TARGET PRODUCT PROFILE

for a test for rhodesiense human African trypanosomiasis diagnosis usable in peripheral health facilities

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Contents

Process of document development

The development of this target product profile (TPP) was led by the WHO Department of Control of Neglected Tropical Diseases (NTD) following standard WHO guidance for TPP development. In order to identify and prioritize diagnostic needs, a WHO NTD Diagnostics Technical Advisory Group (DTAG) was formed, and different subgroups were created to advise on specific NTDs, including a subgroup working on the human African trypanosomiasis (HAT) diagnostic innovation needs. This group of independent experts included leading scientists, public health officials and endemic-country end-user representatives. Standard WHO Declaration of Interest procedures were followed. A landscape analysis of the available products and of the development pipeline was conducted, and the salient areas with unmet needs were identified. Through meetings and remote consultations, the subgroup developed use-cases for the hypothetical tools considered as the main gaps, and gave them an order of priority. A template adapted to the HAT context was agreed and used for the development of the first draft of this TPP (priority N° 1) which underwent several rounds of review by the subgroup members. The ensuing version was reviewed by the DTAG members. Draft version 0.1 was posted on the WHO website for public consultation for 28 days with a proforma comment form. The final version received executive clearance on 7 June 2021.

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1. Background and medical need

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a vector-borne parasitic disease caused by infection with protozoan parasites belonging to the genus Trypanosoma. They are transmitted to humans by bites of tsetse flies, found only in sub-Saharan Africa, which have acquired their infection from human beings or from animals harbouring human-pathogenic parasites.

HAT takes 2 forms, depending on the subspecies of the parasite involved:

- Gambiense human African trypanosomiasis (gHAT), caused by *Trypanosoma brucei gambiense*, found in west and central Africa, currently accounting for 95% of reported cases, has a chronic evolution. A person can be infected for months or even years without major signs or symptoms. When more evident symptoms emerge, the disease is often already in an advanced stage where the central nervous system is affected.
- Rhodesiense human African trypanosomiasis (rHAT), caused by *Trypanosoma brucei rhodesiense,* found in eastern and southern Africa, representing 5% of reported cases, is an acute illness with signs and symptoms observed generally a few weeks after infection. The disease develops rapidly, often provoking multi-organ failure and invading the central nervous system. Epidemic seasonal outbreaks are frequent.

HAT control is based on the screening of populations at risk for case finding and subsequent treatment in order to decrease the reservoir, complemented by targeted vector control in specific settings. Several tools are available or in the pipeline for the screening and diagnosis of gHAT, but similar tools for rHAT are either totally missing or losing ground in the evolving context.

Currently, there are no simple serological tests for rHAT screening and the diagnosis relies on the microscopic confirmation of trypanosomes in blood or other tissues, by either direct (blood, chancre or lymph node aspirate smear) or concentration methods in blood (capillary tube centrifugation or mini-anion exchange centrifugation technique) or cerebrospinal fluid (modified single centrifugation). These methods require a microscope and centrifuges, an electricity source and trained laboratory technicians.

The progressive introduction of rapid diagnostic tests for malaria has resulted in a decrease in the equipment and capacity for microscopy examinations in peripheral health facilities and consequently a reduction in the accidental diagnosis of rHAT, which was common when microscopy was done for malaria parasite detection.

A simple test for rHAT would facilitate the control and surveillance of the disease. In addition to faster prescription of a treatment, it may also help in capturing more information on the occurrence of rHAT transmission, hence recovering the loss of surveillance capacity and possibly strengthening it beyond the previous levels. For this, it would be important to be able to perform it at the location where people seek malaria diagnosis.

2. Use case

A test for diagnosis of rhodesiense human African trypanosomiasis (rHAT) usable in peripheral health facilities,[1] but other locations are conceivable.

[1] Peripheral health facilities: usually of low sophistication, located in the midst of, or at short distance from, communities at risk of rHAT.

3. Technical scope

Ideally, it should be an antigen detection test in a simple format (rapid diagnostic test), but it could also be a molecular test detecting DNA or RNA, or a microscopy-free test able to detect the presence of trypanosomes.

The test should provide immediate results for taking therapeutic decisions by confirming the presence of the infection, but, if not possible, it could be a screening test that, if positive, would be followed by confirmatory microscopic examination (taking into account that parasitaemia is usually high).

In the current context, confirmation is mandatory, but in a future with a safe, short regimen medicine allowing for widened treatment, a screening test to identify individuals to be treated would be desirable.

Target product profile

Diagnostic test attribute	Minimally acceptable	Desirable	Annotations
1. Intended use			
Target species/ subspecies	*T. b. rhodesiense*	*T. b. rhodesiense*	
Target variants/ genotypes/subtypes	*Trypanozoon*[1] specific	Both *T. b. rhodesiense* types (Zambezi and Busoga)	At *Trypanozoon* specificity level, it will fit diagnostic purposes but *T.b. rhodesiense* epidemiology data will be less accurate.
Target population	Human population at risk of rHAT	Human population at risk of rHAT	
Use of information obtained	Identification of rHAT suspects, who could be treated after parasitological confirmation, or on the basis of clinical evaluation.	Confirmation of rHAT case for treatment. Key data for disease surveillance	Ideally, a positive test should trigger therapeutic decisions and disease control measures. Acceptably, these decisions could be reached via parasitological confirmation of a serological suspect, or heightened suspicion from the clinical picture.
Specimen type	Any body fluid or tissue collected without discomfort to the patient disproportionate to the health benefit	Whole blood or any non-invasively collected body fluid (saliva, urine, tears)	Mostly point-of-care testing. Occasionally, specimens could be preserved and transported under certain conditions
Analyte to be detected	Antigens of *Trypanozoon* or whole parasite or *Trypanozoon* DNA/RNA	Antigens of *T. b. rhodesiense* or whole parasite or *T. b. rhodesiense* DNA/RNA	In rHAT, early detection is life-saving. Generation of specific antibodies might take 1–2 weeks, and rHAT evolution is usually acute (except the Zambezi type).
Platform/ technology	Format applicable at peripheral sites combined with higher-level structures	A format applicable at point of care	
Nature of the result	Qualitative	Qualitative	No need of quantitative
Infrastructure level and operating environment	Laboratory at district level and higher-level structures	Peripheral health facilities and mobile laboratories at village level	The closer to the communities at risk, the better
Intended user	Minimally trained laboratory technician	Any health care worker minimally trained	

[1] The subgenus *Trypanozoon* comprises *Trypanosoma brucei brucei* (*Tbb*), *Trypanosoma brucei gambiense* (*Tbg*), *Trypanosoma brucei rhodesiense* (*Tbr*), *Trypanosoma evansi* (*Tev*) and *Trypanosoma equiperdum* (*Teq*). They are morphologically indistinguishable.

2. Assay performance characteristics (individual (patient) or population needs)			
Clinical sensitivity	> 90%	> 99%	Being an acute lethal disease, high sensitivity is needed. It should be at least equal to the parasitology tests currently used.
Clinical specificity	> 85%	> 99%	If a therapeutic decision is taken, specificity required will depend on safety of the medicines used (less safe, higher specificity needed).
Analytical specificity/ cross reactivity	*Trypanozoon*	Both types of *T. b. rhodesiense.*	Diagnosis and treatment is currently based on microscopy, at *Trypanozoon* subgenus level. Epidemiological accuracy would improve if *T.b. rhodesiense* specificity was achieved.
Analytical sensitivity	Corresponding to ≤ 100 parasites/mL in blood	Corresponding to ≤ 10 parasites/mL in blood	Tests detecting antigens or nucleic acid sequences may reach lower detection thresholds than those detecting whole parasites.
Repeatability Intra-reader agreement (different tests, same sample, same reader)	Kappa > 0.8	Kappa > 0.9	
Reproducibility Inter-reader agreement (same test, same sample, different readers)	Kappa > 0.8	Kappa > 0.9	
Quality control included in the test kit	Control on minimal functionality	Availability of positive and negative controls	Depends on the test format
3. Regulatory and normative needs			
Regulatory approvals and standards	Test components manufactured according to GMP (ISO13485:2016)	CE marking (compliant with European Directive 98/79/EC (IVDD 98/79/EC) QMS ISO13485:2016	Quality management system should be defined. Dependence on commercial availability.
Promotional and marketing material	Not applicable	Not applicable	

4. Health care system needs			
4.1. Environment description			
Operating environment	Able to be operated at 10–30 °C at 40– 70% relative humidity	Able to be operated at 10–40 °C at 10–88% relative humidity	The product is designed for professional use only. In some endemic areas (e.g. Malawi, Zambia), ambient temperature may be low sometimes.
Workflow requirements	< 10 steps Simplified pipette devices Result available in < 2 h	< 5 steps No need for precision liquid handling Result available in < 20 min	
4.2. Instrument and device characteristics			
Instrumentation needed	Requiring limited instrumentation: - Portable or hand-held device, ≤ 5 kg, durable for easy safe transport to field - Battery-operated and able to run off standard electricity - No requirement for running water - Resistant to shock and vibration - Long lifespan (5 years) with minimal and easy maintenance. - Requiring cold chain	Not requiring instrumentation Not requiring cold chain	
4.3. Information and communication technology			
User interface and data input requirements	Same	Simple, manual operation. Specimen identifier entered into a logbook and/or a computer or similar. No interface or connectivity needed for data entry.	Especially the decision on treatment should not be dependent on connectivity.
Test result	The test result is qualitative and scored visually or by read-out of a portable device. Test result stable for at least 15 min	The test result is qualitative and scored visually or by read-out of a portable device. Test result stable for at least 30 min	Data output does not require interface or connectivity.
Data capture	Data are recorded in a log book and/or a computer or smartphone	Data are recorded in a log book and/or a computer or smartphone. Integrable into national data and reporting. Test results can be easily stored for posterior interpretation (e.g. electronic result, optical density or intensity, etc., electronic image or video).	Data should be exportable to any database if needed. Storage needs may vary by programme.
Transmission	Test results entered into computer- database and transmitted manually	Data automatically integrated in server databases without need of additional equipment	Transmission should be flexible, depending on connectivity (Email, SMS, phone).

4.4 Reagent and control handling			
Reagents, storage and packaging	Individual packed tests, accompanied by all necessary accessories for sample collection and processing. Stable at 4-8 °C and 40-88% relative humidity for at least 12 months. Instructions for operation are part of each package. In use stability > 30 min after opening the pouch. Reagents ready to use, or within 15 min with max 5 additional steps.	Individual packed tests, accompanied by all necessary accessories for sample collection and processing. Stable at 5-45 °C and 40-88% relative humidity for ≥ 24 months. Transport not needing cold chain. Operating instructions in each package. In use stability > 2 h after opening the pouch. Reagents ready to use or max 2 additional steps needed.	The stability should consider the time frame for distribution from manufacturer, passage through customs and local distribution.
4.5. Sample handling			
Sample volumes	Depending on the type of specimen. For blood (or serum or plasma) ≤ 5 mL. For non-invasive sampling, the volume is less relevant.	Depending on the type of specimen. For blood, ≤ 0.02 mL (finger prick).	A capillary can easily draw 0.05 mL of blood from a finger prick. Extra specimen material is collected at the same time for repeat testing if needed. For other tissues or body fluids, volumes can be specified later on.
Specimen collection and processing	Collecting devices provided with the kit and minimal specimen processing.	No special collecting devices needed. Specimen processing not required.	Special collecting devices are not used routinely in peripheral health centres. Occasionally specimens could be preserved and transported under certain conditions.
Waste management and biosafety	Standard biosafety precautions for handling potentially infectious materials. Waste disposal in biosafety bin following standard guidelines, including sharps containers for disposal of lancets, capillary tubes, etc. Appropriate disposal method for excess specimens and processing consumables (e.g. latrine, incineration). Standard operating procedure provided.	Same as minimal.	

4.6. Distribution, training and support			
User			Defined earlier
Training	Basic specific training needed (1 day)	Basic specific training needed (< 2 h)	
Quality control	Negative and positive control specimens available (not necessarily at the point-of-care level).	Negative and positive control specimen are run in parallel to the test specimen. Proficiency panel available	Depends on type of test. Running negative and positive controls for each sample may triple the price per test. A control per batch/box is an alternative.
Instrument and test supply reliability	Supply guaranteed for ≥ 5 years after marketing. Manufacturer should replace non-functioning units.	Supply guaranteed for ≥ 7 years after marketing. Manufacturer should replace non-functioning units.	
Service and support response time	Minimal external support available. Support response within 1 week.	Minimal external support available. Support response within 1 day.	
5. Commercial and sustainability aspects			
Sustainability	Sustainable production	Sustainable production	Quantities of rHAT tests needed will be smaller, compared with gambiense HAT tests, probably increasing the production costs per unit. As it is a non-profitable area, sustainable funding and a production/access innovative model is needed, with donors ensuring affordability. Advocacy needed.
Pricing of individual test	US$ ≤ 20 (allowing for molecular tests) Excluding sample collection costs	US$ ≤ 1 Excluding sample collection costs	Costs of hardware, shipment of material, sample collection and salaries, are not included here.

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