TARGET PRODUCT PROFILE

HIV TREATMENT AND CARE TEAM

POINT-OF-CARE TESTS FOR DIAGNOSING HIV INFECTION AMONG CHILDREN YOUNGER THAN 18 MONTHS

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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 to diagnose HIV infection among children younger than 18 months.

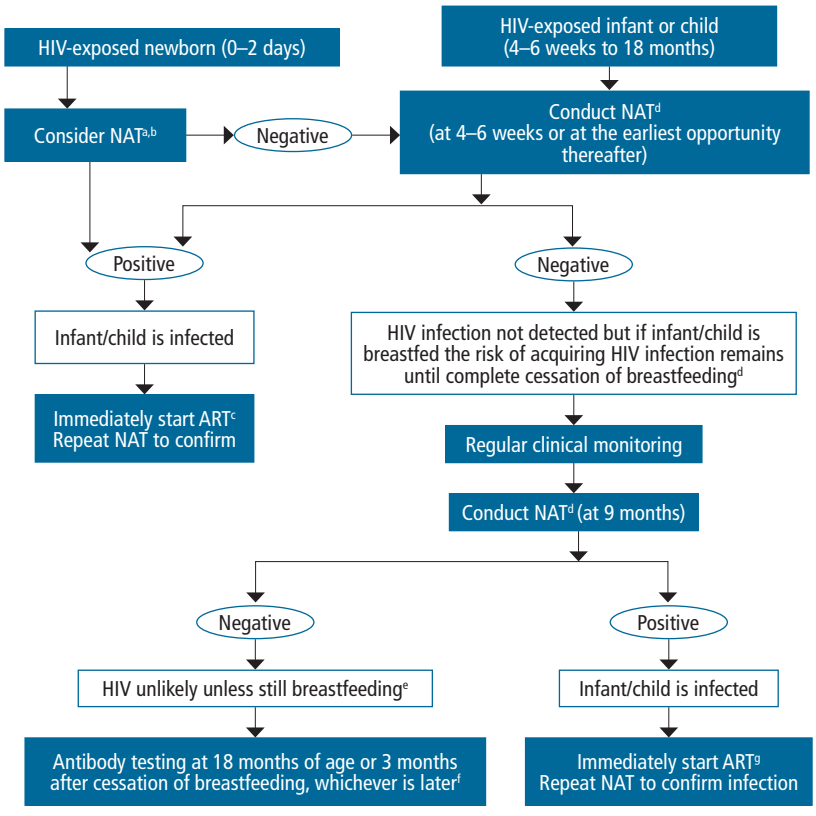
Background

Programmes aimed at eliminating mother-to-child transmission of HIV have substantially reduced the number of children acquiring HIV infection through routine HIV testing of pregnant women and providing antiretroviral therapy to mothers living with HIV *(1)*. In 2018, 82% of mothers living with HIV globally received antiretroviral therapy, up from 44% in 2010. However, preventing mother-to-child transmission requires sustained viral suppression throughout pregnancy, delivery and breastfeeding, and even low-level viraemia is associated with mother-to-child transmission *(2,3)*. For this reason, since 2010, WHO has recommended routine HIV testing for all HIV-exposed infants regardless of maternal antiretroviral therapy status *(4)*.

HIV disease progresses much more rapidly among children than among adults. In sub-Saharan Africa, 50% of perinatally infected infants and 25% of infants infected during breastfeeding die before two years of age without antiretroviral therapy *(5)*; testing HIV-exposed infants and linkage to antiretroviral therapy for those with HIV infection are therefore imperative and time-sensitive interventions that substantially affect morbidity and mortality. To account for transmission risks in utero, at delivery and during breastfeeding, WHO recommends that HIV-exposed infants be tested at age six weeks, nine months, after breastfeeding ends and any time there are signs or symptoms suggesting HIV infection (Fig. 1). Testing HIV-exposed infants at birth for earlier detection of in utero infection may also be considered *(6)*.

Despite longstanding WHO recommendations and significant investments in building testing capacity, in 2018 only 59% of HIV-exposed infants had been tested by two months of age, and testing coverage is even lower later (such as nine months) for HIV-exposed infants who are still breastfeeding *(1)*. The presence of maternal antibodies precludes the use of antibody-based HIV rapid tests to diagnose children younger than 18 months, necessitating virological testing. Because laboratory-based virological tests require sophisticated infrastructure and highly trained personnel, most virological tests for

Fig.1 Revised WHO early infant diagnosis algorithm, 2018



[1] Based on 2016 WHO Consolidated ARV Guidelines, addition of NAT at birth to the existing testing algorithm can be considered.
[2] POC NAT can be used to diagnose HIV infection as well as to confirm positive results.
[3] Start ART without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and mother to child transmission rates decrease, false-positive results are expected to increase: retesting after a first positive NAT is hence important to avoid unnecessary treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be performed before interrupting ART.
[4] For children who were never breastfed, additional testing following a negative NAT at 4–6 weeks is included in this algorithm to account for potential false-negative NAT results.
[5] The risk of HIV transmission remains as long as breastfeeding continues. If the 9-month test is conducted earlier than 3 months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be carried out for final assessment of HIV status.
[6] If breastfeeding extends beyond 18 months, the final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, the final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants younger than 18 months of age NAT should be performed to confirm infection. If the infant is older than 18 months, negative antibody testing confirms that the infant is uninfected; positive antibody testing confirms infant is infected.

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HIV-exposed infants in low- and middle-income countries involve transporting specimens from hundreds of clinics to a few centralized molecular testing sites. This cascade entails numerous steps between sample collection, sample transport, testing, return of results and linkage to care and treatment. As a result, adequate laboratory capacity and support for laboratory systems to perform centralized molecular testing for children younger than 18 months has not always translated into timely diagnostic results for caregivers and health-care providers *(7)*. Delayed return of results is a critical problem given the poor clinical outcomes and high mortality for HIV-infected infants who are not identified and treated early *(8,9)*.

Since countries continue to face challenges with human resources shortages, sample transport and laboratory systems, recognition is growing that centralized testing networks are unlikely to meet all programmatic needs of HIV-exposed infants. Device-based point-of-care technologies recently introduced in clinics for HIV-exposed infants have been shown to substantially reduce the time until results are returned and to accelerate life-saving antiretroviral therapy initiation compared with laboratory-based approaches *(10–13)*. A simple, accurate, device-free and rapid point-of-care test that is feasible even in primary health clinics in low-resource settings could further expand access to virological tests for HIV-exposed infants while providing similar improvements in returning results, antiretroviral therapy initiation times and retention of mother-infant pairs in services for HIV-exposed infants. As a result of these programmatic benefits, even rapid point-of-care tests with lower sensitivities could substantially affect the morbidity and mortality of HIV-exposed infants *(14)*. A simple, ideally device-free, point-of-care early infant diagnosis test could also be used in other high-yield settings other than those intended to prevent mother-to-child transmission (such as malnutrition clinics, inpatient paediatric wards and TB clinics) to improve HIV case-finding among children as recommended by WHO *(15)*. The requirement for multiple virological tests for HIV-exposed infants up to age 18 months as well as the recommendation for a confirmatory test for an initial positive test further underscores the need for a point-of-care virological test that provides immediate results for clinical management.

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 a point-of-care test that enables health-care providers to diagnose HIV infection among children younger than 18 months.

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 an ongoing 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 (16)* describes the prequalification process in detail.

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TARGET PRODUCT PROFILE

OBJECTIVE: TO DETECT HIV INFECTION AT THE POINT OF CARE AMONG CHILDREN YOUNGER THAN 18 MONTHS

CHARACTERISTICS	MINIMAL	OPTIMAL
INTENDED USE		
Primary goal	Easy to use and device-minimal diagnostic test that can be used at the point-of-care (POC) for same-day diagnosis of HIV in children <18 months of age	
Setting	All HIV-burden countries with mother-to-child HIV transmission	
Health care level	All levels including community-based testing, mobile testing, health centers, hospitals; centralized and decentralized; low- and high-volume settings	
Results	Presence or absence of HIV nucleic acids and/or p24 antigen	
Operator	Health care facility staff	Lay counsellor, non-professional staff
Target population	Children < 18 months of age in the determination of HIV infection	
PERFORMANCE		
Equipment	Minimal or ancillary–Small results reader	None required–device free/disposable
Result output	Qualitative	
Result interpretation	Visual manual or reader interpretation required	No interpretation necessary
Clinical sensitivity	80%	98%
Clinical specificity	98%	98%
Reference test	Internationally approved nucleic acid technology	
Invalid/error rate	10%	5%
OPERATIONAL CHARACTERISTICS		
Sample specimen	Finger or heel-prick whole blood	
Sample volume	< 200 µl	< 100 µl
Sample preparation	No more than 5 steps	No more than 3 steps
Additional 3rd party consumables	None required outside of what is provided in test and sample collection kits	
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 positive and negative controls, 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$ 2000	NA: no device required
Target price for cartridge	< US$ 12 per test	< US$ 8 per test

* 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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