

POINT-OF-CARE CD4 TESTS TO SUPPORT THE IDENTIFICATION OF INDIVIDUALS WITH ADVANCED HIV DISEASE

03 APRIL 2020



This target product profile describes the optimal and minimal product characteristics of an ideally device-free point-of-care test that enables health-care providers caring for people living with HIV older than five years to screen for advanced HIV disease by determining CD4 count.

Background

Over the course of the HIV epidemic, global guidance has evolved to initiate people living with HIV on antiretroviral therapy earlier in the course of infection in response to evidence showing significant morbidity and mortality benefits. This culminated in the 2015 release of WHO guidelines that recommended antiretroviral therapy for all people living with HIV regardless of CD4 count or clinical stage ("test and treat") (1). The expansion of antiretroviral therapy access and elimination of CD4 eligibility criteria have led to increased CD4 counts at antiretroviral therapy initiation in most settings and subsequent modest decreases in morbidity and mortality related to HIV (2–4).

Declines in the number of people dying from AIDS-related causes have recently plateaued, however, and many people living with HIV – more than one third in some settings – continue to present with a CD4 count of less than 200 cells/mm³ (1,5–7); an additional number present to care again after a period of disengagement with a low CD4 cell count (8). Even after starting antiretroviral therapy, people with severe immunosuppression have a high risk of death (9,10). To address the morbidity and mortality in this group, WHO released *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy* in 2017 (11). For adults, adolescents and children five years and older, advanced HIV disease is defined as a CD4 count of less than 200 cells/mm³ or a WHO stage 3 or 4 event. All children younger than five years are considered to have advanced HIV disease at presentation given their increased risk for disease progression and mortality regardless of immune status (11). The guidelines define a package of interventions for people with advanced HIV disease aimed at reducing morbidity and mortality from major HIV-associated infections, such as tuberculosis, cryptococcal meningitis,

severe bacterial infections, toxoplasmosis and *Pneumocystis jirovecii* pneumonia.

CD4 count testing is the gateway to identifying people with advanced HIV disease at HIV diagnosis, when they return to care after treatment interruption, when they are unstable on treatment or when they present with acute and/or severe illness possibly caused by an opportunistic infection. Clinical evaluation is poorly reliable as a proxy for CD4 count; there is no consistent correlation between CD4 count and signs and symptoms, and up to 50% of the people with advanced HIV disease may be asymptomatic (12).

Since CD4 testing is critical for assessing immune status, access to CD4 cell count is an essential component of high-quality services for people living with HIV. The changing indications for CD4 testing (which is no longer required to determine eligibility for treatment initiation or to monitor treatment) have led some actors engaged in providing or supporting HIV care in low- and middle-income countries to give lower priority to CD4 access. This decrease in perceived value may threaten access to timely CD4 testing if CD4 testing networks are not adapted to the needs of advanced HIV disease screening. Although the absolute volume of CD4 testing required may decrease, it will remain a critical diagnostic test for people living with HIV. Analyses suggest that, although most low- and middle-income countries have sufficient aggregate CD4 capacity to conduct advanced HIV disease screening, many HIV facilities do not have access to timely CD4 testing (13).

Given the high risk of short-term morbidity and mortality among people with advanced HIV disease, rapid and simple CD4 testing is essential to improving outcomes in both the outpatient

and inpatient settings. This need has led some programmes to supplement centralized CD4 testing networks with point-of-care devices, since laboratory-based CD4 platforms have technical and human resource requirements that make them impractical for many health-care settings. Point-of-care devices for CD4 testing can alleviate many of these challenges while also providing the immediate return of results and expedited clinical management that are important for severely immunosuppressed people. In addition, point-of-care CD4 testing has been shown to improve retention in care and be both feasible and acceptable (14). Device-based point-of-care testing, however, can also suffer from challenges, such as device breakdowns, high capital costs, poor service and maintenance and underutilization. A simple, accurate, low-cost, device-free and rapid test for determining CD4 count can ensure access to advanced HIV disease screening at every level and accelerate the decline in global HIV-related mortality.

Document objective

The objective of a target product profile is to inform product developers of key test characteristics and performance specifications that are required to meet the needs of end-users for a defined use case. This target product profile describes the optimal and minimal product characteristics of an ideally device-free point-of-care test that enables health-care providers caring for people living with HIV older than five years to screen for advanced HIV disease by determining CD4 count.

The intended audience is diagnostic technology developers, regulatory agencies, procurement agencies, donors and funders of diagnostic research.

Methods

This target product profile is the result of a consultative process among many stakeholders in the global health and scientific community. The WHO Global HIV, Hepatitis and STIs programme developed a draft version of the target product profile, which included a list of performance and operational characteristics. An iterative approach was taken to obtain inputs over several rounds of feedback and consultation from more than 100 experts and key stakeholders, including representatives of health ministries and national HIV programmes, implementers, diagnostics experts, donors, clinicians and manufacturers.

WHO prequalification

The WHO prequalification process acts as an international assurance of quality, safety, efficacy and suitability for low- and middle-income country programmes. WHO encourages manufacturers of diagnostic technologies to be aware of the WHO prequalification process, even at the early stages of development, and to discuss the product and the regulatory requirements with WHO. The *Overview of the WHO prequalification of in vitro diagnostics assessment (15)*

describes the prequalification process in detail.

Acknowledgements

The Global HIV, Hepatitis, and STIs Programme at WHO prepared this document with input from key stakeholders. WHO gratefully acknowledges the many individuals and institutions that provided valuable contributions in the compilation and review of this target product profile, including the WHO Department of Essential Medicines and Health Products, WHO Regional Office for Africa, Clinton Health Access Initiative, Elizabeth Glaser Pediatric AIDS Foundation, Foundation for Innovative New Diagnostics, Médecins Sans Frontières, Office of the United States Global AIDS Coordinator, South Africa National Health Laboratory Service, Global Fund to Fight AIDS, Tuberculosis and Malaria, UNICEF, Unitaid and United States Centers for Disease Control and Prevention. This document was prepared following public consultations and consideration of all comments and suggestions by stakeholders.

TARGET PRODUCT PROFILE

OBJECTIVE: TO MEASURE CD4 T CELLS TO SUPPORT THE IDENTIFICATION OF INDIVIDUALS OLDER THAN FIVE YEARS WITH ADVANCED HIV DISEASE

CHARACTERISTICS		MINIMAL	OPTIMAL
INTENDED USE			
Primary goal	Easy to use and device-minimal test that can be used at the point-of-care (POC) for same-day identification of advanced HIV disease in people living with HIV		
Setting	All countries, with an emphasis on resource-limited settings with high burden of HIV		
Health care level	All levels including community-based testing, mobile testing, health centers, hospitals; centralized and decentralized; low- and high-volume settings		
Results	Absolute CD4 T lymphocytes quantification in cells/microliter (or mm ³ equivalent)		
Operator	Health care facility staff	Lay counsellor, non-professional staff	
Target population	Individuals > 5 years old newly diagnosed with HIV, returning to care, suspected of failing treatment, or suspected of advanced disease		
PERFORMANCE			
Equipment	Minimal or ancillary - Small results reader	None required	
Result output	Semi-quantitative	Quantitative	
Result interpretation	Visual manual or reader interpretation required	No interpretation necessary	
CD4 threshold, if used	200 cells/mm ³	200 cells/mm ³ or 100 cells/mm ³ and 200 cells/mm ³	
Clinical sensitivity	80%*	90%	
Clinical specificity	80%**	90%	
Precision (co-efficient of variation)	< 15%	< 10%	
Reference test	Internationally approved CD4 technology		
Invalid/error rate	10%	5%	
OPERATIONAL CHARACTERISTICS			
Sample specimen	Finger-prick whole blood		
Sample volume	≤ 100 microliters	≤ 50 microliters	
Sample preparation	No more than 5 steps	No more than 3 steps	
Total time to test result	< 40 minutes	< 20 minutes	
Additional 3rd party consumables	None required outside of what is provided in test kit/sample collection bundle		
Cold chain	None required		
Power requirements	Battery or solar-power operated; > 6 hours rechargeable battery life	None required	
Water requirements	None required		
Test kit components	All materials for test included	All materials for test and sample preparation included	
Test kit stability	12 months at 10–30°C; 50% humidity	18 months at 2–35°C; 80% humidity	
Operating conditions	15–30°C; altitude up to 1000 meters	10–40°C; altitude up to 2000 meters	
Sample stability pre-testing	5 minutes	3 hours	
Result validity stability	1 hour	5 hours	
Safety precautions	Self-contained system; only standard blood collection safety precautions needed and all materials are free of components with a GHS classification H (particularly H350, H340, H360)***		
Waste disposal requirements	Biosafety trash for all materials		
QUALITY ASSURANCE			
Training required	2 days	<1 day	
Routine service and maintenance	None, swap out or replace ancillary device when needed	None required as device-free	
Calibration	None required		
Quality control	Internal procedural control(s)	Internal procedural control(s), External quality assessment (EQA) material compatible	
Regulatory requirements	Manufactured under ISO 13485:2003 certified; WHO prequalified; or authorized for use by a regulatory authority of the founding members of the Global Harmonization Task Force for <i>in vitro</i> diagnostic use		
Connectivity	If device-based: Remote export of data possible If no device: Export could be available with separate 3rd party reader	Test is compatible with readers and other data capture devices	
TARGET PROCUREMENT PRICE			
Target price for device	≤ US\$ 200	NA: no device required	
Target price for cartridge	< US\$ 6 per test	< US\$ 3 per test	

*Lower sensitivity selected to improve ability to decentralize CD4 testing and expand access; in addition, patients may be retested at later time based on clinical indication

**Lower specificity selected to improve ability to decentralize CD4 testing and expand access; in addition, WHO staging can also identify advanced HIV disease

***Globally Harmonized System of Classification and Labelling of Chemicals; H350: may cause cancer; H340: may cause genetic defects; H360: may damage fertility of the unborn child

References

1. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (<https://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en>, accessed 2 March 2020).
2. Auld AF, Shiraishi RW, Obobo I, Ross C, Bateganya M, Pelletier V et al. Trends in prevalence of advanced HIV disease at antiretroviral therapy enrollment – 10 countries, 2004–2015. *MMWR Morb Mortal Wkly Rep.* 2017;66:558–63.
3. UNAIDS 2019 data. Geneva: UNAIDS; 2019 (<https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data>, accessed 2 March 2020).
4. IeDea Cohere Cohort Collaborations, Anderegg N, Panayidou K, Abo Y, Alejos B, Althoff KN, et al. Global trends in CD4 cell count at the start of antiretroviral therapy: collaborative study of treatment programs. *Clin Infect Dis.* 2018;66:893–903.
5. Carmona S, Bor J, Nattey C, Maughan-Brown B, Maskew M, Fox MP et al. Persistent high burden of advanced HIV disease among patients seeking care in South Africa's National HIV Program: data from a nationwide laboratory cohort. *Clin Infect Dis.* 2018;66(Suppl. 2):S111–7.
6. Brennan AT, Maskew M, Larson BA, Tsikhutsu I, Bii M, Vezzi L et al. Who is seeking antiretroviral treatment for HIV now? Characteristics of patients presenting in Kenya and
7. Belaunzarán-Zamudio PF, Caro-Vega YN, Shepherd BE, Rebeiro PF, Crabtree-Ramírez BE et al. The population impact of late presentation with advanced HIV disease and delayed antiretroviral therapy in adults receiving HIV care in Latin America. *Am J Epidemiol.* 2019; kwz252. doi: 10.1093/aje/kwz252.
8. Osler M, Hilderbrand K, Goemaere E, Ford N, Smith M, Meintjes G et al. The continuing burden of advanced HIV disease over 10 years of increasing antiretroviral therapy coverage in South Africa. *Clin Infect Dis.* 2018;66(Suppl. 2):S118–25.
9. Walker AS, Prendergast AJ, Mugenyi P, Munderi P, Hakim J, Kekitiinwa A et al. Mortality in the year following antiretroviral therapy initiation in HIV-infected adults and children in Uganda and Zimbabwe. *Clin Infect Dis.* 2012; 55:1707–18.
10. Croxford S, Kitching A, Desai S, Kall M, Edelstein M, Skingsley A et al. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. *Lancet Public Health.* 2017;2:e35–46.
11. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017 (<https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en>, accessed 2 March 2020).
12. Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C et al. Enhanced prophylaxis plus
13. 2019 HIV market report. The state of HIV treatment, testing, and prevention in low- and middle-income countries. Boston: Clinton Health Access Initiative; 2019 (https://clintonhealthaccess.org/content/uploads/2019/09/201920CHAI20HIV20Market20Report_FINAL-1.pdf, accessed 2 March 2020).
14. Vojnov L, Markby J, Boeke C, Harris L, Ford N, Peter T. POC CD4 testing improves linkage to HIV care and timeliness of ART initiation in a public health approach: a systematic review and meta-analysis. *PLoS One.* 2016;11:e0155256.
15. Overview of the WHO prequalification of in vitro diagnostics assessment. Geneva: World Health Organization; 2018 (<https://apps.who.int/medicinedocs/documents/s23361en/s23361en.pdf>, accessed 2 March 2020).

预览已结束，完整报告链接和二维码如下：

https://www.yunbaogao.cn/report/index/report?reportId=5_24720

