TARGET PRODUCT PROFILE

for a gambiense human African trypanosomiasis test to identify individuals to receive widened treatment

World Health Organization

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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 HAT TPPs. The draft of this TPP (rated as priority N° 2) 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.

Acknowledgements

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1. Background

Human African Trypanosomiasis (HAT) is a life-threatening parasitic infection transmitted by the tsetse fly, that is endemic in Sub-Saharan Africa. Having caused devastating epidemics during the 20th century, its incidence has fallen to historically low levels thanks to sustained and coordinated efforts over the past 20 years. Two trypanosome subspecies cause the disease, with distinct epidemiology: T*rypanosoma brucei rhodesiense* (*Tbr*), found in eastern and southern Africa, is harboured by wild and domestic animals which constitute its reservoir, being transmitted occasionally to humans; and *Trypanosoma brucei gambiense* (*Tbg*), in western and central Africa, with humans as the main reservoir, accounting for about 95% of the total caseload.

HAT diagnosis relies on laboratory techniques because clinical signs and symptoms are unspecific. Serodiagnostic tests exist only for *Tbg* and are based on the detection of specific antibodies, thus they are not confirmatory of infection. With the current low disease prevalence, the positive predictive value of serological tests is particularly low. Field-applicable tools include the card agglutination test for trypanosomiasis (CATT) used mainly in active screening by specialized mobile teams, and the rapid diagnostic tests that are more suitable for individual testing at point-of-care. Parasitological confirmation of *Tbg* infection requires microscopic examination of body fluids through laborious methods performed by skilled personnel. The best performing parasitological tests reach 85-95% diagnostic sensitivity at best but are more complex than tests with lower sensitivity.

In gambiense HAT (g-HAT) it has been observed since long that repeated rounds of serological screening followed by treatment of cases detected can bring down the prevalence to low levels, and this has been the cornerstone strategy of g-HAT control and elimination. But it is known that among seropositive but microscopically unconfirmed individuals there is a variable proportion that harbours the parasite and could perpetuate the reservoir. It has not been possible so far to recommend treatment on the basis of suspicion alone, because current treatments are logistically challenging and not sufficiently safe. The expected advent of a safer and easy-to-use treatment, would favourably tip the benefit-risk balance and allow for treating highly suspected individuals (widened treatment). A simple diagnostic tool to identify individuals eligible for treatment would be the ideal complement for a powerful elimination approach.

2. Use case

Diagnostic tool to identify individuals with suspected but microscopically unconfirmed g-HAT infection, eligible for treatment with safe and easy-to-use medicines.

3. Technical scope

It could be any method of high sensitivity but simple enough to be applicable at the point-of care. The sensitive parasitological methods currently used to confirm a *Tbg* infection are complex because they require specialized materials and equipment for concentrating the parasites, which often depend on a source of electricity, and which are often unavailable at the point-of care in HAT endemic regions. In the future, easier parasitological methods could arise.

The envisioned tool could be in any format, as long as it is simple and requires minimal specialized training.

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

4. Medical need

The safety profile and administration characteristics of the medicines currently available are not appropriate for their extended use in suspected but parasitologically unconfirmed cases. With the possible advent of a safe, effective and simpler anti-trypanosome treatment, it would be conceivable to widen the criteria of eligibility for treatment, to include individuals without parasitological confirmation but with a high degree of suspicion of harbouring parasites. Such type of "widened treatment" intervention would benefit infected individuals for whom the current diagnostic methods fail to confirm the infection. Simultaneously, it would benefit the community by further suppressing certain parasite reservoirs that perpetuate the risk of transmission.

The needed tool should identify individuals with a high degree of suspicion of infection (independently of symptoms) that can be considered sufficient to justify treatment with a medicine that has a good safety profile.

Ideally, with one test it should be possible to reach a therapeutic decision. A tandem of two simple sequential tests would also be acceptable.

Ideally, the test should be usable in peripheral health facilities[1], and in mobile labs at village level in zero infrastructure conditions.

A test fulfilling this profile, thought in relation to a safe and easy-to-use medicine that is expected to emerge with time, would nonetheless have a significant role even in the absence of such medicine.

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

Target product profile

Diagnostic test attribute	Minimally acceptable	Desirable	Annotations
1. Intended use			
Target taxon/ species / subspecies/type	*Trypanozoon*	*T. b. gambiense (Tbg)*	Already now, in a g-HAT area, all trypanosomes that are being observed microscopically in human body fluids grant a treatment, without further knowledge of the subspecies.
Target population	Individuals at risk of g-HAT	Individuals at risk of g-HAT	
Use of information obtained	Preselection of g-HAT suspects for treatment. Use of a second sequential test to narrow down the selection might be necessary.	Identification of g-HAT suspects for treatment.	Ideally, a positive test should trigger treatment. Specimens should be collected and sent for remote testing with higher specificity, to follow up the HAT epidemiological status of a region.
Type of specimen collected	Any specimen collected without discomfort to the patient disproportionate to the health benefit	Any non-invasively collected specimen	Minimally invasive (fingerprick, skin microbiopsy) or non-invasive (saliva, urine, tears…) Possible techniques without specimen collection
Analyte to be detected	Antibodies, antigens of *Trypanozoon* or whole parasite or *Trypanozoon* specific nucleic acids	*Tbg* specific antibodies, *Tbg* antigens, whole parasite or *Tbg* specific nucleic acids	Antibodies may linger from a previous infection. Whole parasite detection with lens-free optical methods is currently under research.
Nature of the result	Qualitative	Qualitative	No need of quantitation
Infrastructure level and operating environment	First-line peripheral health facilities followed by laboratory at next-level structures	Peripheral health facilities and mobile labs at village level (zero infrastructure conditions)	The closer to the communities at risk, the better
Intended user	Minimally trained lab technician	Any minimally trained individual	

[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	>95%	> 99%	It should be at least equal to the most sensitive parasitological tests currently used. False negatives result in non-treatment with risk of death and yield lower incidence estimates.
Clinical specificity	>95%	>99%	Specificity required will depend mainly on safety of the medicines used (less safe, higher specificity needed. False positives lead to unnecessary treatment and overestimate of the disease incidence.
Analytical specificity / cross reactivity	*Trypanozoon*	Both types of *T. b. gambiense (Tbg1* and *2).*	Diagnosis and treatment are currently based on microscopy, at *Trypanozoon* subgenus level.
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 instruments/ environment, same sample, same reader)	Kappa > 0.92	Kappa > 0.96	
Reproducibility Inter-reader agreement (different tests, other instruments/environment, same sample, same reader or different readers)	Kappa > 0.9	Kappa > 0.94	
Quality control	Control of functionality included per test.	Control of individual functionality, positive and negative controls for batch testing, possibly for kit testing	Depends on the test format Positive and negative controls available for batch testing. Pos and Neg controls per kits must be temperature stable.A proficiency panel would be useful.

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	The new CE marking rules, more demanding, may entail unrealistic production costs. 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	Can be operated at 10-30°C and 40-70% relative humidity	Can be operated at 10-40°C and 10-88% relative humidity	
Workflow requirements	<10 steps Simplified pipette devices Result available in < 2 hours	< 5 steps No need for precision liquid handling Result available in < 20 minutes	
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.	Not requiring instrumentation	Total cost of instrumentation and devices needed to perform testing should take into account that first-line facilities need to perform it. Adapted to the infrastructure level defined above
4.3. Information and communication technology			
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 minutes	The test result is qualitative and scored visually or by read-out of a portable device. Test result stable for at least 30 minutes	Data output does not require interface or connectivity
Recording of results and data capture	Results are recorded in a log book and/or a computer or smartphone	Results 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 retrospective interpretation (e.g. electronic result, optical density or intensity, etc, electronic image or video).	Data includes results and demographics/other information. Data should be exportable to any database if needed. Storage needs may vary per program. Especially the decision on treatment should not be dependent on connectivity.
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) Data format should be compatible with healthcare databases (JSON, DHIS2) supporting seamless transmission to them if required.

4.4 Reagent and control handling			
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).
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 and bench aids are part of each package. In use stability >½ hour after opening the pouch. Reagents ready to use, or within 15 mins with max 5 additional steps.	Individual packed tests, accompanied by all necessary accessories for sample collection and processing. Stable at 4-45 °C and 40-88% relative humidity for ≥ 24 months. 1 week transport stress at 50 °C Transport not needing cold chain Operating instructions and bench aids in each package. In use stability >2 hours 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.	Depending on the type of specimen. For blood ≤0.07 mL (finger prick, capillary tube).	Extra specimen material can be collected at the same time for repeat and/or remote testing if needed. For other tissues or body fluids, volumes can be specified later on, but should be collectable with minimal efforts
Specimen collection and processing	Routinely used collecting devices, minimal specimen processing.	Collecting devices provided with the kit, minimal or no specimen processing.	Special collecting devices are not used routinely in peripheral health centres. Occasionally, left-over 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 lancets, capillary tubes, etc. Appropriate disposal method for excess specimens and processing consumables (e.g. latrine, incineration). SOP provided.	Same as minimal.	

4.6. Distribution, training and support			
Training	Basic specific training needed (1 day)	Basic specific training needed (less than 2 hours)	
Instrument and test supply reliability	Supply guaranteed for ≥ 5 years after marketing. Manufacturer should replace non-functioning tests or instruments	Supply guaranteed for ≥ 7 years after marketing. Manufacturer should replace non-functioning tests or instruments	
Service and support response time	External support available. Support response within 1 week.	External support available. Support response within 1 day.	
5. Commercial and sustainability aspects			
Sustainability	Sustainable production	Sustainable production	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	≤20 USD Excluding specimen collection costs	≤1 USD Excluding specimen collection costs	Costs of hardware, shipment of material, sample collection, and salaries, are not included here. A 1 USD test would be applicable in mass screening situations, while a 20 USD test would rather be a second-line sequential test.

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