HAT Platform

REGIONAL PLATFORM FOR CLINICAL RESEARCH

NEWSLETTER N°13, July - August 2013

Joint Scientific HAT meeting HAT PLATFORM - EANETT

From 04 to 07 June 2013, Nairobi, KENYA

n°13

Contents

Editorial

Dr Kadima Augustin ; HAT Platform Coordinator

This 13th issue of our Newsletter is issued in a very eventful 2013 year: DNDi marks its 10th anniversary, HAT Platform scientific activities abound, and all actors in the field of sleeping sickness are fully committed to eliminating the disease by 2020, despite the stagnation in disease prevalence seen in 2012.

This Newsletter reviews all our successes so far, with pictures as well as articles. Rapid diagnostic tests, new molecules for treatments, and forums are all helping us reach our common goal. However, it is essential that we do not let these efforts go to waste whilst the mobilization to eliminate sleeping sickness and certain other neglected diseases is gaining momentum.

As always, any suggestions to help us improve this Newsletter are most welcome.

We hope you will enjoy this issue.

Dr K. Ebeja Augustin
HAT Platform Coordinator

Editorial committee:
Chairman: Augustin Kadima Ebeja

Members: Olaf Valverde ; Charles Wam boga ; Sylvestre Mbadingaï ; Gédéon Vatunga ; Richard Laku ; Victor Kande and Nicolas Mbongo

Advisers: José Ramon, Cecilia Schmid and Laurence Flévaud.

HAT Platform coordination address
Avenue Révolution No 4, quartier SOCIMAT
Kinshasa, Gombe

République Démocratique du Congo
Email: aebeja@dndi.org
Tél: 00243 81 081 22 38

HAT epidemiology in the HAT Platform countries at the end of 2012

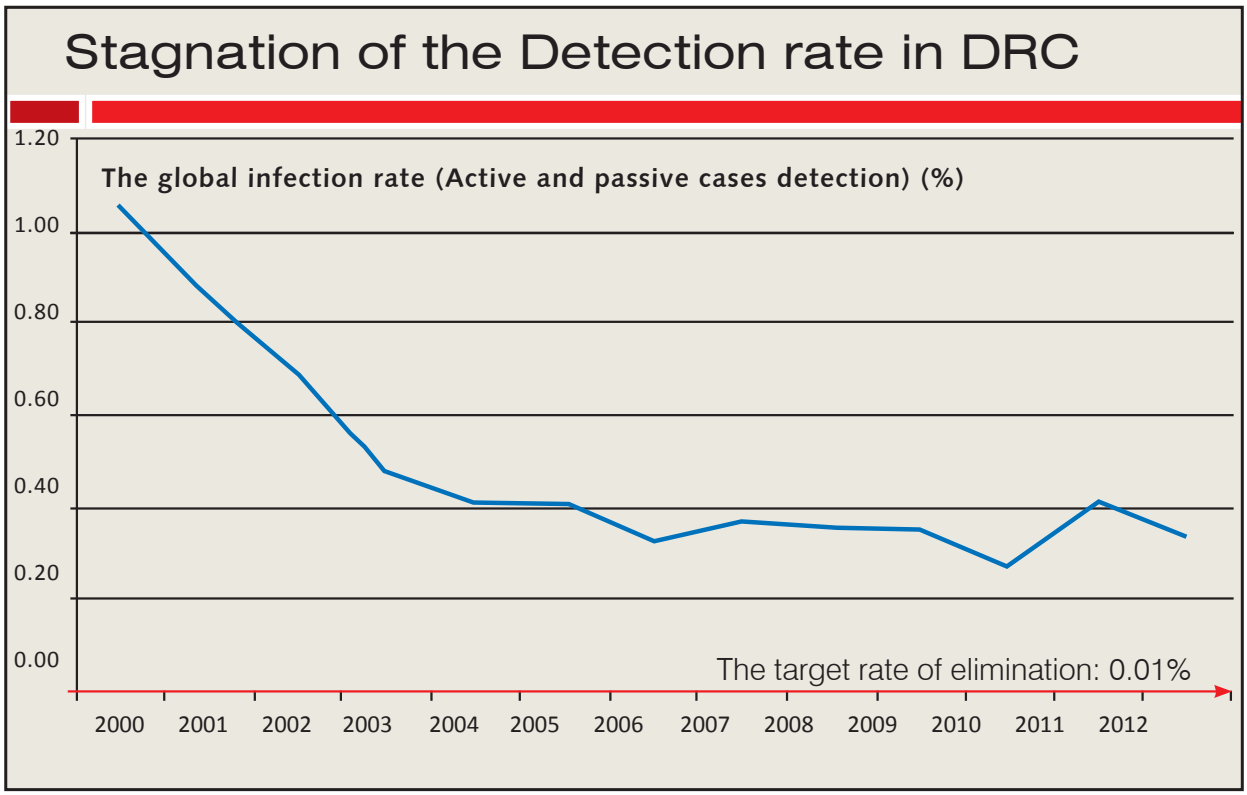
This is a brief review of the HAT situation in the seven Platform member countries between 2010 and 2012.
The table below shows the number of cases in each country, as well as annual variations in the last two columns. The variation column shows increases with positive numbers, and decreases by a – sign.

HAT Platform Countries \ Cases and years	Number of cases			Variation in %	
	2010	2011	2012	2010-11	2011-12
DRC	5629	5595	5969	-0.6	6.7
CAR	425	122	401	-71.3	229
South Sudan	247	297	327	20.2	10
Chad	212	247	197	16.5	-20.2
Uganda	225	123	99	-45.3	-19.5
Angola	210	154	69	-26.7	-55.2
Republic of Congo	87	61	40	-29.9	-34.3
Total HAT Platform	7035	6599	7102	-6.2	7.6

In 2012, only 4 countries declared over 100 cases. The comparison between 2010 and 2012 shows a clear stagnation of HAT cases throughout the HAT Platform countries. In 2012, the largest increases in terms of quantity (374 in DRC and 249 in CAR) were clearly related to enhanced active screening activities in both these countries. Likewise, reductions are also associated with a decrease in active screening activities. The strong reduction in the number of cases initiated in 1999, slowed down as of 2003, and has stopped since 2010.

Democratic Republic of Congo (DRC)
En 2014, the backing provided by the Belgian government via the Belgian Technical Cooperation programme will be replaced by support from the Institute of Tropical Medicine in Antwerp, which has yet to be defined. The National HAT Control Programme is pursuing its activities of integration into the national health system, especially in areas with a lower prevalence, but vertical support through active screening actions must be maintained.

DRC reports 84.4% of all cases within the HAT Platform countries. The graph below shows a slowing down followed by a stagnation of the detection rate in the country (number of cases per total number of people examined through active and passive screening). This indicator considers the intensity of the control activity as a parameter to measure variations in the proportion of cases detected.

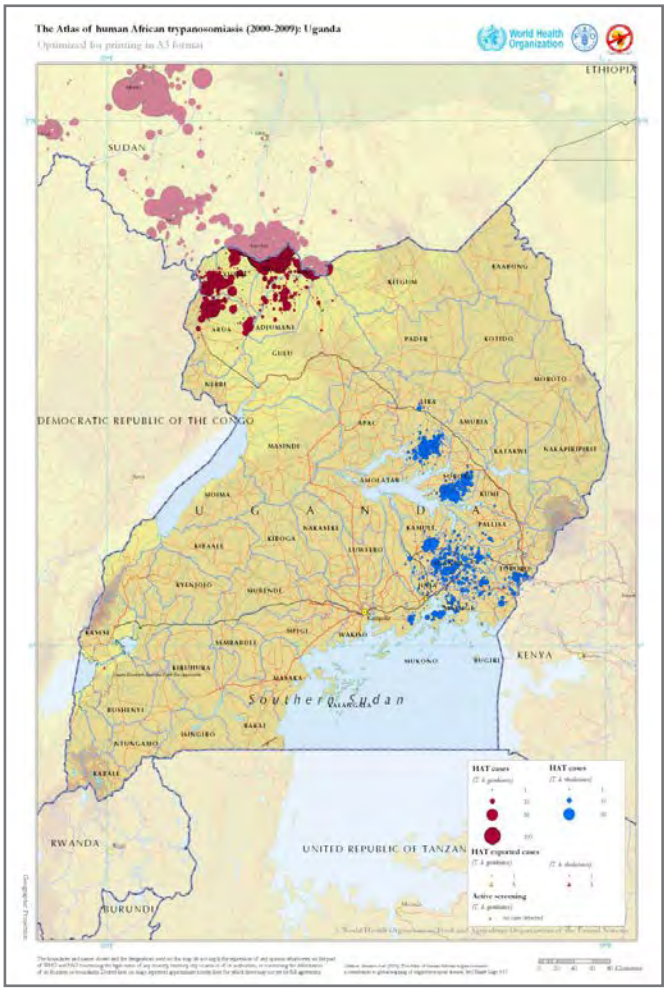


Central African Republic (CAR)

The drop in the number of HAT cases recorded in 2011 was followed by a major rebound, partly due to the resumption of active screening by MSF in the Batangafo foci (Ouham, 314 cases). The number of cases also rose in the three other foci of Nola (31 cases), Lobaye (14 cases) and Haut Mbomou (42 cases). However, at the end of 2012 and beginning of 2013, the armed conflict in the country reduced active screening activities. A total of 403 cases of HAT were recorded in the Central African Republic, bringing the detection rate to 2.4% out of 16,850 people examined in 2012. The National HAT Control Programme (PNLTHA) prepared an action plan identifying precisely the higher risk areas, but funding of active screening remains uncertain.

South Sudan

This new country has seven active foci, and the number of reported HAT cases is on the rise. However, the situation in South Sudan is unusual as the number of CATT-positive individuals is high, but the number of confirmed parasite cases is lower. The active screening campaign carried out by MSF in Kajo Keji detected 11 parasitologically confirmed cases and 84 serological cases (CATT dilution 1/8 and 1/16), but only 3 of those cases were confirmed with immune trypanolysis tests. The rise in cases seen this year is also associated with an increase in active screening activities, partly due to greater governmental involvement with support from WHO and an MSF mobile team.



Chad

HAT control interventions in the four historical foci in 2012 resulted in the screening of 21,616 people, i.e. 64.4% of the estimated population living in the visited villages in the Mandoul foci. Active screening thus dropped by 46% (39,910 en 2011) following MSF's departure from the Moissala foci. A total of 197 cases were diagnosed, 77 through passive screening and 120 through active screening. The Bodo Catholic Health Centre treated 104 cases (53%), of which 102 were in the late-stage of the disease. The overall detection rate was 0.9%. No active screening activities were carried out in Moissala, Tapol and Goré. Besides, no cases were detected passively in these three foci. A new district hospital was inaugurated in Bodo, but they do not yet have the means to diagnose and treat HAT cases.

Uganda

The drop in T.b. gambiense cases recorded in 2011 in northwest Uganda is confirmed (from 44 in 2011 down to 23 in 2012), but the T.b. rhodesiense foci in the central and southwest regions remain active, albeit with a slight reduction from 80 to 76 cases. However, late-stage trypanosomiasis is on the rise (40 in 2011 vs. 61 in 2012), with a large number of cases in Lwala hospital (61 cases, 76% of all cases). The geographical distribution of cases between 2000 and 2009 is shown in the HAT Atlas map below (source: WHO).

Angola

For the first time, passive screening overtook active screening activities. Passive screening is generalized and stable for all patients in certain highly endemic provinces, particularly Kwanza Norte and Uige, with 47,447 people screened passively out of 61,387 examined (77.3%). Out of the 69 cases reported, only 4 were detected actively. The drop in detection rate continued in 2012. Cases are still concentrated around 5 provinces in the north west of the country: Bengo (20), Luanda (18), Kwanza Norte (16), Uige (8) and Zaire (7). All cases except one were diagnosed at the late stage of the disease.

Republic of Congo

Only 40 cases were diagnosed in 2012 out of 49,883 people examined, i.e. a detection rate of 0.08%. MSF supported active screening efforts and helped provide equipment for the treatment centres. However, the Ngabé and Ignié foci, amongst those generating the largest number of HAT cases, were not examined. Passive screening in Brazzaville (12), Nkayi/Loudima (6) and Mossaka (9) produced 28 cases. The 12 cases detected actively were very widely spread over 5 of the 7 screening campaigns, mainly around Mossaka-Loukolela (9), an area which was only partly covered. Only 5 of these cases were in the early stage of the disease (12.5%).

In conclusion, it is important to acknowledge the hard work of national programme personnel, despite limited support from their governments, which covers only salaries and expenses for only minimum activity. The effort of the Belgian government and their decision to continue to provide support in the DRC, as well as the continuous support of WHO and the strong presence of MSF in the most complex environments helped detect more cases this year.

Clearly, even with the engagement of the international community, for example with the London Declaration in January 2012, the much-needed increase in funding for the fight against the disease is still to come. Since 2005, the momentum in case reduction has almost come to a halt, and without massive efforts, the plan to eliminate sleeping sickness by 2020 will be difficult to realize.

Dr Olaf Valverde Mordt,

based on data provided by the national trypanosomiasis control programmes and institute

Latest scientific events and general updates

Meeting of the HAT Platform Steering Committee in Nairobi (Kenya) on 3 June 2013

The meeting started with a reading of the report and recommendations which followed the previous meeting held in Juba, South Sudan on 14 and 15 September 2012. The members of the Steering Committee came to the following conclusions:

Legal advice should be sought to define a legal status for the HAT Platform. A task force was created to provide proposals to the Steering Committee, based, for instance, on the initiative for patients with Chagas disease living outside their country, or on the status of EDCTP representation in South Africa. The representation of DNDi in Kinshasa could also make suggestions.

The Platform's member countries listed the strengths of the implementation of the action plans adopted in the past years: participation in the Platform meetings; training of technicians, nurses, investigators (GLP, GCP, protocols, patient care, pharmacovigilance), and members of ethics committees; training in NECT pharmacovigilance (Uganda, DRC); introduction of NECT in the treatment of late-stage sleeping sickness; subregional collaboration; and publication of activities in the HAT Platform Newsletter. The Platform's financial support (FP6) was highlighted.
The weak points which hindered the countries' actions include the unpredictability of sufficient healthcare agents trained in HAT; low level of contribution of countries to the HAT Platform newsletter; insufficient involvement from Masters or PhD students; lack of funding commitment for research; ethics committees that are non-functional (South Sudan) or paralysed by diverging interests of the medical community (CAR).

The weak points attributed to the Platform coordination included: non-use of trained monitors; exclusion of healthcare workers from certain training sessions in the countries that have no clinical trial sites; progressive breakdown of healthcare centres rehabilitated for a clinical trial once the trial is over.

The following HAT Platform partners presented their achievements :

MSF in CAR

Activities carried out since 2007 show a HAT prevalence between 0.1 and 3.2% (Bossembele).

Operational research conducted in collaboration with FIND included the evaluation of Rapid Diagnostic Tests (RDTs) compared to CATT (FIND), and the clinical trial on fexinidazole (DNDi). Once the ethics committee gave its approval in 2012, the initiation visit and recruitment of the clinical trial on fexinidazole began in 2013 in Bantagafo.

The 2013 prospects include active screening in Kabakota, and on-going studies on fexinidazole and RDTs.

FIND

Two categories of tools are currently being developed:

- Tools to be used in the healthcare centres conducting diagnosis, treatment and post-treatment follow-up: LED fluorescence microscopy, Rapid Diagnostic Test (RDT) on CSP and LAMP test;
- Diagnostic tools to be used in the peripheral regions conducting active and passive screening before sending patients to a referral centre: LED fluorescence microscopy and RDT on blood.

The performance of the prototypes in the field was evaluated in three countries with high, moderate and low endemicity (CAR, DRC and Angola). Results are promising and the prototypes were adopted during a launch meeting organized in Kinshasa in

the presence of administrative and healthcare authorities, under the chairmanship of the Public Health Minister of DRC, His Excellency Dr Félix Kabange.

The government of DRC approved the use of LED fluoroscopy microscope for the parasitological diagnosis of HAT in 2012.

The next stages include: cost-effectiveness studies for different screening strategies, and compared with existing tests; scaling-up in endemic countries and development of second generation RDTs using recombinant antigens.

FIND is also involved in research on HAT stage biomarkers. Neopterin seems to be a good marker.

This work is carried out by FIND in partnership with the University of Makerere (Uganda), TRC-KARI (Kenya), INRB (DRC), UNIKIN (DRC), WHO (Geneva), DNDi (Geneva), ITM (Belgium), Swiss TPH (Switzerland), the University of Glasgow (UK), the University of Cambridge (UK), Standard Diagnostics (South Korea), EIKEN Chemical Co (Japan), ZEISS (Germany), AU-PATTEC…

DNDi

Dr Antoine Tarral presented DNDi's strategy on sleeping sickness. In addition to the currently available NECT treatment, the medium-term (2018) strategy for DNDi is to develop and deliver two drugs against sleeping sickness:

- Fexinidazole, an oral drug: By early June, 90 patients were included in the trial (60 in the fexinidazole group and 30 in the NECT control group).
- Oxaborole (SCYX-7158), oral drug for the treatment of patients with T.b. gambiense or T.b. rhodesiense HAT at the neurological stage.

These clinical trials are still faced with obstacles: difficulties to recruit patients given that the number of HAT cases is dropping, patient follow-up, and security issues in areas of conflict (e.g. CAR).

SWISS TPH

SWISS TPH continues to participate in clinical trials involving the HAT Platform:

- NECT-Field: study closed, data analysis, Master's thesis defence, and final report;
- Fexinidazole: meeting of investigators, initiation of the study, training of regional clinical monitors (1 Swiss TPH, 1 DRC-Kinshasa, 1 DRC-Bunia, CAR-Bangui).

SWISS TPH is also involved in drug discovery (screening, lead optimization, pre-clinical studies), the first stages in drug development and basic research.

ITM Antwerp

The Institute of Tropical Medicine (ITM) in Antwerp, Belgium, has biomedical, clinical sciences, and public health departments.

ITM is involved in HAT control, and conducted optimization studies in collaboration with INRB-Kinshasa on the mini Anion Exchange Centrifugation Technique (mAECT) to monitor trypanosome drug resistance. It also contributed to the development of the NECT-Field protocol and pharmacovigilance, and evaluated the efficacy of new diagnostic technologies. ITM is committed to supply mAECT kits to the National HAT Control Programmes and antigens to FIND.

WHO

WHO published a roadmap on neglected tropical diseases (NTDs) in 2012, where HAT is described as a disease targeted for elimination as a public health problem, i.e. bring its prevalence below one case per 10,000 inhabitants in 90% of existing foci.

After analysis, the Strategic Committee of NTD Coordination considered that elimination should mean zero cases.

The endemic countries attended a meeting organised by WHO in Geneva in December 2012. They concluded that the elimination goal of zero cases was achievable but only by 2030.

The WHO Expert Committee then met in April 2013 to summarize the different approaches to eliminate HAT. The report will be published by the end of 2013.

Funding of the HAT Platform by DNDi

DNDi provides financial support to three platforms (HAT, Chagas disease and Leishmaniasis in East Africa), and to research on drugs against these and other diseases such as malaria, filarial, and

HIV in children.
This financial aid is directed at several areas: TPP (ideal drug), strengthening of local capacities, clinical trials (phases II/III), drug registration, etc.

Besides its coordination office in Geneva, Switzerland, DNDi governance includes operational facilities in Africa, North and Latin America, and Asia.

DNDi is based on a model of public-private partnership. Its financial resources thus come from public and private institutions.

Over the past seven years, i.e. from 2005 to 2012, expenditure of the HAT Platform was distributed approximately as follows: 1/3 for events and meetings, 1/3 for training and 1/3 for consultancy and the Newsletter.

Once the funds have been transferred to disease control and research institutions in the endemic countries, financial procedures require the signatures of both the funder and the scientific committee.

Activities of the second quarter 2013
In order to redirect resources of the Platform activities to the countries (e.g. recent focus on HAT in Brazzaville, Republic of Congo), the number of annual Steering Committee meetings may be reduced from two to one.

Planned activities

- Increase partners' awareness of on-going research
- Organize training sessions (ethics committees, monitors, investigators)
- Evaluate and follow-up the use of new treatment and diagnostic tools

Participation in CISRLT meeting
The formal participation of the HAT Platform in the CISRLT (Conseil International Scientifique sur la Recherche et la Lutte contre les Trypanosomiases) has not yet been decided. However, scientific communications are still accepted even though the deadlines have expired.

Reorientation of the HAT Platform objectives
At the time of its creation in 2005, the HAT Platform only considered taking on the strengthening of clinical trial capacities for sleeping sickness. Since then, the context has somewhat changed with the inclusion of HAT into the list of Neglected Tropical Diseases (NTDs).

To accommodate such an expansion of its operational environment, the HAT Platform had to modify its initial objectives. Examples of this new direction include post-marketing activities (drug resistance, pharmacovigilance…), and non-clinical studies (socio-anthropology, epidemiology, healthcare systems…).

Also, a ***Task Force*** (Uganda, SwissTPH, DRC, Angola) was created to provide recommendations to the Steering Committee, which will then orientate the activities of the HAT Platform appropriately.

Action Plan 2014
The agenda being overloaded due to the celebration of DNDi's 10th anniversary, the Action Plan 2014 was neither presented nor discussed.

Planned interventions include:

- Revaluation of DNDi objectives to take into account the new WHO policy issued in December 2012.
- Improvement of the use of LAMP tests in the field with the optimization of sample conditioning (buffy coat) at the University of Makerere.
- Oxaborole (SCYX-7158) pharmacodynamic study.
- Study on blood biomarkers for late-stage sleeping sickness to reduce lumbar punctures.
- Funding of the HAT Platform at the country level. Current funding of HAT Platform activities in DRC from the funds allocated by the Belgian cooperation to PNLTHA in DRC is an example which could inspire other countries.
- Synergies between the HAT Platform and EANETT, with a possibility of applying for training grants for Masters' Degree programmes, e.g. ITM grants available to programme chief physicians.
- Funding by FIND of certain activities of the HAT Platform if requested explicitly.
- Collaboration between EDCTP and DNDi to implement the conclusions of the stakeholders meeting organized by EDCTP in June 2013 in The Netherlands.
- Updating of the countries' guidelines for the authorization of oxaborole (SCYX-7158) clinical trials, and field visits (potential trial sites) if this drug is to be included within national policies by 2018.

Recommendations

- Reinforce the collaboration between diseases, at the level of control and research organizations/higher education.
- Identify the needs in HAT research to propose to partners.

Suggestions

- Publication of an article on the HAT Platform experience.
- Broaden HAT Platform training, so that trained individuals can switch from a PNLTHA healthcare centre to centres treating other diseases.

Focus on Human African Trypanosomiasis in Republic of Congo

The 'Focus on Human African Trypanosomiasis (HAT)', or sleeping sickness, organized jointly by PNLTHA (Programme National de Lutte contre la THA) and the RoC national public health laboratory LNSP with the support of the HAT Platform, was held in the Salle du Palais des Congrès in Brazzaville from 15 to 17 May 2013.

The objective of this international meeting was to raise awareness and mobilize public authorities, healthcare agents, political, administrative and healthcare authorities in the areas where the disease occurs, as well as other actors on the:

- Continued presence of sleeping sickness in RoC and its fatal outcome if not treated;
- Necessity to improve the management of sleeping sickness to promote the country's sustainable development.

The meeting was attended by agents working in the administrative and operational facilities in the disease foci, representatives of the centre for disease control and epidemiology, of the national public health laboratory, and of the Ministry of Agriculture and Livestock, as well as a delegation from DRC led by Dr K. Ebeja, coordinator of the HAT Platform.

The main points addressed during the 'Focus' on sleeping sickness included:

- The commitment to eliminate HAT as a public health problem;
- The 2020 goals to control or eliminate certain Neglected Tropical Diseases (NTDs) set by WHO;
- The conclusions of the regional advisory meeting on Neglected Tropical Diseases (NTDs) organized by WHO/AFRO in Brazzaville from 20 to 22 March 2013;
- The worrying entomological index in the Imboulou Dam area.

The institutions involved in the control of sleeping sickness then presented oral communications on the work of the Focus: HAT epidemiological situation in RoC (Dr Stéphane Ngampo, PNLTHA) and in DRC (Dr Florent Mbo, PNLTHA); data updates on tsetse flies in the Ngabé foci (Dr Nicolas Mbongo, LNSP); animal trypanosomiasis (Dr Nina, Ministry of Agriculture and Livestock); HAT diagnosis by polysomnography and immunological technique based on B-lymphocytes (Prof. Alain Buguet/Clinique Maman Poto), and the HAT Platform (Dr Kadima Ebeja).
The participants proposed amendments before adopting the following important documents:

- The national sector policy for the control of trypanosomiasis
- The national strategic plan for the control of trypanosomiasis (2013-2017)

They then made the following recommendations:

- Secure greater and more sustainable funding to meet current objectives on the control of this disease;
- Expand the use of existing education and information programmes to change collective behaviour and increase awareness on sleeping sickness in RoC;
- Accelerate the process of integration of control activities in the foci health centres.

The participants asked for major and regular involvement of the decision-makers, development partners, and other sectors concerned, such as the Ministry of Agriculture and Livestock, and

the Ministry of Tourism and the Environment, so that we all combine efforts to control sleeping sickness.

REPORT OF THE 2ND JOINT EANETT/ HAT PLATFORM BI-ANNUAL SCIENTIFIC CONFERENCE HELD AT THE SAROVA PANAFRIC HOTEL, NAIROBI, 4-7 JUNE 2013

The Second Joint EANETT/HAT Platform Scientific Conference was held from 4 to 7 June 2013 at the Sarova Panafric Hotel Nairobi. The conference was supported by the Drugs for Neglected Diseases (DNDi), NIH/Yale University School of Public Health and the Swiss Tropical and Public Health Institute (Swiss TPH). The theme for this year's conference was 'AFRICAN RESEARCHERS – DEVELOPMENT ACTORS'. The conference was attended by over 100 scientists and HAT control managers from various HAT endemic and non-endemic countries. Their participation signaled renewed interest in sleeping sickness research and control as well as capacity strengthening with a view to eliminating the disease.

The first joint EANETT/HAT Platform scientific conference was held from 4-5 October 2010 at the Silver Springs, Nairobi, Kenya. Due to the overwhelming success of this first conference, both the HAT Platform Steering Committee and the EANETT Board of Management committed to further this initiative, hence this second joint conference. EANETT and HAT Platform have since

established long-term collaboration on training on trypanosomiasis and tsetse flies research and control. The second joint scientific conference brought together clinicians/field implementers and researchers from EANETT and HAT Platform member countries working on Human African Trypanosomiasis and other Neglected Tropical Diseases. The purpose of the conference was to create a platform for sharing knowledge/information and enhancing collaborations with the aim of contributing to the elimination of sleeping sickness and other neglected tropical diseases. Other partners or sponsors working in the field of NTDs attended the conference. They included WHO, AU/PATTEC and FIND.

The 2013 Conference coincided with the 10th anniversary event of DNDi, making this Scientific Conference also a special event in terms of publicity and strengthening of collaborations and partnerships. This joint conference is also an important mentorship forum for young anglo- and francophone scientists working on trypanosomiasis and tsetse flies in the region. During the conference, scientific papers were presented under the following thematic areas: Diagnosis, Drug Discovery & Animal Models, Clinical Trials & Treatment, Public Health & Socioeconomics, Vector Biology & Control, and Epidemiology. Keynote speeches were presented by renowned scientists who included Anne Grobler, Rob Don, Antoine Tarral, Solome Bukachi and Hassane Mahamat Hassane. In an effort to integrate HAT in the control of other NTDs, several papers on leishmaniasis were presented.

Emerging areas of research such as nanodiagnostics/nanomedicine, genomics and bioinformatics were recognized as important to HAT elimination. Areas of focus were identified as: (a) establishment of HAT status in all endemic foci (active and dormant); (b) determination of factors that sustain epidemics; (c) social norms and regulatory issues that are an impediment to access to essential medicines and capacity strengthening at all levels (policy, communities, scientists, technical support and disease control managers). The involvement of African researchers in the NIH-supported H3Africa programmes towards personalized medicine was highly commended. This will go a long way in (a) elucidating the factors responsible for the varied host responses to existing treatments that have resulted in high numbers of treatment failures in some HAT foci and (b) designing solutions to address this phenomenon.

Discussions and Recommendations

1. The participants acknowledged that HAT is on the decline in all disease endemic countries and that it is feasible to eliminate the disease caused by T. gambiense (mainly human-human transmission) when compared to T. rhodesiense which has known animal reservoirs. With concerted efforts of researchers, control managers, and policy makers supported by the international community, it is possible to achieve the WHO target of 'one case per 10,000 inhabitants in at least 90% of endemic foci reporting less than 2000 new cases annually at continental level by 2020' (WHO Report, 3-5 December, 2012). Areas for further investigation include the role of animal reservoirs in DRC, RoC, CAR, Angola and South Sudan, as well as the factors that sustain epidemics.
2. All stakeholders in T&T control were encouraged to intensify efforts and lobby for funds from national budget allocations and partners to ensure that HAT resurgence does not occur. Plans should therefore be put in place to bring together all stakeholders involved in disease elimination at individual country and regional levels. PATTEC, EANETT and the HAT Platform will be expected to play an important role in the area of baseline data collection, monitoring & evaluation as well as impact assessment, which are important components of the elimination programme.
3. It was acknowledged with appreciation that the drug research and development pipeline is full and the countries look forward to new products being introduced into the market. The HAT endemic countries commend the efforts of WHO, DNDi and other supporting partners for their roles in these efforts. Capacity strengthening in pharmacovigilance should be undertaken as a matter of urgency. The role of nanotechnology in the development for drugs and diagnostics for HAT and other poverty-related diseases should be explored.

4. It was observed that regulatory issues, which could be an impediment to access to medicines, should be addressed as a matter of urgency. It is expected that WHO and affected countries take leadership in this endeavor. Can these issues be harmonized through the regional bodies?

5. It was recognized that capacity building for stakeholders (all levels) should be undertaken as a matter of urgency. EANETT and HAT Platform should take leadership in this endeavour.

6. The efforts by FIND, WHO, DNDi, national, regional and international academic institutions, PATTEC and research organizations towards development of new diagnostic tests for field application were commended. Researchers and disease control managers look forward to the new, affordable, sensitive and easy to apply tests to support disease elimination activities, one of which is to find new cases.

7. Collection and characterization of field samples (tsetse flies and trypanosomes) should be intensified in order to provide the required information to support product development (all affected countries) and disease elimination. There is a need to understand the social and economic environments in which HAT transmission takes place in order to enhance case finding. To achieve this, research data already generated in different countries, availability of current and new tools for different tsetse species and agro-ecological zones should be adequately communicated.

8. Areas of high risk for disease transmission should be identified through high level advocacy and allocation of funds for control towards elimination (Malawi, South Sudan and all foci in central Africa). Countries such as Zambia, where the disease situation is not well known, should put plans in place to establish presence/absence of disease.

9. The HAT Platform Newsletter is an information sharing tool for HAT Platform activities but also for EANETT activities.

10. This type of meeting should be organized every two years, alternatively with the ISCTRC meeting.

Grace Murilla, PhD
Chairperson
EANETT Board of Management

Augustin Kadima Ebeja
Coordinator
HAT Platform

DNDi's Ten-Year Anniversary

The celebrations for the 10th anniversary of DNDi were held on 5 June 2013 in Nairobi, Kenya. It is always a great pleasure to celebrate the longevity of an organization working for the benefit of others. This ability to stand the test of time is the best proof of DNDi's success, and shows that, ten years on, the project initiators were right. They were able to anticipate and correct deficiencies in research and development for and management of neglected diseases. The need for better therapeutic options, however, is still pressing.

The event, graced by the presence of leading political and scientific figures from Kenya and several other African countries, were attended by some 430 scientists from all the continents.
The main theme was 'A Decade of Research & Development for Neglected Diseases', and the sub-theme 'Endemic Country Research & Development for Patient Access'.

In the opening ceremony, the Director of KEMRI (Dr Solomon Mpoke), the President of DNDi's Board of Directors (Prof. Marcel Tanner), and the Kenyan Cabinet Secretary for Health (Mr James Wainaina Macharia) each welcomed the participants wishing them a fruitful meeting, leading to practical recommendations that can be implemented immediately by the politicians as well as the scientists for the benefit of the populations.

Dr Charles Mgone, Executive Director of EDCTP, presented the innovative partnership in Africa for neglected disease research excellence. Achievements have been made, but there is still much to do.
Lessons learned were presented, with examples provided by the HAT Platform (Dr Augustin Kadima Ebeja), LEAP (Dr Ahmed Musa Mudawi), MenAfriVac, PATH-WHO (Dr Mamoudou Djingarev), ANDI (Dr Solomon Nwaka) and Sanofi (Dr François Bompart). Clearly, there are many sound initiatives and partnerships with African actors, which take into account the needs of the neglected populations and produce concrete results with immediate impact.
A review on a decade of innovations in Africa showed that a lasting environment of research and development has indeed been created (Dr Charles Mgone, EDCTP).

DNDi being honoured for its ten years of existence, its Executive Director, Dr Bernard Pécoul, presented the organization's major achievements in the development of drugs for neglected diseases (six drugs for sleeping sickness (HAT), Chagas disease, leishmaniasis and malaria).

The lessons learned by DNDi include:
- There are still neglected diseases lacking good treatment options.
- Although these results are a good start, available treatments are still far from being optimal.
- The new modern drug which could alter the course of certain neglected diseases has yet to be developed.
- To truly combat neglect, we must all push for more innovation and improved access to new treatments, with adequate coordination between the control programmes.
- Current achievements show that it can be done, in and with the African countries.

As the best has yet to come, discussions and exchanges were held on strategies for neglected diseases, such as how can we produce the tools required for disease elimination.

The video message of the WHO Director-General Dr Margaret Chan started by congratulating DNDi and the other public-private partnerships who played a major role over the past ten years to produce the technical breakthroughs we have today. However, this is not the time for complacency, and we must work even harder because the elimination of neglected diseases, such as HAT, is possible.

The WHO medical officer in charge of Human African Trypanosomiasis, Dr Pere Simarro, presented the programmes proposed by WHO to eliminate several neglected diseases, such as sleeping sickness, visceral leishmaniasis, and lymphatic filariasis, and control others by 2020. He insisted on the fact that new tools (diagnostic and treatment) are necessary to support these strategies.

Over the past ten years, new health tools have been produced by DNDi and other initiatives from public-private partnerships in collaboration with WHO, but they have not yet provided a definitive answer to the research and development shortfalls. WHO recognizes that this collaboration model contributed significantly to the control of neglected diseases, with major reductions in the number of cases, as seen with sleeping sickness.

A discussion panel on the objectives of the elimination of sleeping sickness was held with representatives from research, government and humanitarian organizations (Dr Grace Murilla from KARI-TRC; Prof Marleen Boelaert from ITM Antwerp; Bernard Pécoul from DNDi; Dr Crispin Lumbala from the DRC PNLTHA; Prof. Théophile Josenando from ICCT/MINSA, Angola; and Dr Unni Karunakara from MSF). The arguments put forward by the panel and the questions asked by the participants show that this dream can become reality provided everyone works diligently and more importantly that substantial means are allocated to these efforts.

Political authorities playing a major role in this elimination objective, the Ministers of Health (Mr Ajuide Soumouk, CAR; Dr Musa Bashir Musa, Republic of Sudan) or their representatives (Dr Lomamy Kalema Shodu, DRC; Prof Henri Joseph Parra, RoC) discussed their expectations and their contributions. A key message from this session is that there is political commitment. Before the closing address of the Chairman of DNDi's Board of Directors (Prof. Marcel Tanner), the HAT Platform Coordinator gave a trophy to two key actors, Dr Bernard Pécoul, Executive Director of DNDi since its foundation ten years ago, and Dr Monique Wasunna who has also led for ten years the DNDi Africa office based at the Kenya Medical Research Institute (KEMRI) in Nairobi, Kenya.

Professor Marcel Tanner thanked all the participants and insisted that the success of DNDi is really the success of all those involved, for the benefit of the neglected populations. He said it was high time efforts were stepped up as we were on the right track. He then invited all the participants to celebrate their joint success in this worthy cause, with champagne, wine and all sorts of other drinks, enjoining them to eat and dance together before everyone returned to their own laboratories.








A fresh new look for the Viana research centre

Under colonial rule, the Human African Trypanosomiasis (HAT) control programme in Angola was managed by MCT (Missão de combate ás tripanossomiases), based in Luanda.

This service was divided into several medical sectors distributed throughout the country: Maquela do Zombo, Damba, Uíge, Pombo Cuango, Nambuangongo, Santo António do Zaire, São Salvador do Zaire, Médio Cuanza and Dande Cuanza.
In 1991, the Dande Cuanza medical sector, located in Luanda and used as a base for the mobile teams, was transformed into a hospital centre, due to the exponential rise in sleeping sickness cases in the country.

Due to lack of hospital beds, patients had to be placed for treatment in a large store. During this period, many patients were treated in outpatient services. Late-stage (neurological stage) HAT was treated with injections of melarsoprol every 3 to 4 days for one month.

In 1995, Angola's national HAT control programme entered into a partnership with the Norwegian People's Aid (NPA), initially, for the Kwanza Norte province where the HAT situation was dire. This NGO was involved in population care and infrastructure improvement.
Another partnership was created with the French government, via SCAC (Service de Coopération et d´Action Culturelle), alerted by the precarious conditions in this centre. This cooperation extended to the rehabilitation of several bridges that had been left unfinished.
In April 1999, the newly rehabilitated Viana Centre was inaugurated, as a base for HAT control in the Dande Kwanza sector, focusing mainly on diagnosis and hospitalization of HAT patients. However, the resurgence of civil war in Angola soon paralysed many activities of the mobile teams and brought many refugees from endemic areas to Luanda.

Since then, approximately 30,000 people have been examined at the Viana Referral Centre, with 3,895 new HAT cases being diagnosed and given treatment for early- or late-stage sleeping sickness.
In addition to diagnosis and treatment, the Viana Referral Centre also conducts health promotion activities (IEC), research, and anti-vector control activities in affected areas (tsetse and endemic).

Many studies have been conducted at the centre, including:
1. Impamel II - Study on short-course melarsoprol in 1999

2. Association between HLA and melarsoprol-induced encephalopathy (ICCT/MS/IHMT)

3. Improved phase determination and follow-up of THA patients, based IgM determination in CSP in field conditions in Angola

4. Phase IIa study of DB 289 in HAT treatment (ICCT/MS/IHMT) in Lisbon

5. Pathogenicity of trypanosomiasis (IRD/ ICCT) in 2006

6. Tests of locally made mAECT kits

The Viana Centre currently employs 85 people: 7 physicians, 17 laboratory technicians, 25 nurses and 36 administrative workers. The facilities include two old buildings and three new ones, two of which will be ready and fitted before the end of 2013. The Centre has four distinct sections with a minimum of equipment:
- Laboratory section fully equipped for routine tests and biomolecular tests

2. Clinical section:
- 3 consultation rooms for patients
- 1 intermediate care room for patients in serious condition with oxygenation system
- 8 hospital rooms, with 8 beds in each one of them, bringing the total to 64 beds

3. Administrative section
4. Logistics section

In 2012, ICCT introduced several changes in the building, with innovations such as a fully equipped auditorium with a sound system. The centre, renamed the Centre for Research and Alertness of Trypanosomiasis (sleeping sickness) and other Tropical Diseases (CRIV-DT), expanded its activities, including research, to tropical diseases other than HAT, such as malaria, schistosomiasis, filariasis, and intestinal parasitic diseases.

ICCT hopes to make the Viana Centre a centre of excellence in tropical diseases. The HAT Platform is asked spread the word on this project and facilitate contacts with expert instructors in various fields coming from the partner countries.

Dr Amadeu

Summary of CRIV-DT activities

Year	Population examined	New HAT cases
1999	1912	534
2000	2804	528
2001	3053	627
2002	3433	465
2003	2355	473
2004	2226	332
2005	1930	264
2006	1779	235
2007	1547	116
2008	1308	133
2009	1021	78
2010	2438	43
2011	2105	37

Welcome to our new members

1) Chirac Bulanga

With a bachelor's degree in business economics (Baccalaureate + 5 years), Chirac Bulanga worked in management and administration, human resources, finance and logistics for over 15 years

in DRC and West Africa. His latest employment was with OXFAM GB in Chad, where he served as Business Services Manager (Operations) for 2 years.

He is skilled in budget planning, financial management, including writing reports and financial policy development, personnel selection and recruitment, performance management, personnel salaries and social benefits, and supply, housing, and office management, etc.

He is currently working as Country Operations Manager at DNDi, tasked with the definition of activities, monitoring and implementation of tasks in compliance with DNDi's internal procedures and rules, liaison and representation with Geneva headquarters as well as local partners (PNLTHA, Health Ministry, etc.) for DNDi projects in DRC.

2) Crispin Lumbala

Dr Crispin Lumbala has been working for the National HAT Control Programme (PNLTHA) in DRC since September 2006.

He was appointed provincial coordinating physician in East Kasai until January 2013, and National Director since 22 January 2013. Before joining the PNLTHA, Crispin Lumbala was successively employed as physician Hospital Director in rural areas (Ngandajika, East Kasai), from January 2000 to January 2001, and chief medical officer of rural health zones in East Kasai, DRC, from 2001 to 2006 (chief medical officer of the Kabeya Kamwanga health zone from 2001 to 2003, and chief medical officer of the Ngandajika health zone from 2003 to 2006). Health zones, called health districts in other countries, are the operational units responsible for the implementation of the country's health policies.
Crispin Lumbala holds a degree in medicine, surgery and obstetrics from the University of Lubumbashi, DRC (October 1998). He obtained a Masters Degree in Public Health, specializing in Disease Control (July 2009), from the Institute of Tropical Medicine in Antwerp.
He participated in the NECT-Field study in East Kasai with DNDi and Swiss TPH from April 2009 to May 2010. He was an investigator for the studies on fluorescence microscopy (local investigator), on SD rapid diagnostic tests (primary investigator), and on LAMP (primary co-investigator) with FIND.
He has (co-)authored several scientific publications on HAT.

3) Roch Ouambita-Mabo

Physician specializing in epidemiology, Dr Roch Ouambita-Mabo joined the HAT Platform on 21 January 2013. The new coordinator of the National HAT Control programme (PNLTHA) for CAR has over 10 years of experience in the healthcare system in CAR. He worked in several health districts in the country before

moving to the central office in 2007 as coordinator of the National Access to ARV Programme, then as Director of the Expanded Programme of Immunization before joining the PNLTHA. With all his wealth of knowledge and experience, Dr Roch Ouambita-Mabo will breathe new life into the PNLTHA in CAR, and boost the efforts towards the elimination of this disease at the national, subregional and worldwide levels.
At the time of publication, Dr Ouambita has just been appointed to yet another post, as director of PEV. Even though his appointment to the PNLTHA lasted only one quarter, Dr Roch Ouambita-Mabo impressed us with the quality of his work and the concrete results he achieved. We wish him well in this even more challenging endeavour, for which he was no doubt chosen because of his outstanding qualities.
So once again, goodbye Dr Ouambita!

Dr Augustin Kadima Ebeja
HAT Platform Coordinator

2013-2013 Scientific Meetings

1. 8th European Congress of Tropical Medicine and International Health, 10-13 September 2013, Copenhagen, Denmark
2. XIXe Actualités du Pharo: Les maladies tropicales négligés & communications libres, 16-17 September 2013, Marseille, France
3. XXI Latin American Congress of Parasitology (FLAP) 6-9 October 2013, Guayaquil, Ecuador
4. 32nd General Conference of ISCTRC, 8-12 September 2013, Khartoum, Sudan
5. 9th Congrès International Francophone de la Société de Pathologie Exotique 'Transitions épidémiologiques en Afrique', 12-14 November 2013 in Dakar, Senegal

Investigators' Meeting

DNDIFEX004 in Kinshasa

A meeting of the investigators involved in the Fexinidazole study was held from11 to 12 June2013 in orderto review the first eight months of the study.

Dr Crispin Lumbala, Director of the National HAT Control Programme (PNLTHA), started the meeting with a welcoming address and a presentation of the participants. He noted the commitment of the WHO and the partners to HAT elimination, and mentioned the role of new drugs in achieving this goal. He also described the strengths and weaknesses of HAT control and research in the DRC, as well as the need for investigators to recognize them and work in an open and transparent manner.

Dr Antoine Tarral, Head of the HAT Clinical Programme at DNDi, congratulated the investigators and their teams for their efforts and the quality of their work. He put forward a proposal to create an internal monthly newsletter on the Fexinidazole study, providing an update on its inclusions, difficulties, tips, and any adverse events. He described the wish of DNDi to simplify and shorten the study duration, particularly through the reduction of the sample size from 510 to 390 individuals, and the opening of new sites in order to complete the study in 2016. The necessary amendments will of course be submitted for approval to the relevant authorities.

Séverine Blesson, DNDi's Clinical Manager for HAT, presented an overall review of the study: inclusions started in the first site on 5 October 2012, and 96 patients have been included to date. An initial futility analysis has just been performed and shows that the study may continue; the second futility analysis is scheduled for July 2014 (once 105 patients have had a lumbar puncture) and will be followed by a DSMB meeting in September 2014.

To accelerate the study, a further 2 to 4 sites would be opened, the sample size would be reduced, and if possible the duration of the follow-up period would also be reduced. DNDi is currently examining the possibility of including another new drug (SCYX-7158), currently in its Phase I development stage. An expert meeting is due to take place soon to address these issues.

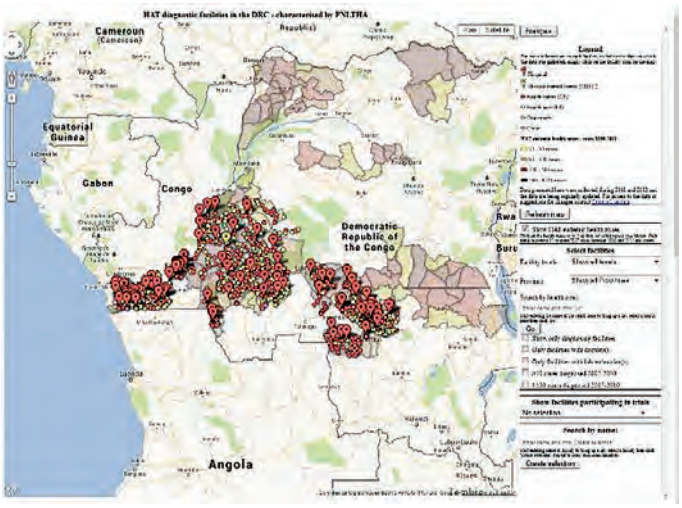
Each site gave a presentation detailing its concerns, and solutions were suggested.

In conclusion, all the participants were happy to see that the study is progressing satisfactorily on the whole. This meeting was perceived as an important opportunity to exchange and harmonize practices.

Dr Augustin K.Ebeja

Update on on-going research

Online map of health facilities in sleeping sickness areas in the DRC is launched



View interactive map.

The Democratic Republic of the Congo (DRC) National Sleeping Sickness Control Programme (PNLTHA) and FIND have launched an online map describing the locations and capacities of health facilities in sleeping sickness endemic areas in the country. This is the outcome of collaboration between the two partners during the past 4 years. In order to make the data on the health facilities easily accessible to everyone, FIND and PNLTHA have published them on Google maps, making it possible to browse and view the underlying attributes of a facility, and to search for and select facilities with particular characteristics. When a user clicks on the map under 'Related links', he/she is directed to the interactive map.

Local experts from PNLTHA were initially trained in the use of hand-held Global Positioning System (GPS) devices, including collection and management of data. One of these PNLTHA experts has in turn been visiting the endemic districts and training teams of nurses on how to use GPS, and to complete a questionnaire on the capacities in health facilities. The nurses are incentivized to visit health facilities in their health zones and record the data during their rounds, which is then compiled and verified by PNLTHA. The data includes the location of the facility, number and level of training of personnel, availability of electricity and water, laboratory equipment, and case reporting history.

To date the teams have characterized 3,844 facilities in 93 health zones in 5 provinces, which includes most of the health zones that were reporting the largest number of cases of sleeping sickness by February 2011. The 93 health zones equate to around 60% of all HAT-endemic health zones in the DRC, and FIND is working with PNLTHA to cover the remaining areas. Subsequently, FIND and PNLTHA will work towards ensuring that the map is updated regularly.
Such online maps could become an important resource for the sleeping sickness community in the future. The data has already been used by FIND and PNLTHA for selecting sites where clinical trials on LED fluorescence microscopy, LAMP and RDT technologies have been undertaken. As part of similar projects supported by FIND, both Uganda and the Republic of Tanzania have produced similar maps.
Users who are interested in accessing more data are encouraged to contact Dr Crispin Lumbala, the Director of PNLTHA on crispinlumbala@gmail.com.

Antigen detection test

Identification of antibodies that are suitable for antigen detection assays and antigens for use in developing antibody detection tests are running concurrently. FIND is working with the Institute of Biotechnology at the University of Brussels, Belgium, to determine the feasibility of using camel heavy-chain antibodies (nanobodies) in tests to detect parasite antigens. A number of promising nanobodies have been identified and are being tested by Standard Diagnostics.

FIND has also worked with the Seattle Biomedical Research Institute (SBRI) to apply the single chain variable fragment (scFv) antibody engineering technology in development of optimized antibody probes for trypanosome antigens in blood. Using a technology called yeast display, high-affinity antibody fragments for a number of T. brucei proteins are generated, and those that are best suited for diagnostic detection in human samples identified. The sensitivity and stability of the probes for the chosen antigens is enhanced further by antibody engineering methods. The outcome will be a set of antibody probes with characteristics of sensitivity, stability, and manufacturability that are superior to probes generated by traditional methods.

The government of Uganda intensifies fight against sleeping sickness

The government of Uganda, in a partnership with the Foundation for Innovative New Diagnostics (FIND), is intensifying surveillance and control of Trypanosoma brucei gambiense human African trypanosomiasis (HAT, or sleeping sickness) in the West Nile region, and Amuru district. This follows the signing of a three-year collaborative agreement between the Coordinating Office for Control of Trypanosomiasis in Uganda (COCTU) of the Uganda Trypanosomiasis Control Council (UTCC) and FIND.

The project will include the use of new tests developed with the support of FIND, and a new approach that is intended to shorten the distance that a sick person has to travel to seek diagnosis. Experts from the Ministry of Health (MOH), the Ministry of Agriculture, Animal Industry and Fisheries (MAAIF) and Makerere University are leading this initiative, which if successful could lead to elimination of T.b. gambiense HAT in the country, and serve as a model for replication in other endemic countries.
The new project is being implemented in 166 health facilities

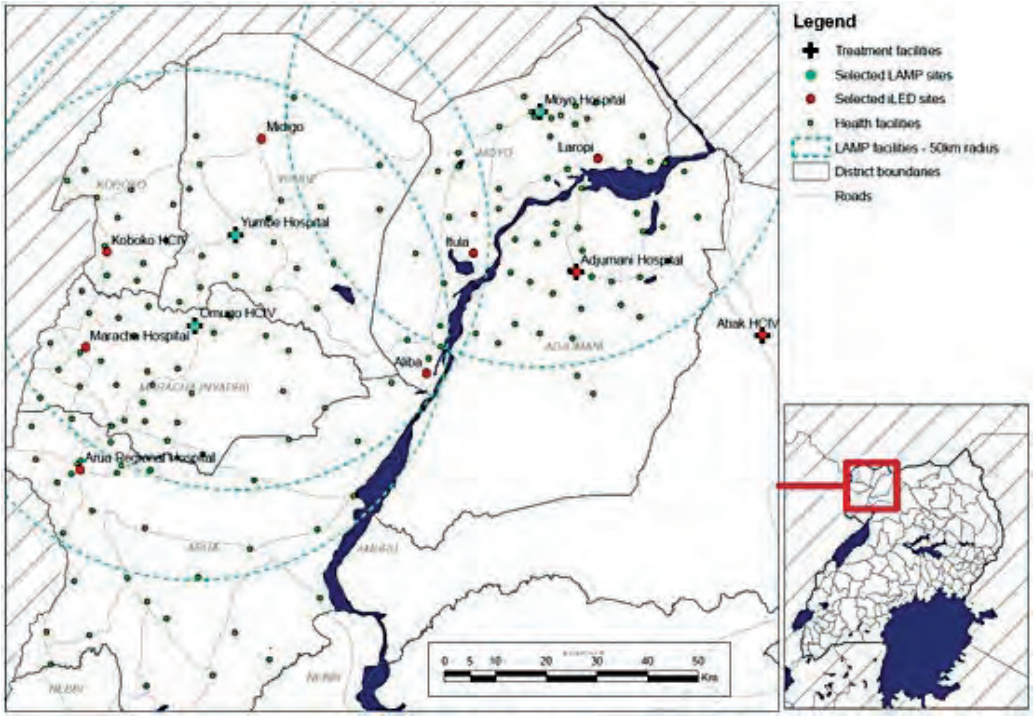


Figure 1

spread across the T.b. gambiense sleeping sickness belt of Uganda, in an approach that combines screening of suspected patients with a recently developed rapid test, followed by confirmation of these cases by LED fluorescence microscopy. This will be complemented with detection of parasite DNA using a highly sensitive and simple molecular method known as LAMP. All the health facilities in the project area were geo-referenced and characterized by the government of Uganda in an earlier project with support from FIND. This has made it easier to identify the facilities in which to install different diagnostics for HAT.

The map of the 5 districts in north-western Uganda that are endemic for T.b. gambiense sleeping sickness, shows the health facilities participating in the project. All facilities will screen patients using a new rapid test. Positive cases will be referred to microscopy centres for confirmation, and if found negative, samples dried on filter papers will be transported to the LAMP centres for molecular testing. The results of LAMP will be communicated to the first health centre by mobile phone and adequate measures taken. All data on individuals tested and on the stocks of kits in each health facility are communicated to the coordination office of the Ministry of Health, responsible for the day to day management of the project.

All participating health facilities will be stocked with the rapid tests after appropriate training is carried out, while microscopy and molecular tests are being located at strategic centres in all the districts. In this new approach, a sick person who visits the nearest health centre will be tested using the rapid test. Those who are positive with the rapid test will be referred to the nearest microscopy centre for confirmatory diagnosis, and if they are found to be negative by microscopy, a blood sample will be taken on filter paper and sent to the LAMP centre for molecular testing.

Various departments in Uganda have been collaborating with FIND to develop the tests that are being implemented in this new project. Most of the work on LED fluorescence microscopy was carried out in partnership with Makerere University, Lwala Hospital and the National Livestock Resources Research Institute (NALIRRI), while Makerere University and Lwala Hospital have been at the forefront in research on LAMP for both T.b. rhodesiense and T.b. gambiense in Uganda and the DRC. The new project is an extension of the long-term relationship between FIND and the government of Uganda, with which they collaborate on other diseases such as tuberculosis and malaria.

Funding for this project comes from the government of Uganda, as well as through FIND, the Bill and Melinda Gates Foundation (BMGF), Department for International Development (DFID) of the UK, and the German Federal Ministry of Education and Research.

Rapid Diagnostic Tests and Clinical/ Laboratory Predictors of Tropical Diseases in Neurological Disorders in DRC (Nidiag-Neuro)

Déby Mukendi[1] , Jean-Roger Kalo[1], Barbara Barbe[2], Philippe Gillet[2], Cedric Yansouni[3], Andrea Winkler[4], Pascal Lutumba[1], Muyembe Jean-Jacques[1], Jan Jacobs[2], Emmanuel Bottieau[2]

1. National Institute of Biomedical Research, Kinshasa, Democratic Republic of Congo
2. Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
3. Centre for Tropical Diseases, McGill University Health Centre, Montréal, Canada
4. Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Germany

The worldwide impact of neurological disorders is enormous, and it is increased in poor settings, due to lack of diagnosis and treatment facilities as well as delayed management. In sub-Saharan Africa, the few observational studies conducted over the past 20 years show that neurological disorders accounted for 7 to 24% of all admissions. Central nervous system (CNS) infections were suspected in one third of all patients admitted with neurological symptoms, with a specific microbial aetiology identified in half of these. Most CNS infections may be considered as 'severe and treatable diseases', e.g. human African trypanosomiasis (HAT), cerebral malaria, bacterial meningitis, CNS tuberculosis, etc.

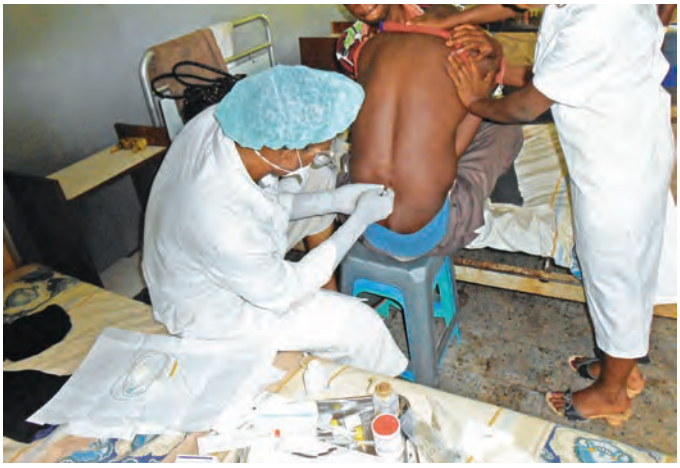
If left untreated, death or serious sequelae occur (mortality rates were as high as 30% in the above-mentioned studies), but the outcome may be favourable with timely and appropriate management.
In poor settings, such conditions should be targeted in priority in the clinical decision-making process. Unfortunately, most neuro-infections present with non-specific symptoms in their early stages, leading to important diagnostic delays. Moreover, they require advanced diagnostic technology, which is not available in most tropical rural settings: here, you have to rely on clinical judgment and first-line laboratory results, the confirming or excluding powers of which are limited or unknown. Several rapid diagnostic tests (RDTs) have been developed recently for conditions like malaria or HIV, but their diagnostic contribution has not been evaluated in a multi-disease approach.
Thus, this research aims at improving the early diagnosis of severe and treatable neglected and non-neglected infectious diseases, which present with neurological symptoms, in the province of Bandundu, DRC, by combining classic clinical predictors with a panel of simple point-of-care rapid diagnostic tests.

The evaluation of existing algorithms and elaboration/validation of new guidelines will be described in a subsequent protocol.

- **Objective:** diagnostic
- **Type of study:** non-interventional
- **Eligibility:**
  Allowed age of inclusion: over 5 years
  Gender admissible in the study: both male and female

Inclusion criteria

- Patients > 5 years-old AND
- Altered state of consciousness (confusion to coma) AND/OR
- Changes of sleep pattern (daytime slumber, night insomnia) AND/OR
- Cognitive decline AND/OR
- Changes in personality/behaviour (e.g. bouts of mania) AND/OR
- Epileptic seizure(s) AND/OR
- Daily severe/progressive headache AND/OR meningismus (headache, neck stiffness, nausea/vomiting, photophobia)



- Cranial nerve lesions AND/OR sensory-motor deficits or other focal neurological signs (e.g. dysphagia, dysarthria, ataxia, dystonia...) AND/OR
- Gait disorders (e.g. spastic or ataxic gait)

Exclusion criteria

- Those unwilling or unable to give written informed consent (either directly or via proxy)
- Those unable in the physician's opinion to comply with the study requirements
- Neurological symptom unequivocally related with recent trauma
- Neurological symptom as sequelae of previous well-esta blished neurological events (e.g. stroke…)
- First seizure below 6 years of age

Preliminary results

Introduction

Due to the lack in diagnostic means, very little is known about the causes of neurological disorders in rural African areas. A clinical and diagnostic study was launched for this purpose in September 2012 at the Mosango HGR (Hôpital Général de Référence) in the province of Bandundu, DRC.

Methods

All the patients over 5 years old, admitted to this hospital with progressive neurological symptoms, and who agreed to participate, themselves or by proxy, are examined prospectively by a neurologist investigator. Systematic laboratory tests are performed on blood and cerebrospinal fluid (CSF) samples. The patients are monitored for 6 months after being discharged from hospital. The blood and CSF samples are sent to the referral laboratories (Kinshasa and Europe) for further tests.

Results

By April 2013, 67 patients had been included (men: 54%; average age: 38 years). Among these 67 patients, 34 (51%) had been previously treated with antibiotics and/or antimalarials. The main presenting signs included: altered state of consciousness (n=28; 36%), focal deficit (n=14; 21%) and seizures (n=11, 16%). An infectious aetiology was suspected or confirmed in at least 32 patients (45%): bacterial meningoencephalitis (n=13; 19%), human African trypanosomiasis (n=6; 9%), cerebral tuberculosis or complicated Pott's disease (n=6; 9%) and septic shock (n=4; 6%). Eleven patients (16%) died and seven (10%) left the hospital with severe neurological sequelae.

Conclusions

Approximately half the patients admitted to the Bandundu hospital with a neurological disorder have treatable infections. Morbidity and mortality rates are high, hence the paramount importance to diagnose these conditions as early as possible.

Fexinidazole

The first clinical trial on this molecule was launched on 5 October 2012, to test its efficacy and safety in patients with late-stage HAT. Since then, the study was extended to 6 new sites, 5 in DRC and 1 in CAR. The study is progressing well, without too many logistical problems, but the recruitment rate is lower than initially anticipated. By 10 July 2013, 108 patients were included in the study.

The investigator meeting, held in Kinshasa in the presence of Dr Kande, the Primary Investigator, and Dr Lumbala, Director of the PNLTHA and partner for the management of 4 sites, was considered as very positive by the organizers, the investigators and the representatives of the nursing staff involved in the study.

Fruitful exchanges took place on numerous practical issues, with an update on pharmacovigilance and cardiology. To hasten the study progression, DNDi is considering opening 4 additional sites, all in DRC. Preparatory work will start soon in two sites already chosen. Fexinidazole will also be evaluated in the treatment of visceral leishmaniasis and Chagas disease (American trypanosomiasis).

SCYX-7158 (molecule belonging to the oxaborole family)

The drug entered the Phase I stage of its development in France in February 2012. Given its long half-life, SCYX-7158 treatment requires only a single dose. A gradual dose increase is currently tested in healthy volunteers (8 volunteers per dose tested). The maximum dose reached so far is 200 mg, and the safety is ex-

cellent. If the safety analysis confirms this finding, Phase II/III is expected to start mid-2014.

A new rapid test on the horizon for HAT screening

Lauren Sullivan; University of Dundee.

Similar to the FIND and SD rapid diagnostic test (RDT) but based on different antigens the Dundee RDT, together with BBIsolutions, offers a complementary assay for screening of T. b. gambiense and potentially for T. b. rhodesiense infections. As with other RDTs, this low cost rapid test has the potential to improve active and passive screening campaigns with its limited equipment, ease of use and sensitive results.

The antigens were discovered by a non-biased proteomics approach (described in Sullivan ***et al.***, 2013, PLoS NTD) and by a candidate approach (manuscript in preparation) during the course of an MRC-funded PhD studentship, with further support from a Wellcome Trust programme grant. The premise for this RDT relies on detecting antibodies generated in infected individuals.

Recently a virtual field trial was carried out, using patient samples from the WHO HAT specimen bank, together with the un-optimized Dundee prototype RDT. While further investment is required for optimal test output, the antigens performed remarkably well considering time spent on developing this test. Early estimates suggest >97% sensitivity and >80% specificity for T. b. gambiense infections. In addition, the test could be optimized for T. b. rhodesiense infections as it also showed some promise with >83 % sensitivity and >85 % specificity.

The Dundee RDT for diagnosis of HAT. A negative test has one or two lines while a positive test has three lines.

Currently, we are in collaboration with Foundation for Innovative New Diagnostics (FIND), where an independent virtual field study is being carried out with collaborators Dr Jeremy Sternberg in the University of Aberdeen. The RDTs are being compared with the most promising antigens and depending on the outcome of the study will determine which antigens should be carried forward for further development with the aim of taking the best diagnostic antigens to the field.

New rapid tests for antibody detection serodiagnosis in Trypanosoma brucei gambiense sleeping sickness

Philippe Büscher1*, Dieudonné Mumba Ngoyi2, Patient Pati Pyana2, Pascal Mertens3, Thierry Leclipteux3, Quentin Gilleman3, Oumou Camara4, Mamadou Camara4, Mamadou Leno4, Hassan Sakande5, Emilie Dama5, Bruno Bucheton6, Vincent Jamonneau5,6 , Veerle Lejon6

1 Institute of Tropical Medicine, Department of Biomedical Sciences, Antwerp, Belgium

2 Institut National de Recherche Biomédicale, Department of Parasitology, Kinshasa Gombe, Democratic Republic of the Congo

3 Coris BioConcept, Crealys Park, Gembloux, Belgium

4 Programme National de Lutte contre la Trypanosomose Humaine Africaine, Conakry, Guinée

5 Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (CIRDES), Bobo-Dioulasso, Burkina Faso

6 Institut de Recherche pour le Développement, UMR 177 IRD-CIRAD INTERTRYP, Campus International de Baillarguet, Montpellier, France

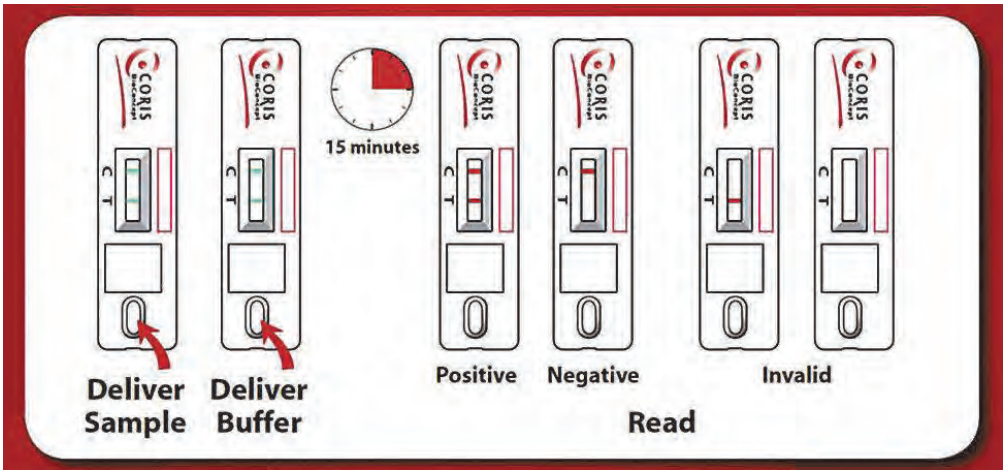
* Tel: +32 3 247 63 71, email: pbuscher@itg.be

Keywords: Trypanosoma brucei gambiense, human African trypanosomiasis, sleeping sickness, diagnosis, rapid diagnostic test

Since 1998, a spectacular reduction of the incidence of sleeping sickness due to Trypanosoma brucei (T.b.) gambiense is observed. This has been possible by the large scale implementation of a serodiagnostic test, the Card Agglutination Test for Trypanosomiasis CATT/T.b.gambiense). CATT is a rapid diagnostic test that allows screening of entire village populations for persons that carry trypanosome specific antibodies limiting the number of time consuming parasitological examinations to persons with a positive CATT result. The CATT test, that is conditioned as 50 tests/vial, is designed for mass screening by specialized mobile teams and necessitates a cold chain for proper storage.

It is therefore not appropriate for decentralized implementation in peripheral health facilities with low numbers of suspects to expect. With the steadily decreasing prevalence, and subsequent reduction of budgets for active screening of the population at risk, an individual rapid diagnostic test with high specificity that is stable at ambient temperature, that can be used at the level of peripheral health facilities and that can be performed after minimal training, is considered essential to reach elimination of HAT (Simarro et al. 2008). To this end, the Institute of Tropical Medicine Antwerp (ITM) participated in the development of the Standard Diagnostics Bioline HAT rapid test, in collaboration with FIND Diagnostics (http://www.finddiagnostics.org/programs/hat-ond/).

We here report on two other rapid tests for serodiagnosis of sleeping sickness due to T.b. gambiense. The HAT Sero-Strip and HAT Sero-K-SeT have been developed in collaboration with a Belgian diagnostic company, Coris BioConcept (www.corisbio.com), within the framework of the NIDIAG network, a project supported by the European Commission (Grant Agreement 260260, www.nidiag.org). The tests fulfill the ASSURED criteria (affordable, sensitive, specific, user friendly, rapid, robust, equipment free and deliverable) (Mabey et al. 2004). The antigen in these tests is a combination of variant surface glycoproteins (VSGs) of T.b. gambiense that have been proven to be highly specific and



sensitive in other test formats such as ELISA, latex agglutination and immune trypanolysis. HAT Sero-K-SeT and HAT Sero-Strip, are immunochromatographic tests consisting of a sample pad, a nitrocellulose membrane and an absorbent pad, backed with a plastic carrier strip.

In the HAT Sero-K-SeT, this strip has been mounted in a plastic housing with a sample application well and a test reading window and is individually sealed in a plastic-aluminium pouch. In the HAT Sero-Strip format, 20 test strips are packed in one vial. Both tests can be performed on plasma as well as on whole blood. In the HAT Sero-K-SeT, 30 μl of blood or 15 μl of plasma are dispensed in the sample application window followed by 2 drops of migration buffer. After 15 minutes, the test result is read as (1) positive if both the control and the test line are visible, (2) negative if only the control line is visible, (3) invalid if the control line is not visible.

In the HAT Sero-Strip, 30 μl of blood or 15 μl of plasma are mixed with 100 μl of migration buffer in a 5 ml plastic reaction tube where after the strip is dipped in the specimen/buffer mixture. After 15 minutes, the test result is read as above. Both tests underwent phase I evaluation on archived specimens from sleeping sickness patients diagnosed and treated in East Kasai Province in the Democratic Republic of the Congo (DRC).

Specimens from endemic controls were obtained from the World Health Organization Human African Trypanosomiasis Specimen Bank (http://www.who.int/trypanosomiasis_african/research/en/). For HAT Sero-Strip, the sensitivity was 97.5% and the specificity was 98.0% while with HAT Sero-K-SeT, a sensitivity of 93.9% and a specificity of 99.0% was observed (Büscher et al. 2013).

Next, a phase II evaluation study was initiated in collaboration with the National Sleeping Sickness Control Programme and the Institut National de Recherche Biomédicale to test the diagnostic performance of the HAT Sero-K-SeT under field conditions in Bandundu Province, DRC. Preliminary data on 493 persons, of which 134 parasitologically confirmed patients, yielded 98.5% sensitivity and 98.6% specificity for the HAT Sero-K-SeT compared to 95.5% sensitivity and 97.2% specificity for the CATT on whole blood.

Further, in Guinea, HAT Sero-K-SeT was 100% specific on 23 endemic controls and 96.0% sensitive on 25 parasitologically confirmed patients, while CATT on whole blood was 100% specific and 100% sensitive. These data will further be analysed taking into account results obtained in the immune trypanolysis test, being the reference test for gambiense-specific antibodies (Van Meirvenne et al. 1995). In the meantime, a phase III evaluation of the HAT Sero-K-SeT has started as part of a broader study on the differential diagnosis of neurological and fever syndromes within the NIDIAG network. We believe that the HAT Sero-K-SeT and HAT Sero-Strip may become valuable tools in the control and eventually the elimination of gambiense sleeping sickness.

References

Büscher P, Gilleman Q, & Lejon V (2013) Novel rapid diagnostic tests for sleeping sickness. New England Journal of Medicine 368, p 1069-1070.
Mabey D, Peeling RW, Ustianowski A, & Perkins MD (2004) Diagnostics for the developing world. Nature Reviews 2, p 231-240.
Simarro PP, Jannin J, & Cattand P (2008) Eliminating human African trypanosomiasis: Where do we stand and what comes next? PLoS Medicine 5, p 174-180.
Van Meirvenne N, Magnus E, & Büscher P (1995) Evaluation of variant specific trypanolysis tests for serodiagnosis of human infections with Trypanosoma brucei gambiense. Acta Tropica 60, p 189-199.

Voices of HAT patients and caregivers

PATIENT-CAREGIVER PHENOMENON

In March 2013, the HAT Mobile Unit of Isangi (Eastern Province, DRC) was working in the health area of Malinda/ health zone of Yabaondo.

The head nurse Joseph Boila, always present with the mobile team, decided that he too should be tested like all the inhabitants of the village of Malinda. Well he was very lucky because he was detected for trypanosomes, and the lumbar puncture showed that he was still at the early stage of the disease.

Fully aware of the symptoms of the disease, he decided to be treated along with his patients in the health area, but our heroic patient had no intention of leaving his job. So he got his deputy head nurse to inject him very early in the morning, after which he administered pentamidine down to the last dose to his fellow HAT patients.

We are all equal before sleeping sickness, and Joseph is the living proof of the dedication of this generation, who works very hard to fight this disease, and sets the right example.

Espérant Bolimbo
Supervisor

The HAT Platform and DNDi would like to thank the following donors for their support since July 2003:

- Department for International Development (DFID) / UNITED KINGDOM
- Dutch Ministry of Foreign Affairs (DGIS) / THE NETHERLANDS
- European Union - Framework Programme 6
- Médecins Sans Frontières (Doctors without Borders) / INTERNATIONAL
- Medicor Foundation / LIECHTENSTEIN
- Ministry of Foreign and European Affairs (MAEE) / FRANCE
- Republic and Canton of Geneva, Institution Department, International Solidarity / SWITZERLAND
- Spanish Agency for International Development Cooperation (AECID) / SPAIN
- Swiss Agency for Development and Cooperation (SDC) / SWITZERLAND
- A Swiss private foundation and individual donors.

RECENT HAT PUBLICATIONS
December 2012 – June 2013

1. Baker N, de Koning HP, Mäser P, Horn D. Drug resistance in African trypanosomiasis: the melarsoprol and pentamidine story. Trends Parasitol. 2013 Mar;29(3):110-8.

2. Büscher P, Gilleman Q, Lejon V. Rapid diagnostic test for sleeping sickness. N Engl J Med. 2013 Mar 14;368(11):1069-70.

3. Funk S, Nishiura H, Heesterbeek H, Edmunds WJ, Checchi F. Identifying transmission cycles at the human-animal interface: the role of animal reservoirs in maintaining gambiense human african trypanosomiasis. PLoS Comput Biol. 2013;9(1):e1002855.

4. Gillet P, Mumba Ngoyi D, Lukuka A, Kande V, Atua B, van Griensven J, Muyembe JJ, Jacobs J, Lejon V. False positivity of non-targeted infections in malaria rapid diagnostic tests: the case of human african trypanosomiasis. PLoS Negl Trop Dis. 2013 Apr 25;7(4):e2180.

5. Hasker E, Lutumba P, Chappuis F, Kande V, Potet J, De Weggheleire A, Kambo C, Depoortere E, Pécoul B, Boelaert M. Human African trypanosomiasis in the Democratic Republic of the Congo: a looming emergency? PLoS Negl Trop Dis. 2012;6(12):e1950.

6. Kennedy PG. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). Lancet Neurol. 2013 Feb;12(2):186-94.

7. Maurice J. New WHO plan targets the demise of sleeping sickness. Lancet. 2013 Jan 5;381(9860):13-4.

8. Mumba Ngoyi D, Menten J, Pyana PP, Büscher P, Lejon V. Stage determination in sleeping sickness: comparison of two cell counting and two parasite detection techniques. Trop Med Int Health. 2013 Jun;18(6):778-82.

9. Nzoumbou-Boko R, Dethoua M, Gabriel F, Buguet A, Cespuglio R, Courtois P, Daulouède S, Bouteille B, Ngampo S, Mpandzou G, Semballa S, Vincendeau P. Serum arginase, a biomarker of treatment efficacy in human african trypanosomiasis. J Clin Microbiol. 2013 Jul;51(7):2379-81.

10. Thuita JK, Wolf KK, Murilla GA, Liu Q, Mutuku JN, Chen Y, Bridges AS, Mdachi RE, Ismail MA, Ching S, Boykin DW, Hall JE, Tidwell RR, Paine MF, Brun R, Wang MZ. Safety, Pharmacokinetic, and Efficacy Studies of Oral DB868 in a First Stage Vervet Monkey Model of Human African Trypanosomiasis. PLoS Negl Trop Dis. 2013 Jun 6;7(6):e2230.

11. Tiberti N, Matovu E, Hainard A, Enyaru JC, Lejon V, Robin X, Turck N, Ngoyi DM, Krishna S, Bisser S, Courtioux B, Büscher P, Kristensson K, Ndung'u JM, Sanchez JC. New biomarkers for stage determination in Trypanosoma brucei rhodesiense sleeping sickness patients. Clin Transl Med. 2013 Jan 7;2(1):1.

12. Yansouni CP, Bottieau E, Lutumba P, Winkler AS, Lynen L, Büscher P, Jacobs J, Gillet P, Lejon V, Alirol E, Polman K, Utzinger J, Miles MA, Peeling RW, Muyembe JJ, Chappuis F, Boelaert M. Rapid diagnostic tests for neurological infections in central Africa. Lancet Infect Dis. 2013 Jun;13(6):546-58.