TARGET PRODUCT PROFILE

HIV TREATMENT AND CARE TEAM

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

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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/mm^3 *(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/mm^3 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

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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.

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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 *in vitro* 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

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