Technical Brief
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Make It Count: Access to Point-of-Care CD4 Testing Under Threat

A PIMA point-of-care CD4 test device used in an MSF advanced HIV disease programme in Nsanje, Malawi. Photo: Isabel Corthier/MSF

CD4 cells are a type of white blood cell that plays an essential role in the human immune system. These cells are targeted by HIV during infection, and therefore knowing the number of CD4 cells is a crucial parameter in the clinical management of people living with HIV. CD4 tests count the number of these cells in a blood sample.

CD4 testing can be carried out through large, laboratory-based devices or point-of-care devices. While laboratory-based devices can process multiple samples at once and are useful for centralised testing, point-of-care devices allow CD4 testing near the patient, allowing rapid result delivery and hence rapid clinical decision making. Point-of-care CD4 devices are battery-powered equipment or disposable rapid tests, and require minimal or no laboratory infrastructure.

However, global access to point-of-care CD4 devices is under threat due to business decisions by manufacturers responding to a reduction in demand for CD4 tests following the switch from CD4 to viral load for treatment monitoring recommended in WHO guidelines. Despite these changes, however, CD4 testing remains an essential component for management of HIV, including in many HIV programmes run by Médecins Sans Frontières/Doctors Without Borders (MSF).

In this Q&A, we track the evolution of CD4 testing within various WHO guidelines, highlighting the clinical indications for CD4 testing as well as the clinical actions that should be triggered by different CD4 thresholds. We also outline the point-of-care CD4 technologies currently available in the market, and the emerging threats to their supply. In order to ensure sustainable access to lifesaving point-of-care CD4 technologies, we call for actions by industry, countries, donors, global health actors and civil society.

1. Why is CD4 testing an essential tool in the clinical care of people living with HIV?

The clinical indications for performing a CD4 test in people living with HIV (PLHIV) have changed over the last decade. Until 2013, the primary reasons for performing CD4 were to decide eligibility for antiretroviral (ARV) treatment and, in the absence of viral load testing, to act as a monitoring tool for treatment and to determine treatment failure.

Since 2013, viral load monitoring has been recommended by WHO as the preferred approach for HIV treatment monitoring.[1] In 2015, WHO recommended the "treat all" policy stating that all people living with HIV regardless of baseline CD4 count were eligible for ARV treatment.[2] The 2016 WHO consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection not only recommended viral load testing as the preferred monitoring tool, but also stated that CD4 monitoring could be stopped in those who are established on ARV treatment with a suppressed viral load.[3,4,a] These recommendations were maintained in the 2021 WHO consolidated guidelines on HIV prevention, testing, treatment and service delivery (hereinafter "2021 WHO HIV guidelines").[5]

Despite no longer being needed to determine eligibility for ARV treatment and for routine treatment monitoring, **CD4 testing remains an essential tool to diagnose advanced HIV disease (AHD) in people living with HIV.** WHO defines AHD as a CD4 cell count below 200 cells/mm^3 or a WHO clinical stage 3 or 4 of HIV in any adult, adolescent or child ≥ 5 years old. All children below 5 years old with HIV infection are considered as having an advanced disease. **Up to 30%** of people beginning HIV treatment have AHD with severe immune suppression, putting them at very high risk of opportunistic infections (such as tuberculosis and cryptococcal meningitis) and death.[6,7,8]

In 2017, WHO released guidelines for managing AHD (hereinafter "2017 WHO AHD guidelines"), which recommend that "a package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified support interventions" be offered to people with AHD.[9] **As the diagnostic method for detecting AHD, CD4 testing is the gateway to this package of care.**

Without the use of CD4 tests to identify AHD, up to 50% of asymptomatic AHD cases would be missed.[10] CD4 counts are also used to guide starting and stopping of prophylactic cotrimoxazole to prevent bacterial, fungal and protozoan infections in people with AHD and the stopping of pre-emptive fluconazole for the prevention of cryptococcal meningitis.

Late diagnosis of AHD costs lives. A study from 2016 in low- and middle-income countries (LMICs) reported that people living with HIV with a median CD4 count of less than 200 cells at ARV treatment initiation have a 50% higher mortality rate than those with a median CD4 count above 200 cells.[11] With targeted testing and appropriate care for people with AHD, many of these deaths could be prevented.

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[a] WHO has established criteria for determining whether a person is successfully established on ARV treatment. These include:

- receiving ARV treatment for at least six months;
- no current illness, which does not include well-controlled chronic health conditions;
- good understanding of lifelong adherence: adequate adherence counselling provided; and
- evidence of treatment success: at least one suppressed viral load result within the past six months (if viral load is not available: CD4 count >200 cells/mm^3 (CD4 count >350 cells/mm^3 for children 3-5 years old) or weight gain, absence of symptoms and concurrent infections).

2. When is CD4 testing indicated?

As described above, the 2017 WHO AHD guidelines contain a strong recommendation for the provision of the AHD package, triggered by a CD4 count of 200 cells/mm^3 or lower. Therefore, as an indirect recommendation for diagnosis of AHD, it is essential that CD4 tests be performed.

The 2021 WHO HIV guidelines recommend monitoring CD4 counts in the absence of viral load testing to assess response to ARV treatment. In addition, the guidelines outline a number of scenarios for CD4 testing **without explicitly recommending the use of CD4 testing in these scenarios**. These scenarios are detailed in Table 1.

Table 1: CD4 testing scenarios in 2021 WHO HIV guidelines

When	Why
At initiation of ARV treatment	To determine diagnosis of AHD (Sections 4.2; 5.2; 5.3) To determine eligibility for cotrimoxazole prophylaxis (Section 6.3)
At re-engagement in care (no time period out of ARV treatment defined)	To determine diagnosis of AHD (Sections 4.7.4; 5.2; 5.7.1)
At detection of unsuppressed viral load	To determine diagnosis of AHD and contribute to adherence counselling (Sections 5.3; 5.7.1)
At presentation when clinically unwell	To support differential diagnosis of opportunistic infections (Sections 4.7.4; 5.2; 5.7.1)
When established on ARV treatment*	To decide when to stop cotrimoxazole prophylaxis (Section 6.3) To decide when to stop fluconazole pre-emptive treatment or maintenance (Table 5.4)

Most national guidelines now recommend CD4 for the diagnosis of AHD at initiation but standardisation of use for the other indications listed in Table 1 is variable. Two countries now have published algorithms for re-engagement in care (South Africa and Zimbabwe) where CD4 testing is incorporated.[12,13]

3. What CD4 thresholds are currently used to determine clinical action?

Table 2 describes the different CD4 thresholds currently indicated for different clinical actions in the 2021 WHO HIV guidelines and the 2022 WHO guideline for diagnosing, preventing and treating cryptococcal meningitis.[14]

Table 2: CD4 thresholds for clinical actions in 2021 WHO HIV guidelines

Clinical action	CD4 threshold cells/mm^3
Diagnosis of AHD	≤ 200
Use of LF-LAM for TB diagnosis	≤ 200 for inpatient ≤ 100 for outpatient Any CD4 count if symptoms or seriously ill
Use of CrAg screening for cryptococcal meningitis	≤ 100 recommended ≤ 200 to be considered

Clinical action	CD4 threshold cells/mm^3
Starting cotrimoxazole prophylaxis	≤ 350 Or Any CD4 count in settings with high prevalence of malaria or severe bacterial infections
Stopping cotrimoxazole prophylaxis	For adults with HIV who are clinically stable on ARV treatment, with evidence of immune recovery (>350) and viral suppression In settings of low prevalence of malaria and severe bacterial infections, immune recovery may be considered at >200 and where on ART for one year
Starting fluconazole pre-emptive treatment	< 100 recommended < 200 to be considered
Stopping fluconazole pre-emptive treatment	< 100 if VL is suppressed < 200 if VL is not available

4. Where should CD4 testing be performed?

WHO recommends that the package of care for people with AHD, which is dependent on CD4 testing, be offered at both hospitals and decentralised primary care clinics.[15] WHO also recommends out-of-facility ARV treatment initiation. Therefore, having CD4 tests available in mobile or community sites would accelerate the delivery of the AHD package. If point-of-care CD4 tests are not available, adequate sample transport to hubs or hospital laboratories is needed along with timely result delivery. However, in many countries centralised CD4 testing leads to long turnaround time in result delivery (several weeks), possibly leading to delayed care for people with AHD and the risk of more deaths. **While WHO specifically recommends using HIV viral load and early infant diagnosis (EID) testing at the point of care, there is no such specific recommendation to use point-of-care CD4 testing.**

5. Who can perform CD4 testing?

WHO recommends task sharing of specimen collection and point-of-care testing, including CD4 testing, with non-laboratory personnel, be implemented when professional staffing capacity is limited.[16] Such task sharing further supports the ability to perform decentralised point-of-care CD4 testing.[17,18] However, many countries have yet to explicitly outline task sharing with lay health workers in providing HIV testing services in their national polices.[17]

6. What are the currently available WHO-prequalified CD4 technologies?

The WHO-prequalified CD4 technologies are the CyFlow Counter System (Sysmex Partec), Aquios CL flow cytometer (Beckman Coulter), FACSPresto and FACSCount [Becton Dickinson (BD)], PIMA (Abbott) and Visitect (Accubio). Only Visitect, PIMA and FACSPresto are applicable for decentralised testing at the point of care with minimal or no laboratory infrastructure needed. While PIMA and FACSPresto are instrument-based technologies capable of delivering exact CD4 count, Visitect is a lateral-flow based rapid diagnostic test (RDT) providing a semi-quantitative CD4 result as above or below 200 cells/mm^3. While all three technologies can identify people with AHD at the community level, Visitect allows instrument-free identification of AHD which can simplify decentralisation and entry into the AHD package of care. The Visitect test was originally co-developed by Omega Diagnostics and the Burnet Institute, and sold to Accubio Limited, a wholly owned subsidiary of Zhejiang Orient Gene Biotech Co. Ltd., in 2022.

Table 3: WHO prequalified tests/devices for CD4 testing

CD4 test/device	Supplier	Technology	Price per test (in US$)*	Quantitative or semi-quantitative	Lowest level of deployment	Used in MSF operations	Supply from 2024 onwards
FACSPresto	BD	Instrument	$8.2	Quantitative	Out of facility†	Yes	New devices and cartridges discontinued
FACSCount	BD	Instrument	$5.5	Quantitative	District hospital	Yes	New devices and cartridges discontinued
PIMA	Abbott	Instrument	$6.6	Quantitative	Out of facility	Yes	New devices discontinued; CD4 cartridges and services for existing devices still available
Visitect	Accubio	Lateral flow assay	$3.98	Semi-quantitative (Threshold <> 200 cells/mm^3)	Out of facility	Yes	Available
CyFlow Counter	Sysmex Partec	Instrument	$4.8	Quantitative	District hospital	Yes	Available
Aquios CL flow	Beckman Coulter	Instrument	$4-10	Quantitative	District hospital	No	Available

* Prices retrieved from the USAID Global Health Supply Chain Program - https://www.ghsupplychain.org/for-suppliers/products

† Out of facility means outside the healthcare centre, e.g. mobile clinics, drop-in centres, at the person's home.

7. Which CD4 tests are endangered?

Funding for CD4 testing has been declining over the last few years although there is increasing recognition of the benefits of delivering the AHD package of care, which is dependent on knowing a baseline CD4 for people with clinical stage 1 and 2 HIV disease. As noted above, PIMA from Abbott and FACSPresto from BD are the only devices that can deliver absolute quantification of CD4 at the point of care (Table 3). However, in 2022, Abbott informed customers that they will no longer manufacture new PIMA devices. This announcement was followed by BD sharing that they would discontinue their FACSPresto and FACSCount devices and all CD4 commodities from 2024 onwards. While Abbott has committed to continue supplying CD4 cartridges as well as spare parts and services for installed machines, BD will discontinue all commodities and services for FACSPresto and FACSCount by the end of 2024.

8. What is the estimated need for CD4 testing in LMICs?

Modelling by Clinton Health Access Initiative (CHAI) estimates that approximately 8 million CD4 tests are needed annually in low- and middle-income countries (LMICs). This number is based on the estimated need per WHO guidelines: one CD4 test at initiation/reinitiation of ARV treatment and one CD4 test at detection of unsuppressed viral load.

MSF procures an average of at least 50,000 PIMA CD4 cartridges, 3000 FACSPresto CD4 cartridges, 300 FACSCount CD4 cartridges, and 700 CyFlow CD4 cartridges for its operations every year.

9. What is the future need for quantitative versus semi-quantitative CD4 testing?

In March 2023, MSF carried out a survey of clinicians providing care in MSF HIV programmes to determine opinions around the use of quantitative versus semi-quantitative CD4 testing. Of the 35 respondents (66% doctors, 17% clinical officers, 11% nurses, 6% other), 80% work in sub-Saharan African countries. CD4 testing was available for 83% of the respondents. The quantitative PIMA device was the most commonly used testing technology (72% of sites performing CD4 testing) with the semi-quantitative Visitect test available in 21% of sites. 77% of clinicians felt a semi-quantitative test with threshold of more or less than 200 cells/mm^3 would be adequate in more than 75% of clinical cases. Almost all respondents reported that they need a quantitative CD4 test for management of clinically unwell and admitted patients to further differentiate possible opportunistic infection diagnoses such as cytomegalovirus (CMV).

As outlined in Table 2 and reinforced by the survey, different CD4 thresholds call for distinct clinical actions. While quantitative CD4 testing is necessary for many of the clinical actions in Table 2 as well as the diagnosis of opportunistic infections, semi-quantitative CD4 testing can play an important role by decentralising CD4 testing to the community level and thereby facilitating timely entry of people into the AHD package of care. Hence, the complementary use of both quantitative and semi-quantitative CD4 testing technologies is needed in the future to provide optimal care to people living with HIV.

Recommendations

To safeguard access to lifesaving CD4 testing, we urge WHO, national HIV programmes, civil society, test developers and donors to take the following actions.

WHO

- Make a clear recommendation for "when" CD4 should be performed and whether a quantitative/semi-quantitative test should be used;
- Reassess the evidence for the differing CD4 threshold indications in light of the need for future availability at decentralised sites of a semi-quantitative CD4 test, as well as pragmatic implementation of AHD care; and
- Review the evidence regarding the role and impact of point-of-care CD4 testing for the diagnosis of AHD and the timely delivery of the AHD package, and whether a specific recommendation is needed for it.

National HIV programmes

- Include CD4 testing according to 2021 WHO HIV guidelines in their national HIV guidelines;
- Establish CD4 testing targets, carry out forecasting of needed test volumes, and ensure sustainable funding for CD4 tests; and
- Monitor the use of CD4 tests.

Civil society

- Support treatment literacy and generate demand for CD4 testing.

Industry and test developers

- Abbott and BD should reconsider their decisions to stop manufacturing PIMA and FACSPresto devices or transfer the technology to another manufacturer, preferably based in an LMIC, in support of local production initiatives being driven by national governments, WHO and other global health actors;
- Accubio should ensure adequate production and supply capacity to meet the potential increase in demand of the Visitect test, and improve the shelf life of the test beyond 12 months. Accubio should also support decentralised implementation by further simplification of the test procedure or by developing an automated test reader for standardisation and digitisation of results; and
- Other suppliers should consider developing quality-assured quantitative and semi-quantitative point-of-care CD4 tests.

Donors

- Ensure sufficient funding for procurement of CD4 tests and maintenance of devices, as well as training and mentorship of CD4 test users.

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