Framework for the implementation of advanced HIV disease diagnostics in sub-Saharan Africa: programmatic perspectives

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Patients with advanced HIV disease have a high risk of mortality, mainly from tuberculosis and cryptococcal meningitis. The advanced HIV disease management package recommended by WHO, which includes diagnostics, therapeutics, and patient psychosocial support, is barely implemented in many different countries. Here, we present a framework for the implementation of advanced HIV disease diagnostics. Laboratory and point-of-care-based reflex testing, coupled with provider-initiated requested testing, for cryptococcal antigen and urinary *Mycobacterium tuberculosis* lipoprotein-mannan antigen, should be done for all patients with CD4+ cell counts of 200 cells per μL or less. Implementation of the advanced HIV disease package should be encouraged within primary health-care facilities and task shifting of testing to lay cadres could facilitate access to rapid results. Implementation of differentiated antiretroviral therapy delivery models can allow clinicians enough time to focus on the management of patients with advanced HIV disease. Efficient up-referral and post-discharge systems, including the development of patient-centric advanced HIV disease literacy, are also crucial. Implementation of the advanced HIV disease package is feasible at all health-care levels, and it should be part of the core of the global response towards ending AIDS as a public health threat.

Introduction
The decline in HIV/AIDS-related mortality is stalling, despite continuous improvements in antiretroviral therapy (ART) coverage. In 2018, nearly 770,000 people died from AIDS-related diseases, a mere 30,000 less than the previous year. Many HIV programmes in low-income and middle-income countries continue to report substantial proportions of patients who are treatment-naïve and treatment-experienced presenting to care with advanced HIV disease. WHO defines advanced HIV disease as an adult, adolescent, or child older than 5 years with a CD4+ cell count of less than 200 cells per μL, or with a WHO clinical stage 3 or 4 event, and all children younger than 5 years with HIV. Data from a national cohort in South Africa showed that 32% of 65,4868 patients initiating ART in 2016 had advanced HIV disease. Higher rates of advanced HIV disease were also reported across studies in sub-Saharan Africa: 71% in Senegal, 56% in rural Ethiopia, 47.4% in Zimbabwe, and 33% in Kenya. After ART initiation, patients with advanced HIV disease have an estimated 17% risk of mortality, more so among patients who initiate ART with a CD4+ cell count of less than 50 cells per μL.

Although access to ART can prevent people living with HIV from developing advanced HIV disease, a substantial proportion of people who present with advanced HIV disease are treatment-experienced (up to 60%), suggesting that increased access to ART alone is not sufficient to prevent advanced HIV disease. An estimated 25% of people living with HIV will interrupt their treatment at some point after starting ART, with a duration of interruption ranging from a few days to longer than 6 months. Among patients with advanced HIV disease, and with previous ART exposure, up to a quarter die within 48 h of hospital admission, often not responding to first-line ART. Tuberculosis, cryptococcal meningitis, and severe bacterial infection are among the leading causes of morbidity and mortality among people living with HIV in sub-Saharan Africa, accounting for more than 50% of AIDS-related deaths. An earlier diagnosis of advanced HIV disease coupled with prompt medical action, both for treatment and prevention, can reduce mortality, prevent secondary transmission, and reduce the inpatient burden in hospitals.

In 2017, WHO published guidelines for managing advanced HIV disease. The package of interventions includes screening, treatment, or prophylaxis, or a combination, for major opportunistic infections, rapid ART initiation, and intensified adherence support for everyone presenting with advanced HIV disease. Measurement of CD4+ cell count is essential to aid in identifying ambulatory and asymptomatic patients eligible for additional screening tests to identify opportunistic infections. A CD4+ cell count of 200 cells per μL or less triggers screening for *Mycobacterium tuberculosis* bacterial antigen (TB LAM) and cryptococcal antigen (CrAg) by use of point-of-care TB LAM and CrAg lateral flow assays. However, despite the availability of this policy framework and growing awareness, there is very low uptake or demand for the advanced HIV disease package in many low-income and middle-income countries. Reasons for this low demand include the fact that measuring of CD4+ cell count is no longer recommended for ART eligibility and routine monitoring, that few national advanced HIV disease policies and guidelines exist, and that there is little clarity on the
implementation framework, sporadic funding, and high costs for particular commodities (e.g., flucytosine and point-of-care CD4 devices).3

Diagnostics are the first essential step in any disease management and, often, health systems do not sufficiently budget for diagnostic services.4 WHO issued guidance on the use of the inexpensive urine TB LAM lateral flow assay in 2015 to assist in the screening and diagnosis of tuberculosis.5 Despite this guidance, countries with a high HIV or tuberculosis burden are yet to achieve widespread use of urine TB LAM testing, a test with a proven mortality reduction benefit.6 In 2013, the capacity of instruments used for CD4 cell count testing in sub-Saharan Africa was sufficient to meet the needs of people living with HIV; however, CD4 cell count instruments were underused, with only 13-27% of the existing CD4 capacity used across 50 countries.7 In many settings, poor-quality health care, including the poor use of diagnostics, is now a bigger barrier to reducing HIV-related mortality than insufficient access to ART.

With the imminent availability of a repertoire of new point-of-care diagnostics, including the VisiTest CD4 Advanced Disease Lateral Flow Assay (Omega Diagnostics, Scotland, UK), FujilALM urine TB LAM test (Fujifilm, Tokyo, Japan), and point-of-care urine and blood antiretroviral concentration tests (e.g., UrSure, Boston, MA, USA, for tenofovir), most of these essential tests are at risk of being underused. This underuse is because clinical staff are already burdened with high workloads;8 including performing other point-of-care tests, especially in programmes that have not successfullyimplemented differentiated ART delivery models or introduced support staff dedicated to performing diagnostic testing.

There is a need for dynamic and context-specific frameworks for the effective implementation of advanced HIV disease diagnostics.

Framework for implementation of advanced HIV disease diagnostics at different health-care levels

Secondary and tertiary health-care facilities

Advanced HIV disease diagnostics, together with medication plus patient education and counselling, should be implemented systematically in a step-wise approach commencing from decentralised primary health-care testing areas to secondary and tertiary facilities, until a high throughput national coverage screening programme is created. This approach could enable the stimulation of a viable and responsive national supply chain for advanced HIV disease diagnostics, and also speed up principal usage within all levels of care and minimising regional stock-outs. A core minimum of advanced HIV disease diagnostic tests, composed of HIV rapid tests and self tests, CD4 cell counts, urine TB LAM tests, and CrAg tests, are implementable even within areas that have decentralised primary health-care concentrations (figure). Many patients with HIV remain undiagnosed and, in many settings, implementation of HIV testing should precede advanced HIV disease screening.9

Patients with HIV are often admitted to hospital with severe immunosuppression, usually because of opportunistic infections that could have been diagnosed before hospitalisation.10 The simultaneous use of laboratory-based reflex and provider-initiated testing strategies should be considered, especially because studies have shown that screening interventions that rely solely on provider-initiated requests can be poorly implemented.11 Laboratory technicians and testers at the point-of-care should automatically do reflex testing for CrAg routinely in remnant plasma submitted for CD4 testing, after a CD4 cell count result of 200 cells per μL or less; and urine samples should be submitted for TB LAM testing. Seriously ill patients should have urine and blood simultaneously obtained by clinicians or nurses and tested at point-of-care for CrAg and urine TB LAM, regardless of CD4 cell count. Otherwise, patients can be escorted to the laboratory by a health facility navigator, who helps the patient manoeuvre within the health facility for obtaining samples.

The need for a minimum number of diagnostic tests for advanced HIV disease at multiple locations within the same health facility (such as in an inpatient department, outpatient department, or ART clinic) should be assessed in the context of the central laboratory capacity, turnaround time of results, and the human resources to perform such tests at the point-of-care. In a tertiary Médecins Sans Frontières (MSF) HIV referral hospital in Kinshasa, Democratic Republic of the Congo, minimum advanced HIV disease diagnostics were done within the hospital laboratory and also at point-of-care within the inpatient department. In a district hospital supported by MSF in Malawi, these tests were done in the laboratory, in the ART clinic, and within the rapid assessment unit. The rapid assessment unit is a subdivision of the emergency section or outpatient department of a secondary health-care centre that seeks to provide the differentiated management of patients with advanced HIV disease, ensuring the availability of essential diagnostics upon their arrival. In a tertiary provincial hospital supported by MSF in Beira, Mozambique, the tests were done in the emergency laboratory, which is within the emergency section where patients with HIV first seek health care.

Primary health-care facilities

Primary health-care facilities are predominantly the first point of seeking health care among outpatients with HIV and can enable the earlier detection of opportunistic infections while minimising the need for multiple visits. Subsequently, the implementation of the advanced HIV disease package of care should be intensified within these decentralised clinics. Most primary health-care facilities have no laboratories nor laboratory-trained staff. However, minimum advanced HIV disease diagnostics can be implemented at these peripheral facilities, including
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| CD4+ cell count using bench-top instruments and near POC CD4+ for inpatient and outpatient departments and emergency testing | Laboratory technicians (for all laboratory-based tests) | Tertiary-level hospital
- Specialists or senior laboratory technicians | Laboratory and POC-initiated reflex testing including provider-initiated requests |
| Urine TB LAM | Lay cadres, nurses or clinicians (in Rapid Assessment Units, ART clinics, inpatient departments, or emergency rooms) | Secondary-level hospital
- Laboratory technicians and assistants | Advanced HIV disease laboratory test results in less than 3 h |
| C4d and or semi-quantitative C4d LFA | Lay cadres, nurses or clinicians (in Rapid Assessment Units, ART clinics, inpatient departments, or emergency rooms) | Primary-level health care (including peripheral clinics, health posts, and mobile outreach)
- Health-care professionals, trained lay cadres, but no trained laboratory personnel | Advanced HIV disease test results in less than 2 h |
| Rapid HIV test and HIV self-test | Lay cadres, nurses, or clinicians | POC CD4+ cell count instrument | Where laboratory or mini-laboratory does, minimum advanced HIV disease testing must remain available to be used 24/7 at POC for real-time results |
| Cerebrospinal fluid microscopy and culture | Laboratory technicians (for all laboratory-based tests) | Primary level health care with mini-laboratory can have near-POC molecular multi-disease testing device (Mt tuberculosis and resistance to isoniazid, rifampicin, HIV viral load and early infant diagnosis) or Ziehl-Neelsen plus Gram staining and malaria rapid diagnostic tests | |
| Molecular Mycobacterium tuberculosis and resistance to isoniazid testing | Lay cadres, nurses, or clinicians | Select overall responsible person for advanced HIV disease diagnostics | |
| HIV viral load and early infant diagnosis (LFTs, creatine tests, and electrolyte tests) | |
| Blood culture for severe bacterial sepsis | | |
| Gram, Ziehl-Neelsen, or Gram stain | | |
| Malaria, hepatitis B, and hepatitis C rapid diagnostic tests | | |
| Community level: HIV self testing (oral and blood based tests) | |

**Figure:** The building blocks of advanced HIV disease diagnostic tests in different health-care tiers. 
*AMD = advanced HIV disease, ART = antiretroviral therapy, C4d = cryptococcal antigen, LFA = lateral flow assay, LFT = liver function test, POC = point-of-care, TB LAM = tuberculosis lipooarabinomannan antigen. *37 Suspected ART regimen non-response leading to resistance.

In outpatient settings, WHO recommends against the use of urine TB LAM among patients without tuberculosis symptoms and with a CD4+ cell count of 100-200 cells per μL. However, tuberculosis symptom screening is not often implemented in many health facilities and many patients are asymptomatic. For the pragmatic implementation of urine TB LAM through task shifting to lay cadres and because we used the instrument-free Omega Visitekt CD4+ Advanced Disease lateral flow assay in some settings, patients in ambulatory care settings with a CD4+ cell count less than 200 cells per μL had reflex urine TB LAM test. Benefits of the use of TB LAM in ambulatory patients with CD4+ counts less than 200 cells per μL have been shown.

**Advanced HIV disease testing result delivery**
Prompt linkage of testing results to clinicians is the cornerstone of the advanced HIV disease screening programmes.
Sequential points-of-care testing on-site might lead to longer patient waiting times and an increasingly complex patient flow in primary health-care facilities, and could pose potential challenges to implementation. However, effective implementation of differentiated service delivery models, including facility and community-based models, will allow health-care workers enough time to streamline and promptly manage patients with advanced HIV disease. Those testing positive are at a heightened risk of morbidity, loss-to-follow-up, and mortality; hence the need for prompt results to aid the rapid initiation of appropriate therapeutic management, psychosocial support, and prompt referral to secondary health facilities for those eligible.

Within tertiary and secondary institutions supported by MSF, advanced HIV disease screening results are returned to the clinician within 60 min (IQR 40–75) from sample venesection to result submission to the clinicians; and, in primary health-care facilities, the time varies from 35 min to 60 min. The extensive nationwide National Health Laboratory Service in South Africa provides centralised reflex CrAg screening from routinely obtained plasma samples with a CD4⁺ count result of less than 200 cells per μL, and the turnaround time for results for this reflexive CrAg test varies from 24 h to 48 h. However, such a system requires investments in efficient sample transport and result delivery, and a substantial proportion of patients with advanced HIV disease could be lost to follow-up before the result issuance or initiation of clinical management. For low-income and middle-income countries with a high or low HIV burden, a point-of-care-based reflex testing service will minimise the testing burden on central laboratories and also improve the turnaround time for test result delivery.

Within MSF-supported sites, patients testing positive for urine TB LAM are started on tuberculosis treatment, whereas those with a positive CrAg test are started on preemptive antifungal treatment and referred to a health-care facility where a lumbar puncture can be done. Nonetheless, studies have shown that asymptomatic patients with CrAg positive titres greater than 1:160 have a high risk of developing cryptococcal meningitis and use of a point-of-care semiquantitative CrAg test can reduce the time to treatment initiation or referral, or both. Such disease stratification could enable immediate enhanced antifungal therapy (even in primary health-care facilities) because many ambulatory asymptomatic patients refuse lumbar puncture or do not go for referral. The availability and affordability of some essential medicines including fluconazole, flucytosine, and amphotericin B for treatment of cryptococcal meningitis are a challenge in many countries in sub-Saharan Africa.

Advanced HIV disease diagnostic testing workload
With progressive uptake of the advanced HIV disease screening model, CD4⁺ testing volumes across MSF-supported sites (in Democratic Republic of the Congo, eSwatini, Guinea, Kenya, Malawi, Mozambique and South Africa) increased to 34,972 between Jan, 2018, and Jan, 2019, with 31% of tests (10,873 of 34,972) having a CD4⁺ cell count of less than 200 cells per μL. Of these tests, CrAg was positive in 7% whereas urine TB LAM was positive in 24%. An estimated 60% of the advanced HIV disease tests were done in primary health-care facilities, 32% in hospital laboratories, and 8% in point-of-care inpatient department settings (appendix).

Staff workload should be assessed for each context, and the addition of advanced HIV disease tests should be accounted for within each staffing workload. In a rural primary health-care facility (with an estimated ART cohort of 2300) in Nsanje, Malawi, four to seven CD4⁺ tests were done per day within the mini-laboratory (within the ART clinic) by use of the Pima CD4⁺?Analysers (Abbott Laboratories, Chicago, IL, USA) and the lay cadres simultaneously did the reflexive CrAg (IMMY Diagnostics, Norman, OK, USA) and urine Determine TB LAM (Abbott Laboratories) lateral flow assay tests. The testers also did an estimated average of four HIV rapid tests in a day, together with obtaining approximately five dried blood spot samples for HIV viral load and approximately three dried blood spot samples for early infant diagnosis testing at a district laboratory. In busy primary health-care sites (with more than 15 CD4⁺ test requests per day), point-of-care CD4⁺ cell counting by use of one Pima analyser might inadvertently limit the rate of testing for CrAg and urine TB LAM, as it is necessary to wait approximately 20 min for each CD4⁺ result; as such, additional Pima analysers or other point-of-care CD4⁺ devices with a higher throughput (eg, the BD FACSPresto, BD Biosciences, San Diego, California, USA or even the semiquantitative VisiTest CD4⁺ Advanced Disease lateral flow assay) could be made use of in such sites.

Task sharing for the implementation of advanced HIV disease diagnostic tests
Task sharing to meet human resource needs is recommended by WHO, and studies have shown that it improves linkage to care and treatment outcomes. Even though nurses and clinicians can do diagnostic testing for advanced HIV disease, use of a specific lay cadre responsible for the performance, quality assurance, and stock management of these point-of-care tests could facilitate access to rapid and quality results and prompt linkage to care. Lay cadres have successfully tested the CrAg and point-of-care CD4⁺ cell count and this approach should be considered as a way to improve access to these essential diagnostics, especially at primary health-care sites. For primary health-care facilities with large patient volumes (>2000 ART cohort) and without a mini-laboratory, the presence of a lay cadre is crucial. Many national health programmes presently have different medical cadres employed, who could be
responsible for advanced HIV disease diagnostic services at primary health-care facilities. In Malawi, Health Diagnostic Assistants, a lay cadre, have also been used for different roles, including advanced HIV disease point-of-care testing within ART clinics at primary health-care facilities without laboratories. Other countries have lay counsellors, nurse assistants, health-facility navigators, community health workers, or phlebotomists, or a combination, all of whom can potentially take up this role. Insufficient human resources available for these advanced HIV disease point-of-care tests could result in the underuse of these tests and, crucially, jeopardise the quality of testing.

The newly launched instrument-free Visitec CD4 Advanced Disease lateral flow assay and the pipeline urine FijiLAM assay are crucial for expanding screening for advanced HIV disease. However, these point-of-care assays have multiple testing steps and incubation times that require precision; as such, a specific lay cadre could also streamline these and other general point-of-care tests, where busy clinicians would be unable to.

Quality assurance in advanced HIV disease testing
In MSF-supported programmes, quality controls are used to monitor the quality of advanced HIV disease testing. For IMMY CrAg, Pima and FACS Presto CD4 testing, commercial controls are used, whereas for urine Determine TB LAM, because of an absence of commercial controls, remnant urine samples that are positive for TB LAM are frozen in aliquots at the district laboratory and an aliquot is sent fortnightly to primary health-care facilities for blinded testing. Within the integrated hierarchical tiered laboratory system, higher-tier laboratories will need to play an essential role in ongoing quality control support to lower-tier primary health-care facilities in their precinct. In most primary health-care facilities without mini-laboratories, the testing kits (lateral flow assays for TB LAM, CrAg, and Visitec CD4 Advanced Disease, or cartridges for the Pima CD4 or BD FACS Presto analyser-based tests) are stored inside a metal cabinet and the room is monitored for temperature fluctuations. For mobile clinics in Zimbabwe and Malawi, cooler boxes are used to store the tests.

Other opportunities for implementing the advanced HIV disease package
Mentorship in provision of advanced HIV disease services should also focus on good linkage to care, especially because post-discharge mortality rates of up to 30% have been reported. After inpatients are discharged, many are not linked to outpatient care and become lost to follow-up. Patient psychosocial support should be considered to improve the chances of treatment success together with the promotion of advanced HIV disease literacy at the community level.

The renewed commitment to strengthen primary health-care facilities as the foundation for achieving universal health coverage and the WHO Essential Diagnostics List offer national programmes an opportunity to assess and improve quality diagnostic services across different diseases.

Cost of the advanced HIV disease diagnostic package
Not only can missed advanced HIV disease screening opportunities result in morbidity and mortality, but also in substantial health-care and other economic and social costs. Studies have shown that CrAg screening is a cost-effective strategy in places with a CrAg prevalence of more than 0.6%. According to ex-world prices paid by MSF, Determine urine TB LAM costs US$3.50 per test, whereas IMMY CrAg costs US$2.95, and instrument-based point-of-care CD4 cell count tests cost between US$5 and US$8 (with the price excluding the total cost of ownership). However, for swift market demand creation and catalytic procurement in low-income and middle-income countries, the estimated combined cost for these three crucial advanced HIV disease tests should be less than US$7.

Manufacturers should price their products as affordable and fairly as possible, in line with their costs of goods, and prices ought to decrease at frequent intervals to reflect cost savings from improved manufacturing efficiencies, expired royalties, and increased global sales volumes over time. Countries and regions should use proven cost-reducing mechanisms, such as pooled procurement, competition and price transparency, waiver

Panel: Key enablers for successful implementation of the package of care for advanced HIV disease
- National policy and guidelines with nationwide implementation plans to roll out the essential advanced HIV disease package of care
- Sustainable funding for diagnostics and drugs, which include first-line and second-line adult ART, first-line and second-line paediatric ART, tuberculosis medicines, tuberculosis prophylaxis for adults and children, cotrimoxazole, fluotyosine, flucanazole, lopinavir/ritonavir and other opportunistic infections and cancer treatments (eg, for Kaposi sarcoma)
- Reactive national supply chain systems
- Capacity building for health-care workers (including improving triage systems and the early identification of patients at risk) along with task-shifting initiatives for point-of-care diagnostics to enable the earlier detection of opportunistic infections and prompt management
- Educational materials for patients and communities, including civil society groups
- Efficient patient referral systems to specialised sites or providers together with post-discharge linkage to care
- Monitoring and evaluation systems, including designing advanced HIV disease programme indicators and investing in robust monitoring and evaluation systems to enable data-driven setting of targets and monitoring of the implementation progress
- Implementation of differentiated service delivery for ART delivery (both in health facilities and in communities)
- CD4 cell count testing network optimisation to ensure optimal access to CD4 testing, and coexistence of CD4 and HIV viral load testing

ART=antiretroviral therapy.
taxes and duties on products crucial to global health, and regulate price mark-ups by in-country distributors to better reflect a reasonable margin.

Enablers for success

MSF-supported health facilities usually have high-quality care and consistent funding and resources, which might be a challenge for some national programmes. Nonetheless, some of the key enablers for the successful implementation of an advanced HIV disease package include the availability of national plans or policies for advanced HIV disease package implementation and capacity building for health-care workers and resources (panel). Funding requests from countries in Africa to the President’s Emergency Plan For AIDS Relief and Global Fund should ensure the adequate quantification and costing of advanced HIV disease commodities. 8

Conclusions

As the HIV epidemic matures, health systems should evolve to quickly identify patients with advanced HIV disease who are at a high risk of mortality. The implementation of a minimum package of advanced HIV disease diagnostic tests to decentralised levels of the health-care system is feasible and will help to minimise unfavourable patient outcomes and reduce the burden on secondary and tertiary health facilities. The addition of these tests should be accounted for within the staffing workload.

Contributors

ZM conceptualised the article and wrote the original draft. ZM, EF, TE, RB, TR, HB, BS, AM, CVCG, BK, and ES reviewed and edited the Viewpoint. All authors have read and approved the final manuscript.

Declaration of interests

We declare no competing interests

Acknowledgments

We would like to acknowledge all MSF teams implementing the advanced HIV disease package in Malawi, South Africa, Mozambique, Democratic Republic of the Congo, Guinea, Zimbabwe, Eswatini, and Kenya, among other countries.

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