.66–1 days over the same time period, but the availability of CD4 testing reduced from 67% (8/12) of facilities in round 1 to 17% (2/12) facilities in round 3. In Karonga (Malawi), all facilities offered CD4 testing in round 1 (6/6), while no facilities provided CD4 testing by round 3.

Viral load testing was offered by all facilities in all three settings by the third survey round (table 4). In uMkhanyakude, the majority of facilities (88%; 15/17) offered on-site tests, whereas in both Ifakara and Karonga, the majority of facilities reported that samples for viral load testing were only available at another facility (83%; 10/12 facilities in Ifakara and 80%, 4/5 of facilities in Karonga). The average turnaround time for VL tests across the facilities was long in both Ifakara (29.4 days) and Karonga (44.8 days). In uMkhanyakude, the average turnaround was 3.4 days.

**Pre-ART initiation tests availability**—In uMkhanyakude, in line with national policy, the proportion of facilities requiring a CD4 test to initiate ART decreased from 100% in round 2 to 53% in round 3. Similarly, practice in Karonga and Ifakara aligned with the changing policy and in both settings, the proportion of facilities that reported requiring a CD4 test for ART initiation declined from 100% (12 facilities) to 8% (1/12 facilities) between round 2 and 3 in Ifakara, and from 60% (4/6 facilities) to 0% between round 2 and 3 in Karonga.

**Post-ART initiation testing**—In accordance with national policy, in rounds 1 and 2, the majority of facilities (88% [15/17 facilities] and 71% [13/18 facilities], respectively) in uMkhanyakude reported conducting annual post-ART initiation CD4 tests on stable patients, while the information was not available for round 3 (table 5). Also in accordance with national policy in Ifakara, 92% of facilities in round 1 (11/12 facilities), and 100% in round 2 (12/12 facilities), reported the same tests being conducted every six months, despite the limited availability already discussed, with no information available in round 3. In Karonga in round 2, despite policy guiding the use of CD4 tests for complicated cases, it was reported that 60% of facilities [4/6 facilities] were not conducting CD4 tests post ART initiation (nor were they available in the sites) and this information was not collected in round 3.

In all sites, no data were available for round 1 and 2 on the proportion of facilities with VL use to monitor treatment failure. However, in round 3, the majority of facilities in all three sites, in accordance with their respective country policies, reported using VL to monitor treatment failure, followed by clinical symptoms and then CD4 counts in one facility in both uMkhanyakude and Ifakara (table 6). The majority of facilities across all three sites and all three rounds reported conducting pill counts or asking about pill taking to measure ART adherence. In addition to these two mechanisms, all three sites also reported VL testing for this purpose in round 3, albeit at different levels of coverage across facilities (uMkhanyakude 76%; Ifakara 8%; Karonga 60%). The action taken in the event of low adherence varied substantially by round (table 6). Adherence counselling increased substantially from being conducted in almost no facilities in round 1 to the majority of facilities in all sites by rounds 2 and 3.

### **Implementation realities: perspectives of key informants, providers and service users**

Two themes emerged from the analysis of our qualitative data with regards to experiences of using VL and CD4 tests: (i) implementation challenges and (ii) understanding and perceived values of VL and CD4 results.

**Implementation challenges**—Key informants recognised the implementation challenges of conducting both VL and CD4 tests. One KI in Malawi described VL testing as ‘even more demanding’ than CD4 testing. Long turn-around times were frequently mentioned, often attributed to the lack of point-of-care testing and the need to transport samples to facilities with VL machines.

“molecular laboratories are few...maybe there are just 13 molecular laboratories I think,...we have 700 health facilities providing ART so there’s a big logistical challenge to get all the samples into those laboratories and get the results back to the patient. It’s hugely demanding, very, very complicated. It’s a real struggle. (KII, Malawi)

In both Ifakara and Karonga, where VL testing took place in centralised testing facilities, delays were reported.

“The test results take like one or two months, as they are not done here, we take the samples to XXX regional hospital, and sometimes we face challenges when the sample failed to read them, we are then supposed to take samples again and wait for one or two months again”. (IDI, Health care worker, Ifakara)

In practice, systems for the transportation of samples were inefficient due to their high costs which led to some providers waiting to collect multiple samples to make the transportation more economical, leading to longer turnaround time. In some facilities, a lack of refrigeration options compounded the logistical challenges and also contributed to these higher costs:

“I will take the blood to xxx to be kept into the refrigerator...That is also a challenge as you have seen the distance from here to xxx. I have to hire a motor cycle to there. I have to convince them to get 5–10 within a day instead of taking the sample of 1 or two patients...It cost.... Yes. It means I have to assess them on Wednesday those who have reached 6 months qualify for the test. If I get only 3, I will request them to come the next Wednesday knowingly that if I have these 3, the next Wednesday I will not miss other 3 or 4. And, I will pick together and send to xxx” (IDI, Health care worker, Ifakara)

Nevertheless, health workers from some facilities reported gradual improvements in terms of the regularity of returning results:

“there has been some improvement on transportation. We now have riders who bring us those results on Tuesdays and Thursdays”. (IDI, Health care worker, Ifakara)

Some KIs mentioned inadequate training for staff and machine breakdowns as factors which perpetuated slow implementation of routine VL testing:

“It’s not happening most of the time because we don’t have enough capacity...Or the machine is not working well, so there is that breakdown. Sometimes we have the machine, it is working, but our staff do not have the required skills...so that’s the challenge.” (KII, Tanzania)



Some healthcare workers noted similar challenges with CD4 counts, but felt that this was a lesser concern because these tests were no longer needed for assessing eligibility for treatment:

“...we stopped testing for CD4 a long time ago, because our machine is not working and these days it doesn't even matter because it is no longer a criterion for using or not using ARVs”. (IDI, health care worker, Karonga)

In two facilities, health workers felt that procedures for CD4 testing were not always followed, due to a lack of availability of the new guidelines, training in their application, or as a result of being over-worked and having insufficient time.

“Previously we were waiting for six months after putting her on medication...now there is something new... though I have asked for the guidelines but we are yet to receive them” (IDI health care worker, Ifakara)

“You may find those whom I deputise are not acting properly. They may not have tested CD4 for some patients for a long period...maybe due to overwork or they don't have sufficient experience...” (IDI health care worker, Ifakara)

In some cases, where health workers were impeded from systematically implementing the guidelines due to logistical challenges, they developed their own strategies to prioritise the patients that they felt were at greatest need of the tests:

“As part of patient monitoring, each patient on treatment has their VL tested after each six months to see how they are faring and to aid the early detection of any problems. In principle we were supposed to call the lab personnel... but as you have seen our rooms are small and there is no space for that so we made arrangements that when our clients reach the lab, they are given first priority not to stay in queue” (IDI, Health care worker, Ifakara)

In other cases, prioritisation by the health workers was made in terms of spending time on explaining the test results, so that some patients felt unaware of their meaning:

“You find that after taking the blood tests when the results come back. They no longer have enough time to sit down with you...the results came back but they did not explain anything to me. ... You don't get to know about it. You just keep on taking the treatment. They only give you attention if it's your first time taking the treatment. When you have become the regular they no longer care”.(Woman initiated on ART under Option B+, South Africa.)

### **Understanding and perceived values of VL and CD4 results**

In all countries, KIs were well versed on the role of VL testing to monitor treatment adherence. In some instances, the KIs suggested that VL testing had superseded CD4 counts, with some mentioning the redundancy of CD4 testing to assess ART eligibility and its inability to assess non-adherence and the emergence of resistance.

“We now emphasize viral load, that's why we are now using more viral load machines than the CD4, because with the viral load, tests we can capture the viral

count...maybe there is some resistance...in this case a CD4 count will not be as helpful as a viral load test.” (KII, Malawi)

One only participant, in Malawi, articulated the additional role of CD4 over and beyond VL testing, suggesting that there was now a *‘re-appreciation of CD4 count as a tool for risk stratification and to identify patients who are high risk and need extra care’* (KII, Malawi)

Healthcare workers in all settings recognised the value of both CD4 and VL tests to guide the clinical care of their patients. Some health workers appreciated the added value of VL tests over CD4 for determining when to change regimens, however this benefit was somewhat offset by the common delays that were experienced in receiving results back:

“Now things have been improved. Previously the decision to change from first to second line was based on CD4 count and clinical test. But now viral load helps us to know the patient’s status...so it is easier to change to second line although it takes time to wait for results” (health care worker, Ifakara).

However, in each setting, many women living with HIV had no or limited understanding about the meaning or utility of CD4 and VL tests, with some reporting having never heard about them:

I: Has it ever happened that you were taken blood sample to measure your viral load?

R: No, its only today that we have been taken blood sample but we don’t know the purpose of blood sample taken. They only said we are taking blood sample to check if drugs are working properly but if we find that drugs have side effects we change and give another type of drugs. (IDI, Woman living with HIV from routine care and treatment, Malawi)

“I have had about CD4 count but I don’t think I can actually explain what it is”. (IDI, Woman living with HIV initiated under Option B+ during this pregnancy, Malawi)

In Ifakara, all of the women who started ART during their current pregnancy (under Option B+) stated they had never had a CD4 or VL test conducted that they were aware of, although some had heard about CD4 tests from the media and were keen to be tested but did not have the means nor resources to make this happen.

“CD4, I heard it from the media. And, there is a day we came here and we were asked if we have tested for CD4. I said no. They said, I must test. But, they didn’t give me the means to go to test or test me”. (IDI, Woman living with HIV initiated under Option B+ during this pregnancy, Ifakara, Tanzania)

For some women who had received their results, the experience was memorable.

I: Have you ever had a CD4 count

R: Yes I have had one but that was a long time ago

I:How was it then?

R:I think it was fine because it was about 400 if I remember well. (IDI, Woman living with HIV currently not engaged in care, Karonga, Malawi)

Despite the service user reports of limited implementation some participants in all countries expressed a desire for these measures (primarily CD4 counts) to know more about their health.

“I would like to know about CD4, when they increase and decrease, and to know my health progress generally”. (IDI, Woman living with HIV from routine care and treatment, Ifakara, Tanzania)

They help your immune system. To help you when your immune system is very low. When your CD4 count is high then it means you are protected.... Yes, I have measured my CD4 count, I am not sure if I was still protected because they were low...They were low because they were even less than 600. (IDI, Woman living with HIV initiated on ART under Option B+ during this pregnancy, South Africa)

Some KIs raised concerns over how test results were being interpreted and relayed to clients. KIs described that even when providers understood the meaning of virally suppressed results, they sometimes chose to hide the interpretation from patients, believing that it may prompt sexual risk-taking:

“if you are consistent on ARVs and your viral load is at zero, even if you have sex without being protected, you cannot transmit the virus. But we are trying not to relay this message as people may misinterpret it thinking that “now I cannot transmit”. The way we are doing with male circumcision, some are understanding that when I am circumcised it means I will not catch any virus” (KII, Malawi)

“That is an issue: the viral load are not in all facilities. They are so few and patients are not aware when it comes to viral load checking or testing. It is something that it will take a bit of time for people to grasp”. (KII, Tanzania)

Such insinuations were also present amongst healthcare workers. Not all healthcare workers were fully confident in explaining the purpose or the national policies regarding the scheduling of each test, particularly for VL testing. In all sites, some health care workers reported valuing VL tests because they enabled them to assess adherence, or in some cases to check if patients were ‘doing as they are told’. In Karonga and Ifakara, VL testing was reportedly used first and foremost to monitor adherence failure, with very few references made to treatment failure, suggesting a focus on the failings of the women’s treatment taking before questioning the drug effectiveness.

“I’m not sure if I am correct in this...from my knowledge, it is that after you test the mother with viral load and the virus are not detected, it means she takes her medications as it’s indicated and she follows the advice that we give her ...and if the virus are detected it means that the mother is irresponsible and doesn’t follow our guidance so the viral ...load is detectable...so we counsel them on taking their medications...”. (IDI, Health care worker, Karonga)

Some service users also felt that the main purpose of the tests was to enable the health workers to ‘check’ on them.

“...I personally think that it [testing] is because they want to see if you are taking your treatment correctly and to check if there are any changes”. (IDI, Woman initiated ART under Option B+ during this pregnancy, South Africa)

## Discussion

We investigated the extent to which WHO guidelines on CD4 and VL testing have been adopted in national policy, and implemented in health facilities in rural Tanzania, Malawi and South Africa. We also explored challenges to the implementation of these tests from the perspectives of stakeholders, providers and patients. In all three study countries, national policies on the use of CD4 and VL tests for HIV care and treatment were revised during the study period. In line with WHO guidance, VL testing became universally available in all three settings over the study period (World Health Organization, 2017), although significant challenges remain with, for example, long turnaround times to get results.

The picture for CD4 was more mixed. In Tanzania, CD4 counts were no longer required to determine ART eligibility, but were still recommended to detect opportunistic infections, in Malawi CD4 counts may be requested in ‘complex cases’, and in South Africa their role appeared to have increased over time. The availability of CD4 tests showed facility based CD4 testing increased, and turnaround times reduced, over time in South Africa. However, the picture in both Tanzania and Malawi was less positive. Whereas turnaround times for CD4 tests improved in Tanzania, facility-based testing overall greatly reduced. In the surveyed facilities in Malawi, CD4 test coverage went from 100% to zero over the study period. This is of concern given that WHO recommend countries retain their capacity to conduct CD4 testing at diagnosis and up to ART initiation, and CD4 counts remain useful in guiding the clinical management of people failing treatment or re-engaging in care (Rice et al., 2019). Some key informants suggested the promotion of VL testing had, to some degree, diminished the role of CD4 in monitoring and informing clinical decisions. Recent publications have suggested that donor support for CD4 testing has decreased in recent years and that, contrary to WHO guidelines, not only post but also pre-treatment CD4 monitoring has reduced in a number of resource-limited countries, (Medecins sans Frontieres, 2017; Nash & Robertson, 2019; Rice et al., 2019). Related to this, a number of health workers reported that their concern over issues such as a lack of CD4 reagents had lessened (despite CD4 testing still being required for the clinical management of cases). Our finding supports the recent expression of anxiety that guidelines promoting Universal test and treat may be being misinterpreted (Ehrenkranz et al., 2019). Specifically, that the importance of CD4 monitoring in identifying and treating people at risk of advanced disease has been erroneously dismissed due to the attention given to scaling up VL testing.

Our study found sub-optimal implementation of tests, insomuch as inadequate scheduling, long turnaround times (mainly in relation to VL), and procedures not being followed (mainly in relation to CD4) compromised the utility of the markers. Challenges leading to sub-optimal implementation in these settings included lack of facility space, a lack of refrigeration, and suboptimal laboratory capacity. Developments in the use of point of care testing are positive with evidence to suggest such testing is feasible, acceptable and can increase coverage and effectively identify treatment failures (for viral load testing) (Nicholas

et al., 2019; Pham et al., 2016). Our study supports their recommendations of the need for continued efforts to train staff regularly, monitor the programme and promote demand for the tests.

Additionally, our study highlighted various challenges in health worker capacity to communicate the meaning of test results to patients and populations. In all three countries women living with HIV reported knowing nothing or little about either tests and, in some settings, having not received such a test. Other studies have reported similar findings. Potentially as a result of a misinterpretation of the guidelines, CD4 testing has been reported as being no longer recommended (unless VL testing is unavailable) in Cameroon, Kenya, Malawi, Namibia, Swaziland, Thailand and Uganda (United States Agency International Development, 2016). Sub-optimal implementation of VL testing has been reported in Kenya, with only one third of individuals with unsuppressed VL receiving a confirmatory / repeat test as required by national guidelines (Ehrenkranz et al., 2019). In Lesotho, one study found only one quarter of patients with a first unsuppressed VL to be managed correctly according to WHO guidelines following the roll-out of routine VL monitoring (Glass et al., 2019). In addition to the benefits of frontline access, these biomarkers also hold utility for patients by representing a tangible number through which they can measure and understand their health status (Horter et al., 2019; Renju et al., 2017).

Our study has various strengths and limitations that need to be considered when interpreting our data. Firstly, the number and composition of the participants included in the key informant interviews in South Africa differed from the other two countries. In South Africa the five key informants were all from the provincial level and their expertise focused primarily on the policy formulation and adoption, as opposed to the implementation at the facility level. Secondly the surveyed health facilities were included as they served the health and demographic surveillance site populations, and were not nationally representative. However, these facilities did represent those found in rural areas in each country, we recommend that further health systems research of this nature be conducted in more sites within each country to further explore the wider generalisability of our findings. Thirdly the small number of facilities prohibited any statistical analysis of trends. The survey findings are purely descriptive and we allocated arbitrary cut-offs to illustrate low, medium and high levels of implementation across the different facilities. Fourthly the health facility managers at the time of the survey, provided the responses, these may be subject to reporting biases and could lead to skewed estimates of the services available. Fifthly, various changes were made to the facility survey between rounds, meaning some variables were not collected in all three rounds, preventing the longitudinal analysis in these instances. Lastly with regards to the qualitative data, social desirability bias may underlie some of the responses, leading them to overemphasise positive or negative experiences. However, all the interviewers were experienced in building a rapport with their participants and provided a full explanation of the study and rationale in order to mitigate this potential bias. The main strength of this analysis is its provision of a detailed multi-faceted case study looking at the adoption and implementation of different biological marker tests from the perspective of the policy makers, providers and service users at a five year period when international guidance on HIV care and treatment was rapidly changing.

Over the past year or two there have been calls for vigilance and oversight to ensure we retain our capacity to conduct CD4 testing at diagnosis and up to ART initiation whilst scaling up VL testing (Nash & Robertson, 2019; Rice et al., 2019), and for CD4 and VL test results to remain widely available to frontline providers to inform clinical management (Ehrenkranz et al., 2019). In highlighting a perception that the role of CD4 testing has diminished, that the implementation of both CD4 and VL testing is sub-optimal, and challenges in communicating and understanding the utility of these biomarkers, our results support calls for vigilance and oversight. Our findings suggest that more research is needed to explore why current guidance are not adequate to ensure a clear and consistent understanding on the role of the tests at all levels, including at the national level. This guidance should also offer direction as to how to relay this message to sub-national levels.

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**Table 1**  
**HDSS information, facility survey details and qualitative interview participants.**

		South Africa	Malawi	Tanzania
<b>HDSS information</b>	<b>HDSS site name</b>	uMkhanyakude	Karonga	Ifakara
	<b>Size of HDSS site (km<sup>2</sup>)</b>	438	135	2400
	<b>Population of HDSS site</b>	90,000	42,555	170,000
	<b>HIV prevalence in the HDSS</b>	35.20%	9.60%	7%
<b>Facility survey</b>	<b>Dates</b>			
	<i>Round 1</i>	Jan-15	Dec-13	Nov 2013–March 2014
	<i>Round 2</i>	May–June 2016	May–15	Sept–Oct 2015
	<i>Round 3</i>	Dec 2017–Jan 2018	Nov–Dec 2017	Nov–Dec 2017
	<b>No. of facilities</b>	17**	6*	12
	<b>Type of facility</b>			
	<i>Small clinic/ dispensary</i>	16	1	3
	<i>Large clinic/ small health centre</i>	1	2	0
	<i>Large health centre/ sub-district hospital</i>	0	3	6
<i>District/ referral hospital</i>	0	0	3	
<b>Qualitative interivews</b>	<b>Key informant Interviews</b>	5	10	11
	<b>Health care workers</b>	7	6	7
	<b>Service Users</b>			
	<i>HIV+ Pregnant &amp; Post-partum women</i>	8	5	8
	<i>HIV+ women who have transitioned into to routine HIV care</i>	6	7	4
<i>HIV+ women who are currently not engaged in care</i>	5	6	2	

**Table 2**  
**Policy documents reviewed by country and year.**

Country	#	Author	Name	year
Malawi	1	The Ministry of Health	The Clinical Management of HIV in Adults and Children	2011
	2	The Ministry of Health	Consolidated Guidelines for the Use of ART for Treating and Preventing HIV Infection.	2013
	3	The Ministry of Health	Consolidated Strategic Information Guidelines.	2015
	4	The Ministry of Health	Consolidated Guidelines on HIV Testing Services.	2015
	5	The Ministry of Health	National Strategic plan for HIV and AIDS (2015–2020).	2015
	6	The Ministry of Health	Consolidated Guidelines for the Prevention, Diagnosis, Treatment and Care for Key Populations.	2016
	7	The Ministry of Health	Guidelines on HIV Self-Testing and Partner Notification.	2016
	8	The Ministry of Health	National Health Information System Policy.	2016
	9	The Ministry of Health	Consolidated Guidelines for the Use of ART for Treating and Preventing HIV Infection.	2016
	10	The Ministry of Health	Guidelines for the Clinical Management of HIV, 3rd Edition.	2016
	11	The Ministry of Health	HIV testing Services Guidelines.	2016
	12	The Ministry of Health	Guidelines on Patient-Centred HIV patient monitoring and case surveillance.	2017
The United Republic of Tanzania	1	Ministry of Health and Social Welfare	National Guidelines for Comprehensive Care Services for Prevention of Mother-to-Child Transmission of HIV and Keeping Mothers Alive,	2013
	2	The Prime Ministers Office	Third National Multi-sectoral Strategic Framework for HIV and AIDS,	2013
	3	Ministry of Health, Community Development, Gender, Elderly and Children	Antenatal Care Guidelines,	2014
	4	National AIDS Control Programme.	National Guidelines For the Management of HIV and AIDS. Dar es Salaam.	2015
	5	Ministry of Health and Social Welfare	Health Sector Strategic Plan 2015–2020 (HSSP IV): Reaching all Households with Quality Health Care,	2015
	6	Ministry of Health and Social Welfare	National Operational Plan for Scaling up HIV Viral Load testing	2015
	7	Ministry of Health, Community Development, Gender, Elderly and Children	The National Guidelines for the Management of HIV and AIDS, (Sixth Edition).	2017
South Africa	1	National Department of Health	The South African Antiretroviral Treatment Guidelines.	2013
	2	National Department of Health	Guidelines for Maternity Care in South Africa, A Manual for Clinics, Community Health Centres and District Hospitals.	2015
	3	National Department of Health	South African Prevention of Mother to Child Guidelines.	2015
	4	National Department of Health	National HIV Counselling and Testing Policy Guidelines.	2015
	5	National Department of Health	National Consolidated Guidelines for the Prevention of Mother to Child transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults.	2015
	6	National Department of Health	National HIV Testing Services Policy.	2016
	7	National Department of Health	South Africa's National Strategic Plan for HIV, TB and STIs. 2017–2022	2017
	8	National Department of Health	White Paper National Health Insurance for South Africa. Towards Universal Health Coverage.	2017

**Table 3**  
**Selected Policy guidance relating to CD4 and Viral load testing.**

		2013	2015	2017
<b>Use of CD4 counts</b>	<b>South Africa</b>	<ul style="list-style-type: none"> <li>• Pre ART screening to assess ART eligibility</li> <li>• Annual monitoring after ART initiation for adults.</li> </ul>	• Same as 2013	<ul style="list-style-type: none"> <li>• Same as 2013/5</li> <li>• to determine the need for OI prophylaxis</li> <li>• CD4 tests every six months, baseline &gt;200 cells/μL or greater on ART.</li> <li>• routine CD4+ testing stopped once VL is suppressed and remains suppressed.</li> </ul>
	<b>Malawi</b>	<ul style="list-style-type: none"> <li>• Pre ART screening to assess ART eligibility,</li> <li>• no routine scheduled CD4 monitoring</li> </ul>	Same as 2013	<ul style="list-style-type: none"> <li>• Same as 2013/5</li> <li>• targeted CD4 tests by specialists for complicated cases</li> </ul>
	<b>Tanzania</b>	<ul style="list-style-type: none"> <li>• Pre ART screening to assess ART eligibility,</li> <li>• routine monitoring at 6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Same as 2013,</li> <li>• if IRIS or treatment failure is suspected then more frequent testing advised</li> </ul>	<ul style="list-style-type: none"> <li>• Same as 2013/15</li> <li>• additionally, if VL not available should be done at baseline and then every 6 months,</li> </ul>
<b>Where CD4 tests can be conducted</b>	<b>South Africa</b>	Unclear in policy documents	Unclear in policy documents	Unclear in policy documents
	<b>Malawi</b>	District hospitals and high volume sites	All sites	Point of care: ' to prioritise patients for urgent linkage to care and ART initiation'
	<b>Tanzania</b>	Not specified	Zonal and regional hospitals	No-longer specified
<b>Recommended turnaround time for CD4 tests</b>	<b>South Africa</b>	Not mentioned	1 week for pregnant women	Not clear
	<b>Malawi</b>	Next appointment date so can be up to 3 months	CD4 counts no-longer supported	CD4 counts no-longer supported
	<b>Tanzania</b>	Not specified	3–7 days for PMTCT	Not clear
<b>Adherence sessions pre ART</b>	<b>South Africa</b>	Not specified	Not specified	Yes – every visit
	<b>Malawi</b>	Two	Two	Two
	<b>Tanzania</b>	Three	Three	Three
<b>Use of Viral load testing</b>	<b>South Africa</b>	<ul style="list-style-type: none"> <li>• After ART initiation to assess treatment failure</li> <li>• routine at 6months and then annually</li> </ul>	• Same as 2013	<ul style="list-style-type: none"> <li>• Same as 2013/15</li> <li>• to assess drug toxicity</li> </ul>
	<b>Malawi</b>	<ul style="list-style-type: none"> <li>• After ART initiation to assess treatment failure</li> <li>• at 6 months after ART initiation, then 2 years then bi-annual.</li> <li>• if treatment failure suspected before starting 2nd line</li> </ul>	<ul style="list-style-type: none"> <li>• Same as 2013 –</li> <li>• collect catch-up VL sample at the next opportunity if the regular schedule was missed</li> <li>• To assess adherence to 2nd line treatment</li> </ul>	No change
	<b>Tanzania</b>	Not specified	To assess adherence prior to concluding treatment failure, conducted after 6 months unless >1000 copies, then done at 3 months	Same as 2015 plus Viral load every 6 months
<b>Other lab tests required pre ART initiation</b>	<b>South Africa</b>	HB, FBC, Creatinine if TDF, ALT if NVP.	Same as 2013 plus fasting cholesterol and TG	Same as 2015
	<b>Malawi</b>	Confirmatory HIV test to rule out mix up of test results – no other lab tests required at baseline before starting ART.	No change	No change

		2013	2015	2017
<b>Other lab tests required post ART initiation</b>	<b>Tanzania</b>	HB, FBC, Creatine if TDF, ALT for NVP,	Same as 2013, plus rapid test for syphilis and Hepatitis B and C serology.,	Same as 2013
	<b>South Africa</b>	<ul style="list-style-type: none"> <li>• ALT if on NVP &amp; rash or symptoms of Hepatitis,</li> <li>• FBC at month 3 and 6 if on AZT,</li> <li>• Creatinine at month 3 and 6, 1 year then annual if on TDF,</li> <li>• Fasting cholesterol and triglycerides at month 3 if on LPV/</li> </ul>	<ul style="list-style-type: none"> <li>• Same as 2013</li> <li>• SCR and eGRF at 3,6,12 and then annually if on TDF</li> </ul>	Same as 2015
	<b>Malawi</b>	Lab tests focused on CD4 and VL	Same as 2013	Same as 2013
	<b>Tanzania</b>	<ul style="list-style-type: none"> <li>• ALT if on NVP and has rashes of symptoms of hepatitis,</li> <li>• FBC every 6 months,</li> <li>• annual Creatinine,</li> </ul>	<ul style="list-style-type: none"> <li>• ALT If on AZT/3TC/NVP or 2nd line 6 monthly,</li> <li>• FBC, If on AZT week 4 and 6 monthly thereafter,</li> <li>• Creatinine If on TDF every 6 months, if on 2nd line bsln then annually,</li> <li>• Fasting cholesterol and triglycerides if on 2nd line bsln, 6 months and then every 12 months.</li> </ul>	<ul style="list-style-type: none"> <li>• Same as 2015 plus Viral load every 6 months,</li> <li>• urine analysis for TB,</li> <li>• pregnancy tests,</li> <li>• liver and renal function</li> <li>• hepatitis B,</li> </ul>

**Table 4**  
**Availability of CD4 and VL tests by HDSS site and survey round.**

Site (Country) Round	uMkhanyakude			Karonga			Ifakara			
	(South Africa)			(Malawi)			(Tanzania)			
	R1	R2	R3	R1	R2	R3	R1	R2	R3	
Number of facilities	17	18	17	6	6	5	12	12	12	
Timing of survey round	Jan-15	May-June 16	Dec 17-Jan 18	Dec-13	May-15	Nov-Dec 17	Nov 13-Mar 14	Sept-Oct 15	Nov-Dec 17	
Availability and location of CD4 tests	Tests not offered	0%	0%	0%	0%	0%	100%	0%	0%	0%
	At facility	0%	12%	82%	20%	20%	0%	67%	67%	17%
	Patient sent elsewhere	0%	12%	0%	80%	80%	0%	50%	33%	0%
	Sample sent elsewhere	88%	71%	18%	20%	20%	0%	17%	0%	83%
CD4 result turnaround time (average [range]) (days)	3.06 [1-7]	2.47 [1-5]	2.63 [1-5]	1.2 [1-2]	1 [0-2]	No Data	3.58 [0-30]	1.16 [0-7]	1 [1-1]	
Availability of viral load testing	No routine viral load offered	ND	ND	0%	ND	ND	0%	ND	ND	0%
	Viral load offered at the facility	ND	ND	88%	ND	ND	20%	ND	ND	17%
	Viral load offered at another facility	ND	ND	12%	ND	ND	80%	ND	ND	83%
Viral test result turnaround time (average[range]) (days)	ND	ND	3.4 [2-5]	ND	ND	44.8 [30-60]	ND	ND	29.4 [2-90]	

\*Key for colour coding: Red: 0%–25% of facilities implemented, yellow: 26%–79% of facilities implemented; green: 80%–100% of facilities implemented.

**Table 5**  
**Pre-ART initiation tests by HDSS site and survey round.**

Site (Country) Round	uMkhanyakude			Karonga			Ifakara		
	(South Africa)			(Malawi)			(Tanzania)		
	R1	R2	R3	R1	R2	R3	R1	R2	R3
Number of facilities	17	18	17	6	6	5	12	12	12
Timing of survey round	Jan-15	May-June 16	Dec 17-Jan 18	Dec-13	May-15	Nov-Dec 17	Nov 13-Mar 14	Sept-Oct 15	Nov-Dec 17
<b>CD4 tests required prior to ART initiation</b>	94%	100%	53%	100%	60%	0%	92%	100%	8%
<b>What determines ART initiation</b>									
Clinical staging only	0%	0%	0%	20%	20%	0%	0%	0%	0%
Clinical staging or CD4	0%	18%	0%	0%	80%	0%	0%	92%	0%
CD4 only	100%	71%	0%	80%	0%	0%	83%	8%	0%
<b>When is ART initiated for non-pregnant patients</b>									
Clinical stage 4	6%	59%	0%	60%	40%	0%	58%	100%	0%
Clinical stage 3 or 4	53%	65%	0%	100%	80%	0%	50%	100%	0%
CD4 < 250	0%	35%	0%	0%	0%	0%	50%	100%	0%
CD4 < 350	53%	29%	0%	80%	0%	0%	83%	100%	0%
CD4 < 500	65%	100%	0%	0%	80%	0%	0%	8%	0%
All eligible	0%	0%	100%	0%	0%	100%	0%	0%	100%

\* Key for colour coding: Red: 0%–25% of facilities implemented, yellow: 26%–79% of facilities implemented; green: 80%–100% of facilities implemented.

**Table 6**  
**Post ART CD4 testing and adherence monitoring by HDSS site and survey round.**

Site (Country)		uMkhanyakude			Karonga			Ifakara		
		(South Africa)			(Malawi)			(Tanzania)		
Round		R1	R2	R3	R1	R2	R3	R1	R2	R3
Number of facilities		17	18	17	6	6	5	12	12	12
Timing of survey round		Jan-15	May- June16	Dec 17-Jan 18	Dec-13	May-15	Nov- Dec 17	Nov 13 – Mar 14	Sept- Oct 15	Nov- Dec 17
<b>Frequency of CD4 tests on stable ART patients</b>	<b>None</b>	0%	0%	ND	40%	60%	ND	0%	0%	ND
	<b>When sick</b>	0%	0%	ND	0%	0%	ND	0%	0%	ND
	<b>Every 3 months</b>	0%	12%	ND	0%	0%	ND	0%	0%	ND
	<b>Every 6 months</b>	12%	18%	ND	40%	0%	ND	92%	100%	ND
	<b>Annually</b>	88%	71%	ND	0%	0%	ND	0%	0%	ND
<b>Monitoring treatment failure</b>	<b>CD4 counts</b>	ND	ND	18%	ND	ND	0%	ND	ND	25%
	<b>viral loads</b>	ND	ND	71%	ND	ND	100%	ND	ND	100%
	<b>clinical symptoms</b>	ND	ND	24%	ND	ND	80%	ND	ND	100%
<b>Adherence monitoring post ART initiation</b>	<b>None</b>	0%	0%	6%	0%	0%	0%	0%	0%	0%
	<b>Pill counts</b>	35%	12%	18%	100%	100%	100%	58%	33%	100%
	<b>Ask about pill taking</b>	94%	88%	65%	40%	100%	100%	83%	100%	33%
	<b>Viral loads</b>	ND	ND	76%	ND	ND	60%	ND	ND	8%
	<b>CD4 counts</b>	ND	ND	0%	ND	ND	0%	ND	ND	0%
	<b>Asked two weeks after initiation</b>	0%	6%	0%	0%	0%	0%	0%	0%	0%
<b>Action if low adherence for ART patients</b>	<b>file checking</b>	0%	6%	0%	0%	0%	0%	0%	0%	0%
	<b>by visit date</b>	0%	0%	0%	0%	0%	20%	8%	0%	8%
	<b>None</b>	0%	0%	0%	0%	0%	20%	0%	0%	0%
	<b>Stop ART</b>	0%	0%	6%	0%	0%	20%	17%	0%	0%
	<b>Provide a pill box</b>	18%	6%	12%	0%	0%	0%	42%	0%	0%
	<b>support groups</b>	29%	53%	6%	20%	0%	40%	0%	33%	0%
	<b>psycho-social counselling</b>	71%	94%	53%	100%	20%	80%	100%	17%	0%
	<b>home visit</b>	0%	29%	0%	0%	20%	20%	0%	0%	17%
	<b>home-based care</b>	24%	47%	12%	0%	0%	0%	17%	0%	33%
	<b>directly observed therapy</b>	12%	18%	0%	0%	0%	40%	8%	0%	0%
<b>adherence counselling</b>	12%	94%	71%	0%	100%	100%	8%	83%	100%	
<b>reduce refill period</b>	0%	41%	47%	0%	40%	100%	0%	8%	25%	

Site (Country)	uMkhanyakude			Karonga			Ifakara		
	(South Africa)			(Malawi)			(Tanzania)		
Round	R1	R2	R3	R1	R2	R3	R1	R2	R3
Refer client to higher level facility	0%	0%	0%	0%	0%	0%	0%	8%	0%
Insist on bringing a treatment partner	0%	0%	0%	0%	0%	20%	8%	0%	0%

\* Key for colour coding: Red: 0%–25% of facilities implemented, yellow: 26%–79% of facilities implemented; green: 80%–100% of facilities implemented.