



# Developing New Diagnostic Tests for Human African Trypanosomiasis

## Current status and future plans





Enrolment of participants in a clinical trial on a diagnostic test for sleeping sickness.

## **FIND'S PURPOSE**

FIND addresses the market failures that result in the lack of appropriate diagnostic tools in disease-endemic countries. Our expertise is in the development of innovative, field-adapted diagnostics that have significant impact in low-resource settings. We demonstrate how improved diagnostics save lives and resources, and we provide technical support for their introduction and implementation in national health systems. The process requires bringing together knowledge of the needs on the ground with technological know-how, and a sound understanding of the intricacies of developing diagnostics.

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# Overview of FIND

FIND was established in 2003 to bring diagnostic solutions to societies where treatable diseases are rampant and where poverty and poor health are closely intertwined. The diagnostics available in disease-endemic countries are often not well adapted or too costly for use in the field. FIND addresses these challenges by developing diagnostic tests that are field-adapted and affordable. During the past 10 years, we have been developing diagnostic approaches that have been proven in principle, transforming them into effective products for identifying tuberculosis. Strong partnerships with academia, public and private research institutes,

and industry have increased the scope of activities which now includes diagnostics for human African trypanosomiasis (HAT), malaria, HIV/AIDS, leishmaniasis and Chagas disease.

Since 2006, FIND has also been working to upgrade healthcare systems and laboratory standards, so that the new tools can be rolled out in low-resource settings. The impact and effectiveness of these improved diagnostic tests is measured through a continuous flow of information and feedback from the field.

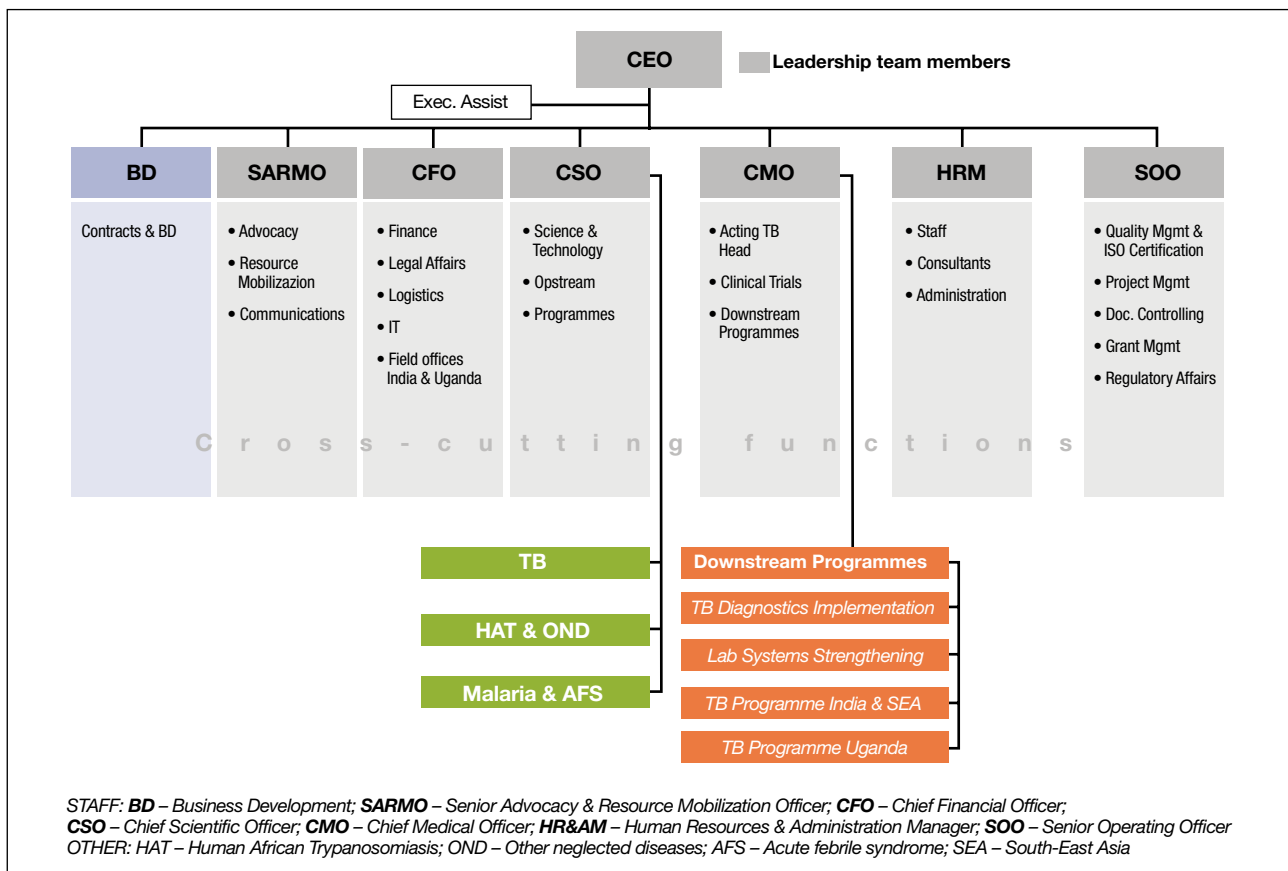


Figure 1: The FIND Organogram

The organization's business model (figure 1) provides an environment for maximizing available expertise across diseases and technologies.

FIND's strategy is to focus on developing diagnostic technology platforms that can be applied to several diseases, thereby reducing product development costs, time and risk, while building on our experience in

facilitating efficient introduction of tests and training of health personnel. The diagnostic tools we work on are intended to improve patient care at an individual level, as well as disease control at a population level. The level of FIND's involvement in development of a technology is dictated by the stage the technology is at on the value chain (figure 2), starting from proof-of-concept to early implementation.

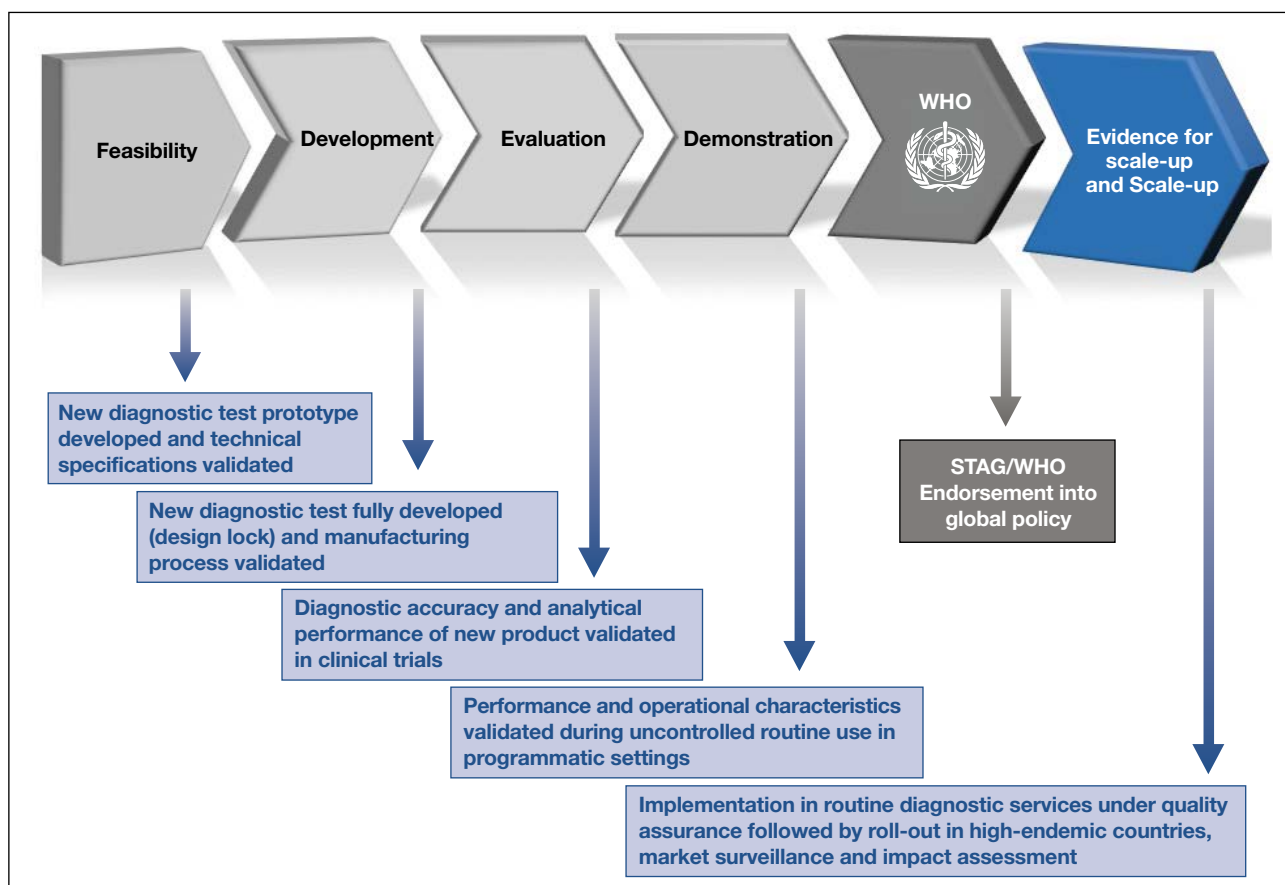


Figure 2: FIND's basic diagnostics development value chain, which can be adapted depending on the disease

FIND's funding base includes, among others, the Bill & Melinda Gates Foundation, UNITAID, the Global Fund to fight AIDS, tuberculosis and malaria,

the governments of the Netherlands, Germany and the United Kingdom, WHO-TB Reach, USAID, and the UBS Optimus Foundation.

# The HAT & OND programme

Human African trypanosomiasis (HAT) was the first neglected tropical disease (NTD) to be included in FIND's portfolio in 2006. The programme was renamed

HAT & other neglected diseases (HAT & OND) after the addition of leishmaniasis in 2010 and Chagas disease in 2012.

## Status of various projects implemented under the HAT & OND programme

### Human African Trypanosomiasis (HAT; sleeping sickness)

#### a) A test for screening populations that are at risk of infection

- i. Further to the successful evaluation of the performance of a prototype 1st generation rapid diagnostic test (RDT) using native trypanosome antigens on more than 14,000 individuals in Angola, the Democratic Republic of the Congo (DRC) and Central African Republic (CAR), the SD BIOLINE HAT test was launched in December 2012. Demonstration studies to further evaluate the performance of the test and determine its cost effectiveness in various diagnostic algorithms are ongoing.
- ii. Development of a 2nd generation RDT using recombinant antigens, which could be effective for both *Trypanosoma brucei gambiense* and *T.b. rhodesiense* HAT, is going on.

#### b) A test for confirming cases of HAT

- i. The mini-anion exchange centrifugation technique (mAECT) was improved and its production successfully transferred to the DRC.
- ii. Evaluation of an LED fluorescence microscope has been completed in the DRC and demonstration studies are going on.
- iii. Evaluation of a molecular test based on loop-mediated isothermal amplification of DNA (LAMP) is going on in the DRC and Uganda.

#### c) A test to determine if HAT patients have brain disease, and to monitor treatment

- Development of an RDT for staging and monitoring treatment by measuring neopterin and/or CXCL13 in CSF is in process.

### Leishmaniasis

#### a) ELISA test for parasite antigens in urine

An ELISA assay for urinary antigens using polyclonal antibodies is being developed in collaboration with DNDi, Kalon Biologicals (UK) and the Royal Tropical Institute (KIT, Netherlands). The test, to be used for case detection and monitoring therapy, is performing well.

#### b) LAMP test to detect parasite DNA

This test is being developed as part of expansion of the LAMP platform, in collaboration with Eiken, KIT and the Institute of Primate Research (IPR, Kenya). Prototype reagents are under evaluation.

### Chagas Disease

#### LAMP test for congenital Chagas disease

Development of the test was initiated in January 2012, in collaboration with INGEBI-CONICET and a Colombian multi-disciplinary team. Feasibility studies and optimization of sample preparation are going on.

## PROJECTS ON DIAGNOSTICS FOR HAT

### Problem and scope

Human African trypanosomiasis (HAT) is a disease of poor rural communities caused by extracellular protozoan parasites of the genus *Trypanosoma*. In early or Stage 1 infection when parasites are in the blood and lymphatic system, treatment is relatively safe and cheap. During this phase, however, clinical signs are not suggestive of HAT, and diagnostic tests have problems of sensitivity and specificity. Many cases, therefore, remain undetected and with time, parasites invade the brain, resulting in late or Stage 2 disease. Treatments of Stage 2 HAT are either lengthy and expensive, and difficult to administer, or cause potentially fatal side effects. Currently, tests to determine the stage of disease are non-specific and insensitive.

FIND and partners are developing and implementing tests for early and accurate diagnosis and staging of HAT patients, in order to ensure safe treatment. Other tests for early detection of treatment failure will ensure proper re-treatment, reduced transmission and accelerated control of the disease.

### Tests for screening

FIND and Standard Diagnostics (SD) have developed a lateral flow rapid diagnostic test (RDT) to screen for *T.b. gambiense* HAT that is cheap and easy to use. The tests are packed individually and are stable at 40°C for up to 25 months; they are performed on fresh blood obtained from a finger prick, and no instrument or electricity is required. The RDT detects host antibodies to infection in populations that are at risk, or in suspect individuals. Positive cases are subjected to further confirmatory methods to identify HAT patients.



The new rapid diagnostic test kit for HAT developed by FIND and Standard Diagnostics; the RDTs on the right show a negative (1 line) and a positive (3 lines) result





The new RDT is an alternative to the card agglutination test for trypanosomiasis (CATT), the primary screening tool used by control programmes in areas where *T.b. gambiense* HAT is endemic.

**Current status**

*1st generation test* – Field evaluation of the prototype has been successfully completed on more than 14,000 individuals at sites in Angola, Central African Republic (CAR) and the Democratic Republic of the Congo (DRC). Job Aids and a manual for training health workers on proper use of the new RDT (in English and French) have also been made.

The SD HAT BIOLINE test was launched at a workshop hosted by the Ministry of Health of the Democratic Republic of the Congo on 6th December 2012 in Kinshasa. Demonstration studies to further evaluate the performance of the test and determine its cost-effectiveness in various diagnostic algorithms are ongoing.

*2nd generation test* – The 1st generation RDT is made using native antigens generated from pathogenic trypanosomes, and is not applicable for *T.b. rhodesiense* HAT. Efforts are therefore being made by FIND and SD to develop a 2nd generation



A technician takes blood after a finger prick during clinical evaluation of the new rapid diagnostic test for sleeping sickness in rural Democratic Republic of the Congo.



The blood sample taken from a finger prick is introduced into the sample well of the rapid diagnostic test. The results of the test are read after only 15 minutes.



Children follow activities during active screening of a community in the Democratic Republic of the Congo, when clinical trials on the new rapid test for HAT were being carried out.



The study monitor discusses a point with the principal investigator (right) during clinical evaluation of the new rapid diagnostic test for sleeping sickness in a village in the Democratic Republic of the Congo.





RDT using recombinant antigens. Such a test would be easier and cheaper to manufacture, thus reducing the cost of the final product. Eight recombinant antigens (GM6, 4 ISGs and 3 VSGs) are being investigated.

*Antigen detection test* – A test that detects parasite antigens is a better indicator of infection than one that detects host antibodies, and could also be useful for monitoring treatment. The challenge has been in the identification of target antigens, since the ones on the surface of the parasite are variable or mutable. Current efforts are focused on using nanobodies, small camel antibodies that are particularly thermostable and that can penetrate the parasite surface coat and detect invariable antigens. Work carried out in collaboration with the Flanders Interuniversity Institute for Biotechnology (VIB) at the University of Brussels has identified a number of promising nanobodies. Their potential in development of a test is being determined in collaboration with SD.

### Future plans

- Conduct demonstration studies of the 1st generation RDT
- Roll out the 1st generation RDT in collaboration with partners
- Develop a 2nd generation RDT based on recombinant antigens
- Develop a 1st generation antigen detection test based on nanobodies

### Tests for confirming cases

Demonstration of parasites in body fluids is the most accurate way to confirm HAT, and is critical in order to avoid the risk of exposing healthy suspects to potentially dangerous therapy. For most *T. b. rhodesiense* patients, parasitaemia is usually high enough for parasites to be seen by direct examination of blood under a light microscope. However, the number of parasites

in *T. b. gambiense* infections is often below the limit of detection of the most sensitive methods that are in clinical use. In the cerebrospinal fluid (CSF), parasites exist in very low numbers, and have to be concentrated before they can be viewed. The most sensitive methods for detecting trypanosomes in blood that are in clinical use include the mini anion exchange centrifugation technique (mAECT) and the capillary tube centrifugation (CTC) method, while the modified single centrifugation (MSC) technique is used to detect trypanosomes in CSF. Although CTC is widely used due to its simplicity and low cost, widespread use of mAECT has been constrained by the high costs associated with it, and by the need for a cold chain.

### Miniature anion exchange centrifugation technique (mAECT)

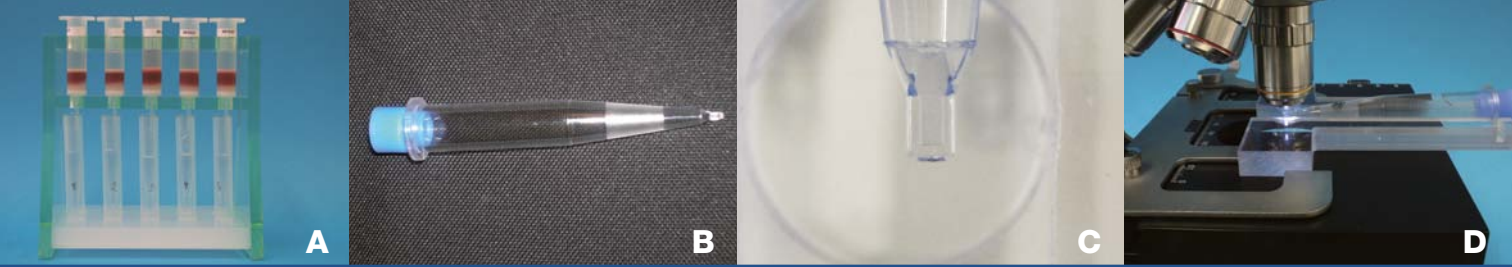
The mAECT is carried out in two stages, including chromatography of samples, then concentration of the eluate by low speed centrifugation and viewing under low magnification microscopy. Similarly with MSC, CSF is collected from a lumbar puncture and centrifuged before viewing. Both mAECT and MSC were, until 2006, manufactured at the Institute of Tropical Medicine (ITM) in Belgium and then shipped to endemic countries – a process that was untenable due to the associated high costs. A partnership between FIND, the ITM and the Institut National de Recherche Biomédicale (INRB) in DRC not only improved components of both mAECT and MSC, but by 2008 had successfully transferred their production to Kinshasa, DRC.

### Current status

Production of mAECT and MSC is done at the INRB. The largest percentage of kits produced is used locally in the DRC, mainly in clinical trials.

### Future plans

- Explore cheaper and more practical methods of separating parasites



Components of the miniature anion exchange centrifugation technique (mAECT) for separation and demonstration of trypanosomes. 350µl of fresh blood or buffy coat is filtered through a DEAE cellulose column, into a collector tube (A). Parasites are concentrated at the bottom of the collector tube (B) by low-speed centrifugation, and the tip examined for motile parasites under a microscope (C&D).

### Fluorescence microscopy

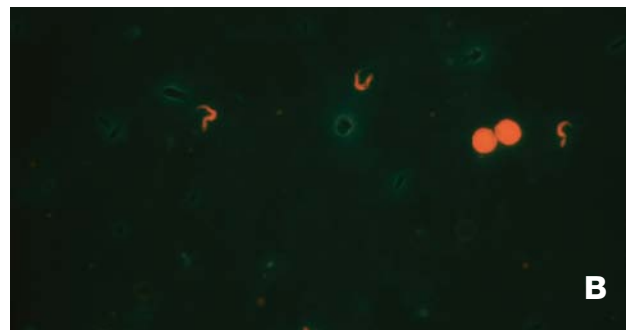
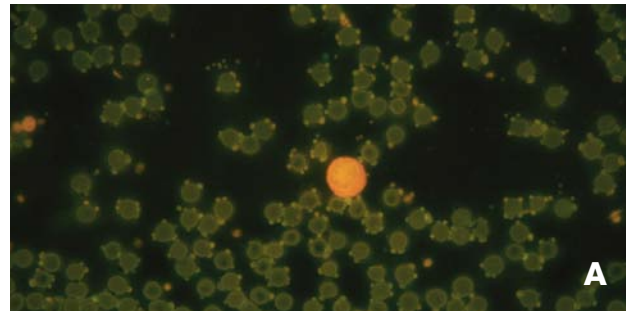
Fluorescence microscopy (FM) is known to increase the sensitivity, speed and ease of demonstration of trypanosomes. In the quantitative buffy coat (QBC) method, blood is collected in capillary tubes that are pre-coated with acridine orange and examined using a microscope with a special objective lens. Implementation of the QBC method has, however, been impossible for HAT due to the high cost of the equipment. FIND has been exploring cheaper options to improve detection of parasites using an LED fluorescence microscope.

### LED FM on whole blood, and blood after lysis and concentration

The Primo Star iLED fluorescence microscope was developed jointly by FIND and Carl Zeiss.

The microscope has high-grade optics, uses reflected rather than transmitted blue light for fluorescence applications, and permits easy switching between fluorescent and bright light viewing. It can be operated on battery power, does not need a dark room, and uses an inexpensive bulb with a life of more than 10,000 hours.

The Primo Star iLED was initially evaluated using experimental infections by a number of laboratories in Africa, including the National Livestock Resources Research Institute (NALIRRI) and Makerere University in Uganda, University of Kinshasa and INRB in DRC. Acridine orange, a common fluorochrome stain, was used for staining trypanosomes. The studies showed that the speed of reading and sensitivity are higher with this method, when compared with common bright field microscopy using



The dual purpose Primo Star iLED microscope developed by FIND and Carl Zeiss is easily switched to view samples by either bright or fluorescent light. Panel A shows a thin smear made from infected blood and stained with acridine orange. In panel B, the red blood cells have been lysed before preparation of the smear.



Carl Zeiss has developed a plastic box that enables easy and safe transportation of the microscope during active screening programmes (C&D). Panel E shows a technician operating an LED fluorescence microscope using solar energy in eastern Democratic Republic of the Congo. (Photos C&D are courtesy of Carl Zeiss AG)

Giemsa staining. The diagnostic capacity of the method is significantly enhanced when staining of samples is preceded by lysis of red blood cells using ammonium chloride or commercial lysis buffer.

### Current status

Clinical evaluation of the LED microscope using the red blood cell lysis and acridine orange staining methods has been completed at several sites in DRC and Uganda. The trial in the DRC was done in collaboration with the national HAT control programme and the SwissTPH, while the one in Uganda was done in collaboration with Makerere University and Lwala hospital. Based on the excellent results from these studies, the Ministry of Health of DRC approved the use of these new methods for routine diagnosis of HAT on 7th December 2012.

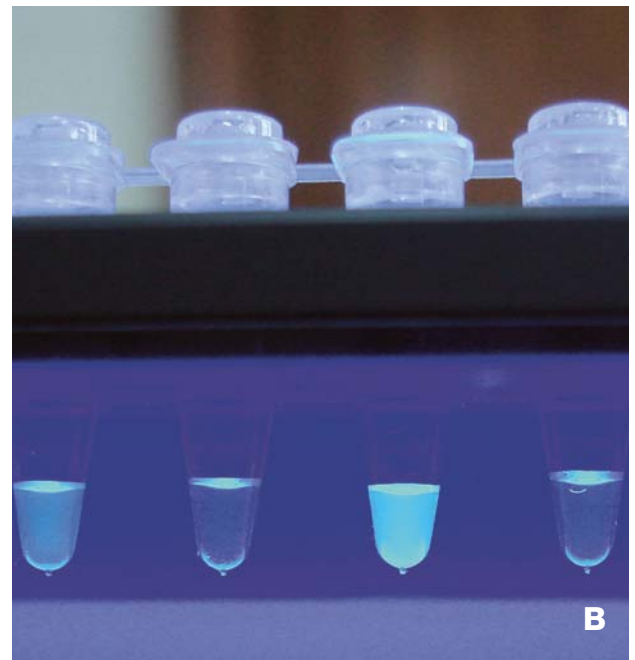
### Future plans

- Demonstration/early implementation of LED microscopy in diagnosis of HAT

### Molecular detection

Detection of trypanosome DNA from body fluids of a HAT patient could be a significant improvement on parasitological examination. Loop-mediated isothermal amplification (LAMP) of DNA is a promising molecular technique that shows high sensitivity and specificity.

The test amplifies target DNA at a constant temperature, meaning that it can be carried out with minimal equipment. Furthermore, positive samples fluoresce under LED light. The test can be performed by staff with minimal experience in molecular biology.



The Loopamp™ LF-160 incubator (A) used to perform the HAT LAMP reaction. After extraction of DNA, the LAMP reaction is kept at a constant temperature of 65°C for 40 minutes. The results are visualized under LED light (B). PC- Positive control, NC- Negative control. (Photo on the right is courtesy of E. Matovu)





In 2008, FIND signed a development agreement with Eiken Chemical Company, Ltd. (Japan), the owner of the patent rights to LAMP, and completed development of a LAMP kit for HAT in 2011. The reagents for LAMP are dried on the inside part of the cap of the reaction tube, which can be stored at room temperature. When test samples are added, the tubes are heated at constant temperature in an incubator, and the results read visually using LED light. The test can be performed on blood, either fresh or dried on filter papers, or buffy coat, or microscopy slides.

### **Current status**

Clinical evaluation of the HAT LAMP kit is being carried out at multiple sites in the DRC and Uganda. Prospects of using the same test in drug screening studies, and for monitoring treatment, are also being explored.

### **Future plans**

- Demonstration/early implementation studies
- Cost-effectiveness studies to guide novel strategies for introduction of LAMP in diagnosis of HAT



A technician takes blood from a finger prick during clinical evaluation of the new LAMP test for sleeping sickness in Bandundu province, Democratic Republic of the Congo.



## Tests for staging and confirmation of cure

Determining what stage of disease a HAT patient is in is crucial for deciding what treatment should be given. In early or Stage 1 disease, the infection is confined to the haemolymphatic system. In late or Stage 2 disease, parasites have penetrated the central nervous system (CNS) and, depending on the duration of the infection, the CNS would be at various stages of damage. To distinguish the two stages, a lumbar puncture is performed and the CSF examined for presence of parasites, and the number of white cells counted. These parameters, however, suffer from insufficient sensitivity and, in the case of white cell count, of specificity as well. Because of these shortcomings, the invasive character of a lumbar puncture and toxicity of the drugs used to treat late stage disease, improved markers for staging are needed.



After treatment, patients are followed up for 24 months to confirm cure or detect relapses. Since relapses are mainly of CNS origin, and parasites are often difficult to find in blood, follow-up largely relies on lumbar puncture and CSF examination.

### Current status

FIND partners, led by scientists at the University of Geneva, have identified and validated unique molecules in the CSF of HAT patients that have great potential in determining the stage of disease. The concentration of these molecules in the CSF also falls quickly in patients whose treatment is successful. Based on these findings, FIND, Standard Diagnostics, and other partners are exploring the feasibility of using either neopterin or CXCL13, which were among the best markers for *T.b. gambiense* HAT, to develop a dual purpose rapid test for both staging and monitoring treatment.

Further preliminary studies at the University of Geneva have led to identification of blood biomarkers that could be used to confirm cure and detect relapses. If certified, the use of these markers could eliminate the need for lumbar punctures during follow-up.

### Future plans

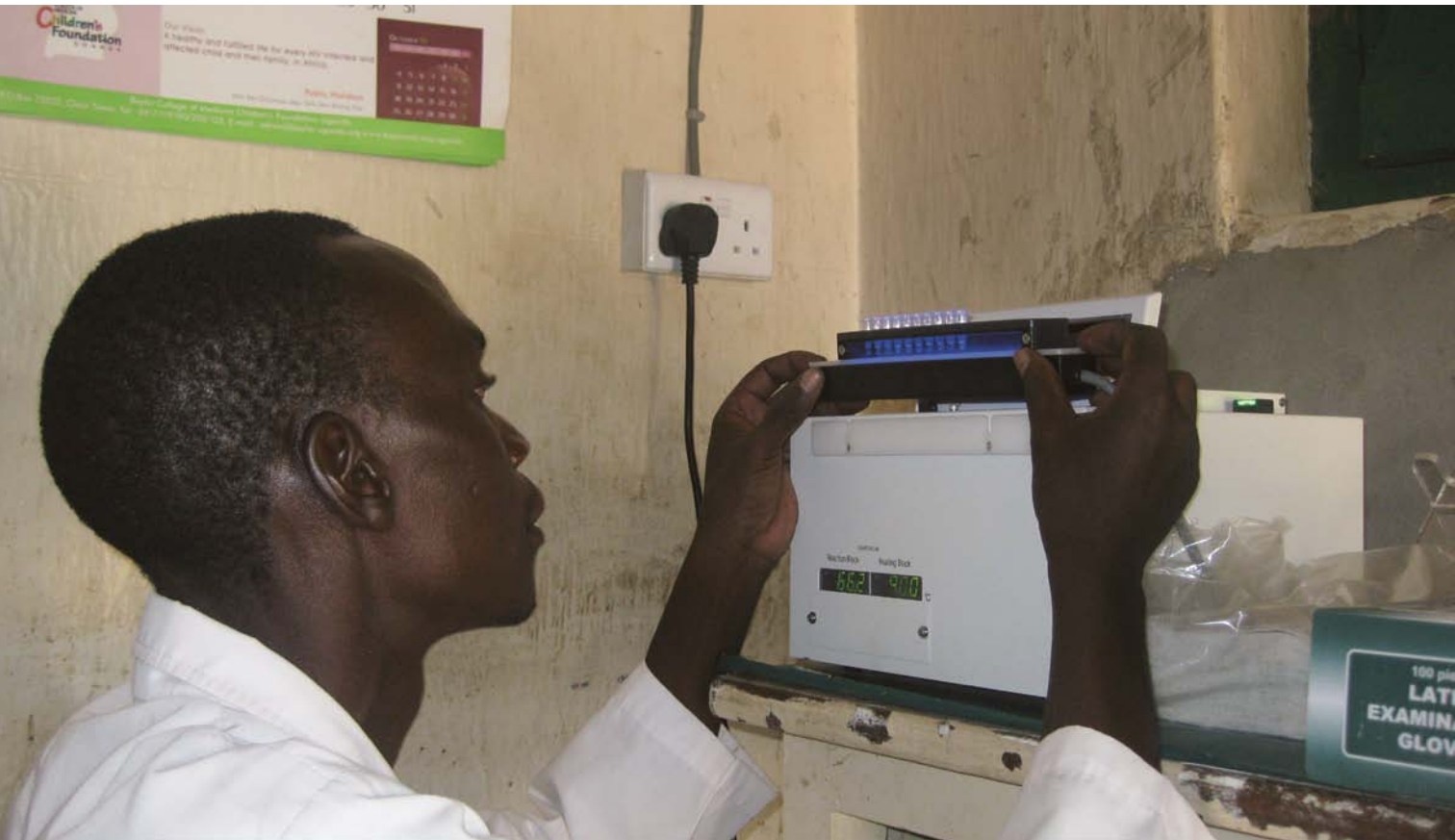
- Complete development and evaluation of an RDT for staging and monitoring treatment
- Further work to identify blood biomarkers for monitoring effectiveness of therapy

Blood samples collected on filter paper from suspected cases of HAT during active screening are held to dry using clips on a specially designed stand to prevent them from being blown away. Dry samples are stored individually in plastic pouches containing a desiccant, and sent to a LAMP centre for testing.





A technician applies blood from a participant on a filter paper at a rural health centre in the Democratic Republic of the Congo during clinical evaluation of LAMP for the diagnosis of HAT. The sample is left to dry at ambient temperature, then stored in a plastic pouch containing a desiccant, before being sent to a LAMP centre for testing.



A technician reads the results of LAMP at a rural hospital in Uganda, where the test is being evaluated for the diagnosis of *T.b. rhodesiense* HAT.



## **Biological samples to support test development**

A critical obstacle in development of improved assays for HAT is access to carefully collected and stored biological materials.

### **Current status**

FIND and the World Health Organization (WHO) have addressed this problem by establishing a HAT specimen bank, which is owned by the WHO. The Institut Pasteur in Paris hosts the WHO specimen bank, storing samples and dispatching them to research institutions and other users after approval by an Exit Committee of WHO.

Additional specimen collections are available at the Institute of Tropical Neurology (INT) in Limoges France, and Makerere University in Uganda, for use on FIND-supported activities. The number of samples in these collections is increasing as new clinical studies are carried out.

## **FUNDING**

The current funders for HAT diagnostics at FIND include the Bill & Melinda Gates Foundation, EU-FP7 Programme, DFID (UK), UBS Optimus Foundation and the German government.

## **AGREEMENTS WITH PARTNERS**

Most activities with our partners are based on contractual agreements. FIND has, in addition to such agreements, signed a Memorandum of Understanding with the following strategic organizations, among others:

- World Health Organization
- Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC)
- Médecins Sans Frontières – Spain

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Viewing the results of a HAT LAMP test in Eastern DRC.

FIND provides the necessary expertise, capacity and facilities needed to drive the R&D process, through partnerships with academia, industry and endemic country governments. We also help create the necessary conditions for widespread implementation of these tools through collection of evidence, sharing knowledge and technology transfer.





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