HAT Platform

REGIONAL PLATFORM FOR CLINICAL RESEARCH

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Training of trainers

from 10 to 11 September 2013, Entebbe, UGANDA

REGIONAL PLATFORM FOR CLINICAL RESEARCH
HUMAN AFRICAN TRYPANOSOMIASIS HAT

HAT Platform secretariat:

Avenue Révolution No 4, quartier SOCIMAT
Kinshasa, Gombe
Democratic Republique of the Congo
Email: aebeja@dndi.org
Tél: 00243 81 081 22 38

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Editorial

Dr Augustin Kadima Ebeja ; HAT Platform Coordinator

We often hear that those who stand still go backwards, but what about our Platform? Since its creation in 2005, our network has grown in size: from 5 member countries initially, it now includes 8 member countries and several more are applying for membership, such as Gabon, Guinea and Ivory Coast.

Over the past 8 years, the HAT Platform achieved major steps:

- Training programmes were set up for ethics committee members in all the member countries, as well as for monitors, investigating physicians, laboratory technicians and nurses;
- Thirteen newsletters have been published so far, as well as a guidance document on the ethical review of research in the DRC;
- Scientific meetings, recently in partnership with EANETT, and steering committee meetings have been organized;
- Various partners have provided multifaceted contributions to support on-going clinical trials.

However, during the last steering committee meeting in June 2013, questions were raised on the objectives of the HAT Platform. The current trend is for health ministries to merge control programmes of different neglected diseases instead of keeping them separate. Consequently, now that the HAT Platform has made some progress on its initial objectives for Human African trypanosomiasis (HAT), they must be redefined based on the current situation, knowing that some neglected tropical diseases (NTDs) have been targeted for elimination.

It will be impossible to do everything all at once and our resources are limited. From a practical point of view, this change will require the establishment of a partnership with the experts and directors of the organizations focusing on other NTDs. The World Health Organization (WHO) has led the way by merging the annual meetings of HAT and leprosy control programmes in sub-Saharan Africa (see resolutions in the article below).

It may also be an opportune time to extend our sphere of operations beyond clinical research and formally include epidemiological or public health considerations, with the same ultimate goal of NTD elimination.
The debate has started and we look forward to all your contributions.

This fourteenth newsletter also brings you information on the latest scientific events associated with our Platform, as well as on the progress made by on-going trials.

We would also like to thank all our readers and wish everyone a happy New Year.

Latest scientific events and miscellaneous information

A. Trainer training on the protection of human subjects and Good Clinical Practice in Entebbe

(Augustin Kadima Ebeja)

Training plays an important role in the implementation of clinical studies conducted for the HAT Platform, because it is a necessity with any new technique, but also because one of the Platform's main objectives is to strengthen research capacities.

So with the financial support of DNDi, PPD (Pharma Product Development) organized a trainer training session in Uganda on 10-11 September 2013, led by five facilitators from our HAT Platform (one for Uganda and four from the DRC). The session was attended by representatives from several African countries: Kenya, Malawi, Mozambique, Ghana, Nigeria, Ethiopia, South Africa, Uganda and the DRC. The session was divided into a theoretical part and a practical part.

Theoretical part

It is essential for trainers to have a good understanding of the subject to be taught, and hence be able to answer any questions put to them.

The session on the protection of human subjects and good clinical practice was divided into 10 sections: 1) introduction to clinical research; 2) guidance and regulation documents; 3) investigator responsibilities; 4) ethics; 5) institutional review board (IRB) / independent ethics committee (IEC); 6) informed consent; 7) safety / safety supervision; 8) documentation sources, essential documents; 9) investigation products; and 10) quality management.

Practical part

Trainers must develop specific skills to pass on knowledge. Several techniques were presented, ranging from the identification of the population targeted by the training, to the definition of training objectives. The preparation of study material, as well as time management before, during and at the end of the training session play a major part in the success of the training.

To help participants understand correctly all the procedures (principles), 6 working groups were created with 4 to 6 people in each. Each group worked on one of the themes addressed in the theoretical part, before presenting it to the rest of the participants. Any errors were discussed and corrected.

Conclusion

Trainers, whom we generally refer to as facilitators, must take seriously this task of communicating a precise message based on identified needs. They must express themselves clearly, maintain visual contact with the audience, move about freely, and most importantly, they must avoid standing in front of the slide projector. We hope our members learned much more from these sessions than we are able to list here. We strive to improve the quality of our training sessions, and hope that the partners who were asking for these sessions will now use these trained trainers.

B. ISCTRC 32nd General Conference

Over 200 scientists attended the conference on *T&T Research and Control for Sustainable Agriculture and Rural Development: Promoting Partnership and Learning Agenda in the Context of African Renaissance*, held on September 8-12, 2013, in Khartoum, Sudan. The participants came from tsetse-infested countries, international organizations, research institutes and the private sector.

The president of Sudan's national organization committee, Dr Ahmed Abdul-Rahman, welcomed the participants and thanked the African Union for choosing Sudan to host the 32nd ISCTRC

conference. Dr Sadou Maiga, Chairman of the ISCTRC Executive Council, presented the Council's steering activities.

The Director of the African Union Inter-African Bureau for Animal Resources (AU-IBAR), Professor Ahmed El-Sawalhy, presented the general objectives of the conference, which included information sharing, a review of Tse-tse and Ttypanomiasis control technologies, strategies and political options, the identification of research gaps, and recommendations for the next two years. He thanked the Government of Sudan for hosting the conference.

Her Excellency Mrs Tumusiime Rhoda Peace, Commissioner for Rural Economy and Agriculture of the African Union Commission, urged the participants to consider the progress achieved so far in the control of trypanosomiasis, which continues to cause heavy economic losses to rural households in Africa. The Commissioner urged African countries to adopt the national and regional pacts of the Comprehensive Africa Agriculture Development Program (CAADP) to ensure that the problem of tsetse flies and trypanosomiasis receives due attention. She asked the African countries to include tsetse flies and trypanosomiasis control in their poverty reduction strategies. She praised the African Union - Pan African Tsetse and Trypanosomiasis Eradication Campaign (UA-PATTEC) for having launched projects which produced major benefits for rural communities.

Dr Fayçal Hassan Ibrahim, the Sudanese Minister for Livestock, Fisheries and Rangeland, described the negative impact of trypanosomiasis on the rural development of his country, and urged scientists and development partners to find a sustainable solution to the problem.

The conference was officially opened by the First Vice President of the Republic of the Sudan, His Excellency Ali Osman Muhammed Taha. He highlighted the importance of the joint African cooperation and the role of Pan Africanism in the development of Africa, as well as the determining influence on food safety of livestock and cattle protection against diseases. The First Vice President encouraged platforms such as ISCTRC to maintain their commitment to T&T control.
Over five days, 95 documents were presented, 70 as oral presentations and 25 as posters. The topics included the contribution of international organizations; reports from PATTEC and the countries; human and animal African trypanosomiasis; tsetse biology, control and eradication; and the use of land, environment and socio-economics.

Capacity gaps remain in the control and elimination of tsetse and trypanosomiasis, but the number of young African scientists interested in T&T research and publication has increased. It was also encouraging to note the increasing synergy between actors in endemic countries, international organizations, research institutes, development partners and the private sector in T&T control. This improved synergy had been facilitated by efficient advocacy from AU-PATTEC.

However, progress has been achieved in the development of new diagnostic tools and new treatments. Dr Veerle Lejon (IRD, France) presented a review of the interference of HAT with malaria tests, with some tests producing false positive results in HAT-negative patients. Research on non-invasive methods for the early detection of late-stage Human African Trypanosomiasis (HAT) is still of prime importance.

The need to use appropriate drug combinations and dosages to treat HAT was emphasized. Professor Mumba (DRC) presented a review of available data comparing treatments of early-stage HAT with pentamidine for 3 or 7 days. The commitment of the countries to the elimination of HAT, as evidenced by the declining incidence of the disease, was praised. Professor Matovu (Uganda) presented an important experiment based on the Kaberamaido elimination model. Endemic countries were however cautioned not to relax their efforts on HAT surveillance. Disease risk mapping by Cecchi (FAO) and the very comprehensive presentation on the elimination requirements by Dr Franco (WHO) provided a clear overview of the possible scenarios.

Tsetse genetic profiling was presented as a step towards the development of area-wide tsetse control and/or eradication.

The participants were in favour of the adoption of an integrated approach to the management of T&T, using methods suited to the circumstances. Some of the methods include the use of sequential aerosol technique (SAT), ground spraying, insecticide impregnated targets and screens, sterile insect technique (SIT), and chemotherapy. These efforts are aimed at improving both human and animal health. Professor Lehane (UK) presented a study on a major innovation based on mini tsetse fly traps. Suggestions were

made to involve the United Nations Environment Programme (UNEP) in the formulation and implementation of tsetse control programmes.

The participants asked AU-PATTEC to play a leading role in the identification of management and resource challenges facing member countries in T&T control, and to suggest sustainable solutions to address these challenges.

C. Validation of the national HAT control policy in Chad

A workshop on the validation of the national HAT control policy document in Chad was held on September 18-19, 2013, in the CEFOD (*Centre d'Études et de Formation pour le Développement*) multimedia room.
The workshop objectives included:

1. An examination of the proposed document
2. The proposal of amendments
3. A validation of the final document.

The opening ceremony was presided by the Minister of Public Health, accompanied by the WHO representative, and the Director General of the Livestock Research for Development Institute.

In her welcoming address, the Director of Preventive Health, Environment and Disease Control gave a brief overview of the HAT epidemiology in Chad, before presenting the National HAT Control Programme, its objectives and the reasons for its relocation in the south of the country, close to the transmission areas. This programme has no national guidelines. Control activities are based either on the instructions of OCEAC subregional HAT control programme, or on the WHO guidelines. Given this deficiency at the national level, a document on the national policy on HAT control was created to define strategies and intervention standards to fight this disease effectively in its various foci and eliminate HAT from Chad.

In his opening address, the Minister of Public Health expressed his gratitude to the various international experts who agreed to participate in this workshop. Known in Chad since 1912, sleeping sickness is still a major public health concern. An average 369 new cases are reported every year, and according to the WHO, Chad is the third country with the highest HAT incidence behind the DRC and CAR. After thanking the HAT Platform for organizing the workshop, the Minister of Public Health ended his speech by expressing a wish that the contributions of the participants may improve the document and make it as operational as possible in the interest of Chad's population and economy.

The 35 participants then designated the workshop's managing committee, which was followed by two series of communications. The first series was divided into three presentations: « HAT management: course, diagnosis, treatment, and prospects » by Dr Augustin Ebeja, « HAT epidemiology » by Dr Francis Louis, and « Vector control and HAT elimination » by Dr Lisette Kohagne Tongue. The salient points of these communications are given below:

- There are three types of trypanosomiasis: human African trypanosomiasis (HAT), American trypanosomiasis and animal African trypanosomiasis. HAT, caused by two trypanosome sub-species, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, occurs exclusively in sub-Saharan Africa. Although disease control efforts have led to a marked drop in the number of new cases reported every year, thousands of patients are still diagnosed in the DRC and hundreds in Angola and Chad. The number of new cases has been stagnating for at least three years despite regular screening activities and the treatment of patients. Diagnosis is still based on a two-step strategy set up in the '70s: a serological diagnosis and a parasitological diagnosis which helps confirm the stage of the disease. Early-stage sleeping sickness is treated with pentamidine, and late-stage with NECT (Nifurtimox Eflornithine Combination Therapy). Other molecules are currently being tested to improve the treatment. The main objective of the HAT Platform, which includes 8 countries (Sudan, South Sudan, Uganda, RoC, DRC, CAR, Angola and Chad) is to build and strengthen clinical research capacities and methodologies in the HAT endemic countries. Its different activities include strengthening capacities, regulatory aspects, facilitation of on-going research, advocacy, and communication. Achievements include training of ethics committees, clinical monitors, laboratory technicians and physicians. The HAT Platform publishes a biannual newsletter covering all HAT control activities.

- The complex HAT transmission cycle includes man as the main host, but domestic and wild animals can also act as potential reservoirs. To interrupt the parasite transmission, the reservoirs must be cleared by targeting both hosts (man and domestic and wild animals) and the vector. The objectives of HAT control include the elimination of HAT as a public health concern, i.e. bring its incidence down to less than one case diagnosed per year per 10'000 exposed inhabitants by 2020, and eliminate the disease totally (i.e. 0 case/year) by 2030. There are 3 types of foci: high to very high transmission foci (areas reporting an annual average of at least one new case per 1'000 inhabitants), moderate transmission foci (areas reporting an annual average of at least one new case per 10'000 inhabitants but less than one new case per 1'000 inhabitants), and low to very low transmission foci (areas reporting an annual average of at least one new case per 1'000'000 inhabitants, but less than one new case per 10'000 inhabitants). There are no moderate transmission foci in Chad.

- Vector control is a necessary step in the process of HAT elimination, as a reduction in vector population helps break the transmission cycle and clear the tsetse, animal and human reservoirs of parasites. Several methods and tools are available for vector control. Although effective, they each have their own drawbacks, and the choice of a method is based on various criteria, including the type of endemicity and the particular tsetse species involved. It is always more cost-effective to combine at least two control methods. Vector control is a multidisciplinary action that requires the combined effort of all those involved to succeed.

The second series of communication, entitled « HAT situation in Chad », presented by Peka Mallaye, described the disease's prevalence, number of foci, control efforts to date, constraints, and main challenges.

These two series of communications were each followed by a discussion.

Dr Louis presented the document to be validated, and following an exchange of comments and suggestions, modifications were made directly.

The recommendations to improve the document were as follows:

1. Include veterinarians within the Platform
2. Create a table of contents
3. Add a paragraph on expected results
4. Remove the paragraph on background information and add it as an appendix
5. Modify the numbering of paragraphs
6. Remove the paragraph on WHO intervention strategies, but not the section on algorithms, and add it as an appendix
7. Define passive screening and active screening
8. Define treatment failure
9. Develop further the paragraph on community mobilization by including advocacy
10. Explain the surveillance system mentioned in the document.

All the modifications were adopted and the document was validated unanimously. The final version of the document on the national policy for the elimination of human African trypanosomiasis in Chad (***Document de politique national d'élimination de la trypanosomiase humaine africaine du Tchad***) will be made available to all.

D. Annual meeting of the directors of the leprosy and human African trypanosomiasis control programmes

The World Health Organization (WHO) organized this meeting in Yaoundé, Cameroon, on 11-13 November 2013, to help reduce further the social and economic burden of leprosy and human African trypanosomiasis in the WHO African Region.

A total of 78 participants attended this 3-day workshop to:

- Analyse the epidemiological patterns of leprosy at the district level, and those of HAT in the endemic foci in the region;
- Review the follow-up and evaluation indicators, as well as the new report forms;
- Review the regional strategic plans for leprosy and HAT control;
- Agree on a regional framework on the coordination of the management of leprosy and HAT cases in the African Region;
- Make recommendations to integrate correctly leprosy and HAT within the package of integrated interventions on the control of neglected tropical diseases.

Our HAT Platform contributed to the discussions by highlighting clinical research as one of the necessary tools to eliminate these two neglected diseases.

The challenges and priorities for HAT were defined as follows:

1. Complete the situation analysis in the 7 countries where it is still unknown: Burundi, Ethiopia, Gambia, Liberia, Mozambique, Niger, and Senegal.
2. Consolidate the implementation of adapted control and monitoring measures within the national health systems by strengthening the capacities of local healthcare teams for HAT diagnosis and management.
3. Maintain the approach combining the use of the mobile teams and that of existing healthcare facilities in the highly endemic areas: Angola, Central African Republic, Chad, Ivory Coast, RoC, DRC, Guinea and Uganda.
4. Establish an effective coordination with veterinary services and natural resource management services, which deal with wild and domestic animals as well as with vector and reservoir control.
5. Support research on new tools to accelerate the current control process and boost the involvement of healthcare services in HAT monitoring and control, to maintain and prolong the results achieved so far.

The challenges and priorities for leprosy were defined as follows:

1. Establish an inventory of the basic structures to be kept in place for the integration.
2. Reinforce in a coordinated way the capacities of the basic structures to be integrated with the rest of the activities.
3. Combine leprosy and HAT screening during consultations in HAT diagnosis and treatment centres.
4. Create guidelines and train the personnel of HAT screening centres to combine HAT and leprosy activities.
5. Reinforce the capacities of the HAT mobile teams to screen

leprosy during population surveys on trypanosomiasis in the foci.

6. Other neglected tropical diseases may be included in the activity package of the HAT mobile teams.
7. Provide a coordination mechanism at the country level for all the actors involved in the control of neglected tropical diseases.
8. Bring partners to adopt the national policies on the control of neglected tropical diseases.

Our Platform was presented as a model for strengthening capacities. However, we insist on the fact that the mobilization of research resources must continue if the elimination of neglected tropical diseases is to be achieved. Research has contributed and will continue to contribute to the achievement of this objective.

Research & Development for Diseases of the Poor: A 10-Year Analysis of Impact of the DNDi Model

From the Press Release
[Paris, France & Geneva, Switzerland – 5 December 2013

A DNDi report provides real and estimated costs of repurposing drugs and new chemical entities, evoking the lessons learned based on alternative pathways and partnerships

Today, at a scientific meeting at Institut Pasteur, France, entitled 'Best Science for the Most Neglected: Where Do We Stand Ten Years On?', co-organized with Institut Pasteur and MSF and in collaboration with PLOS, the Drugs for Neglected Diseases initiative (DNDi) marks its 10-year anniversary by issuing a report that explores the lessons learned from a decade of research and development (R&D) of new treatments for neglected diseases via a cost-effective, innovative, not-for-profit drug development model. The report also comes at the time of discussions at the WHO aiming at gaining Member State agreement on 'demonstration projects' meant to provide evidence for the feasibility and sustainability of collaborative and open approaches to R&D for the health needs of developing countries.

The DNDi report, entitled 'An Innovative Approach to R&D for Neglected Patients: Ten Years of Experience and Lessons Learned by DNDi', provides elements to stimulate current discussions on the way forward for sustainable mechanisms to provide health tools for developing countries. The report describes four key pillars of the open R&D model: patient-centricity; open access to knowledge and patient access to treatments; financial and scientific independence; and building and sustaining solid alliances with public and private partners, including in endemic countries.

DNDi was founded in 2003 to address a systemic lack of R&D for certain neglected diseases. A recent *Lancet Global Health* publication showed a persistent deficiency in new therapies for neglected diseases, despite some progress over the past decade. From 2000 to 2011, of all new drugs and vaccines approved for all diseases, 4% were for neglected diseases – which represent an 11% health burden – with progress being mainly in reformulating already existing drugs. Of the new drugs, only 1% were for neglected diseases.

'MSF was the initiator of the DNDi experiment and we see concrete results for patients already, which are improving and saving lives in the field today', said Dr Joanne Liu, President of MSF International. 'MSF is proud to renew its commitment, both in terms of funding and collaboration in the field, to the initiative for the years to come.'

In ten years, DNDi has established over 350 collaborations in 43 countries, including with 20 pharmaceutical and biotechnology companies, and with over 50 universities and research institutes. With its partners, DNDi has conducted 25 clinical studies from Phase I until Phase IV implementation / pharmacovigilance studies, while strengthening research capacities in the countries where the diseases occur, notably through the set-up of clinical research platforms. These efforts have led to the implementation of six improved treatments to answer urgent needs of patients with malaria, sleeping sickness, visceral leishmaniasis, and Chagas disease. DNDi has invested significantly in upstream research and access to compound libraries, data, and knowledge sources to identify new chemical entities, 12 of which are currently in pre-clinical and clinical development.

'We are convinced of the relevance and role of Institut Pasteur and its international network in upstream research on neglected diseases and our decade of engagement in DNDi is set to take on

a new dimension', said Professor Christian Bréchot, President of Institut Pasteur. 'Fundamental knowledge of these diseases and translational research still have much to contribute to the science applied to the benefit of these patients.'

Since its inception, DNDi has raised, from public and private funding sources, EUR 277 million of the EUR 400 million needed to deliver 11 to 13 new treatments by 2018, according to the DNDi Business Plan. The analysis of the business model, through selected case studies of treatments delivered and new chemical entities underway, offers insight into the DNDi's R&D costs: EUR 12 million to develop and monitor implementation of a fixed-dose combination therapy for malaria (ASAQ – over 250 million treatments distributed by Sanofi); EUR 6.8 million to develop an improved treatment option for sleeping sickness (NECT – now used to treat 96% of all late-stage patients); EUR 11.5 million to develop a new combination therapy for kala-azar in Africa (SSG&PM – 23,000 patients treated in East Africa since 2010); and estimates for development and registration, EUR 38.3 million for a new chemical entity (SCYX-7158) and EUR 26.5 million for a rediscovered new chemical entity (fexinidazole), both oral treatments for sleeping sickness.
Based on its experience, DNDi concludes that its cost of development ranges from EUR 6-20 million for an improved treatment, and EUR 30-40 million for a new chemical entity. However, the usual attrition in the field of R&D for infectious diseases, and the inherent risk of failure, should be taken into account, bringing the cost range of an improved treatment to EUR 10-40 million, and EUR 100-150 million for a new chemical entity. These estimations do not include the in-kind contributions from DNDi's many partners.

'Today, after ten years, we know that when we push the boundaries of innovative business models, we can develop and deliver safe, adapted, and affordable treatments for diseases affecting millions of the patients in neglected disease-endemic countries, who lack access to health technologies because they can't pay', said Dr Bernard Pécoul, Executive Director of DNDi. 'But we have yet to deliver the breakthroughs needed for radical change, and we need to consolidate the successes of the past to create truly sustainable mechanisms, including financing and coordination, for R&D in the field of neglected diseases.'

About the event and two DNDi projects awarded

Celebrating its 10-year anniversary, DNDi and two of its founding partners, Institut Pasteur and MSF, co-hosted a special scientific conference at Institut Pasteur in Paris, France. The event, with over 400 attendees - key actors in the field of research and development for neglected diseases, including international scientists, product developers, policy-makers, and civil society organizations - explored the scientific aspects of the past decade of innovation for neglected diseases carried out by various innovative initiatives, including DNDi.

In addition, a special ceremony was held to celebrate the DNDi Project and Partnership of the Year Awards. Nominated by the DNDi Scientific Advisory Committee and selected by the DNDi Board of Directors, two special awards were granted for their achievements in the past year. The Project of the Year was awarded to the first-ever placebo-controlled study in adults with Chagas disease, the E1224 Project: the Phase 2 double-blind, randomized, controlled trial conducted in Bolivia, evaluated the safety and efficacy of E1224. The Partnership of the Year was awarded to the Paediatric HIV Programme, which has brought together key partners to advance rapidly towards the delivery of an urgently needed, child-adapted 4-in1 antiretroviral treatment for infants and toddlers with HIV.

On the same occasion, DNDi and PLOS launched a special on-line Collection, 'PLOS & DNDi: A Decade of Open Access and Neglected Tropical Diseases R&D', which also marked the 10-year anniversary of PLOS, an open access scientific journal, which has contributed to a more open neglected disease research landscape.

Scientific meetings scheduled for 2014

Conferences, Meetings, Symposia of Interest
HAT and neglected diseases - 2014

Name	Date	Location
6th Asean Congress of Tropical Medecine and Parasitology :Global Challenges in Tropical Deseases: Bridging Gaps and Building Partnerships http://www.actmp2014.com	March 5-7	Kuala Lumpur; Malaysia
16th International Congress on Infectious Diseases (ICID) www.isid.org/icid	Apr 2-5	Capetown, South Africa
British Society for Parasitology (BSP) Spring Meeting 2014 http://www.bsp.uk.net/news-and-events/bsp-events/bsp-spring-meeting-2014-cambridge-university/	Apr 6-9	Cambridge, UK
Geneva Health Forum http://ghf.globalhealthforum.net/	April 15-17	Geneva Swizerland
European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	May 10-13	Barcelona, Spain
MSF Scientific Day http://www.msf.org.uk/msf-scientific-day	May 23	London, UK
International Course on African Trypanosomiasis ICAT 6	June 16 – 28	Kinshasa, DRC
7th EDCTP Forum: "The partnership journey: New horizon for better health" http://www.edctpforum.org/	June 30-July 2	Berlin, Germany
II International Congress of Parasitology, ICOPA http://www.icopa2014.com/	Aug 10-15	Hotel Camino Real Mexico City, Mexico
Joint Annual Meeting, Swiss Society for Infectious Diseases SSI, Swiss Society for Hospital Hygiene SSHH, and FMH http://www.sstmp.ch/	August 28-29	Aarau, Swizerland
Joint Scientific Annual meeting HATPLATFORM-EANETT	September 16-18	Kinshasa, DRC
Royal Society of Tropical Medecine and Hygiene (RSTMH) http://www.rstmh.org/home	September 25-27	St Aldate's, Oxford
45th Union World Conference on Lung Health Barcelona.worldlunghealth.org	Oct 28 – Nov 1	Barcelona, Spain
ASTMH Meeting; 63rd Annual meeting http://www.astmh.org/Home.htm	Nov 2 – 6	Sheraton New Orleans; Louisiana USA

Update on on-going research

A. Makerere University and Astel Diagnostics, together with six partners, developed a simple screening test to detect the sleeping sickness parasite in tsetse flies

MAKERERE UNIVERSITY
P.O. Box 7062 Kampala Uganda
Cables: "MAKUNIKA"
Tel: 256--414-532401
Website:http://cns.mak.ac.ug.
COLLEGE OF NATURAL SCIENCES

KAMPALA, Uganda - Makerere University, in collaboration with a Ugandan manufacturer Astel Diagnostics Ltd, and six other implementing agencies from Congo, the Democratic Republic of Congo, Malawi, South Sudan, Sudan and Tanzania, have successfully developed a new test that can accurately detect parasites in tsetse flies that cause sleeping sickness.

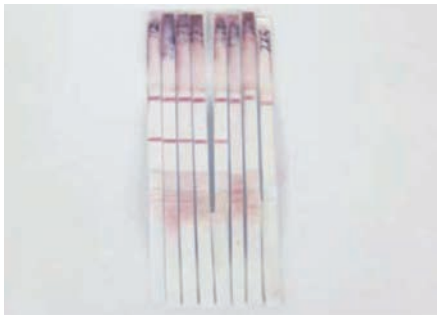
The project, which was coordinated by Professor John Kiboko Enyaru of the Department of Biochemistry and Sports Science at Makerere who was the Principal Investigator, was funded through a five-year research grant from the Bill & Melinda Gates Foundation.

Professor Enyaru looks over the work being carried out by the collaborators.Professor John Kiboko Enyaru of the Department of Biochemistry and Sports Science at Makerere was the Principal Investigator

"The new Lateral Flow Test helps to identify areas of potential sleeping sickness outbreaks that can be prioritized for tsetse control to pre-empt an outbreak," Enyaru commented.

Sleeping sickness is a tropical disease that is transmitted to humans by the bite of an infected tsetse fly (Glossina genus). Tsetse flies acquire the infection from another human being or animal harboring the human pathogenic parasites. The disease invades the central nervous system and can be fatal if not treated. In domestic animals, the disease is known as nagana (a Zulu word meaning «to be depressed») and causes wasting and loss of productivity.

Trypanosoma brucei is the technical name of the parasite that causes human African trypanosomiasis, also known as sleeping sickness. The objective of this project was to develop a test that can easily be used to detect this parasite in tsetse flies. The test needed to be simple, sensitive, specific, rapid, and easy to use without specialized training. With those criteria in mind, Astel Diagnostics (the collaborator) has developed a Lateral Flow Test (LFT) that can detect T. brucei in tsetse flies. The test was then evaluated in conjunction with the six other agencies.



Sample of test results using tsetse fly midguts from Dokolo, UgandaThe picture shows the results of the LFT. Each strip represents a test on one midgut. The top line indicates the control line while the bottom line shows a positive result. The three strips on the right showed negative results.

"The search for a simple test for the detection of potential sleeping sickness parasites in the tsetse fly vector was needed. This test will soon be commercially available," said Dr. James Thuo Njuguna, the Production Manager at Astel Diagnostics, Uganda.

There are three related parasites in this species: Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense and Trypanosoma brucei brucei. The rhodesiense subspecies affects humans in Eastern and Southern Africa but can also infect domestic animals while the gambiense subspecies affects humans in Western and Central Africa and its role in animals is not well known. The third subspecies, brucei brucei, affects livestock but does not infect humans. The LFT test detects all three subspecies but does not differentiate between them.

This new test developed by Astel can be used to map out and monitor geographical foci with tsetse flies carrying the potential sleeping sickness parasites and prioritize them for tsetse control. Given current efforts by programs such as the Pan-African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) to eliminate the disease in both humans and animals, this would be a key tool to achieving their goal.

The collaborators evaluating samples collected from the field.

The test, which was developed as a substitute for the current inefficient and unreliable technology that exists, is cheap, simple and rapid. It gives results within 20 minutes, is read by the naked eye, and can be performed by personnel with minimal training.

Participating Members

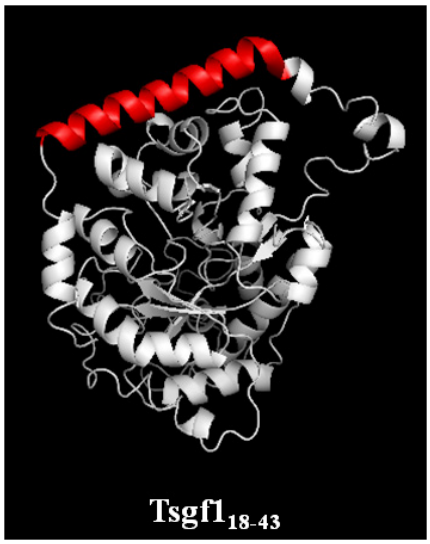
- Principal Investigator - Prof. John Kiboko Enyaru
- Department of Biochemistry and Sports Science, College of Natural Sciences, Makerere University
- Dr. Mubarak Mustafa – Tropical Medicine Research Institute (Khartoum, Sudan)
- Dr. Yassir Mohammed- Tropical Medicine Research Institute (Khartoum, Sudan)
- Dr Erneo Ochi, Ministry of Animal Resources and fisheries, Juba, South Sudan
- Yatta Samuel – Department of Basic Science, University of Juba (South Sudan)
- Dr Nicolas Mbongo - Laboratoire National de Santé Publique (Brazzaville CONGO)
- Dr Philemon Mansinsa-National Program of Human African Trypanosomiasis (Kinshasa, DRC)
- Prof. John Chisi, College of Medicine, University of Malawi
- Enock Matovu – Associate Professor, College of Veterinary Medicine, Makerere University
- Vincent Alibu – Lecturer (Biochemistry), College of Natural Sciences, Makerere University
- James Thuo Njuguna, and Vinand M Nantulya, Astel Diagnostics
- Dr. Imna Malele- Tsetse and Trypanosomiasis Research Institute, Tanga, Tanzania.

B. Study of the human immune response to *Glossina* salivary gland antigens and applications to vector control

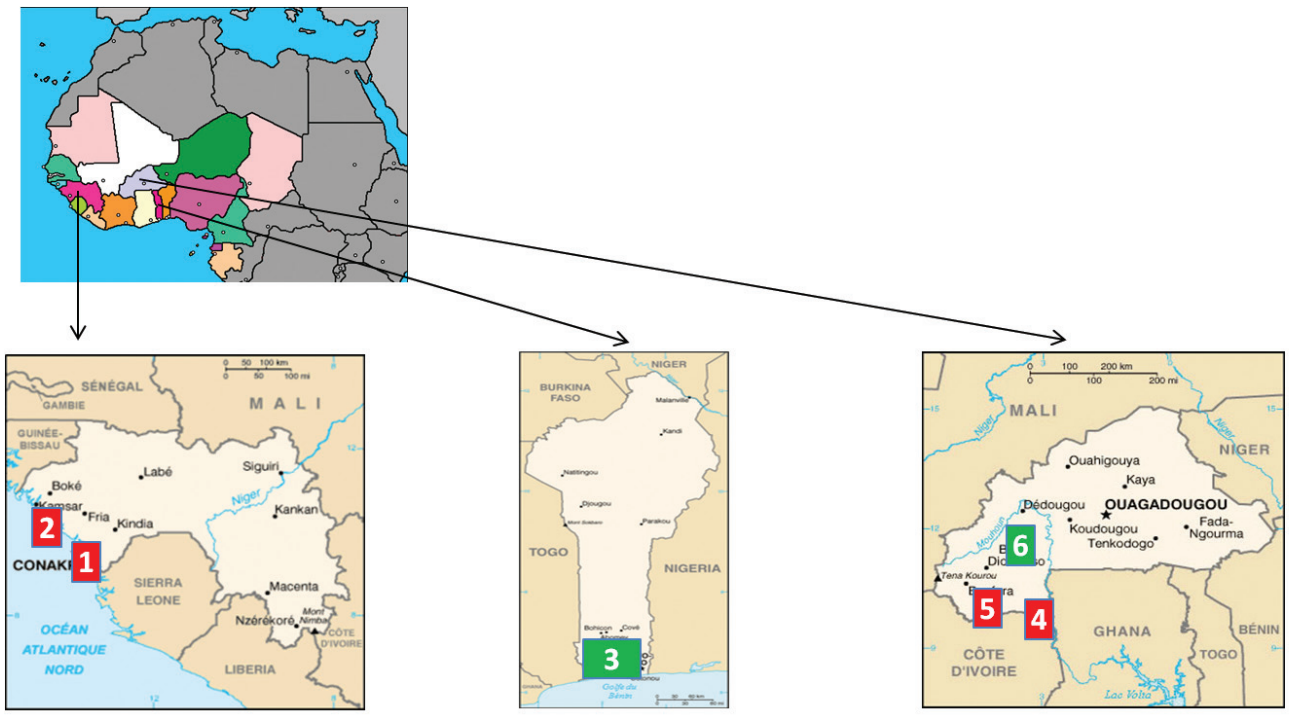
Emilie Dama, *Sylvie Cornelie, Martin Bienvenu Somda, Mamadou Camara, Zakaria Bengaly, Roger Kambire, Fabrice Courtin, Vincent Jamonneau, Philippe Solano, Anne Poinsignon, Franck Remoue, Adrien Marie Gaston Belem, Bruno Bucheton*

Summary

The saliva of tsetse flies, and of most blood-sucking arthropods, includes numerous active components whose main function is to interfere with the host's hemostatic response. Studies have shown that antibodies against certain immunogenic salivary proteins can be used as biomarkers of exposure, to provide a more accurate measure of direct man-vector contact than tsetse fly traps. The objective of this study was to (i) evaluate the total IgG response to the saliva of *Glossina palpalis gambiensis* as a biomarker of the exposure to tsetse flies, and (ii) improve the specificity of this tool through the use of specific synthetic peptides. Saliva from *Glossina palpalis gambiensis* was collected and its immune reactivity was evaluated by indirect ELISA on human plasma from active foci in Guinea and historical foci in Burkina Faso, but also on individuals who had not been exposed to tsetse flies in the town of Bobo-Dioulasso. The total anti-saliva responses were stronger in the areas infested with *Glossina*. However, specificity problems were suspected with this biomarker. An approach combining proteomics and bioinformatics helped identify potential biomarker candidates. Three specific peptides from three proteins were found in *Glossina* saliva, reacting specifically with the plasma of individuals exposed to *Glossina palpalis gambiensis* in Guinea: adenosine deaminase (ADA), Tsetse Salivary Growth Factor 1 (Tsgf1), and Antigen 5 (Ag5). The same samples, along with others from unexposed areas in the south of Benin and Bordeaux (France), were used to evaluate these potential synthetic biomarkers. The most promising results in terms of antigenicity and specificity were obtained with the synthetic peptide defined on an epitope of Tsgf1 ($Tsgf1_{18-43}$). A good correlation was observed between IgG responses to this peptide and to total saliva, as well as a significant association between strong antibody response to $Tsgf1_{18-43}$ and a high risk of being infected with *T. b. gambiense*. In conclusion, biomarkers of exposure based on the $Tsgf1_{18-43}$ peptide offer an alternative and/or additional tool to entomological approaches, providing a more effective evaluation of vector control campaigns.



Keywords: human African trypanosomiasis, Trypanosoma brucei gambiense, Glossina, saliva, biomarker of exposure, vector control, epidemiology.



Guinea Conakry
1:Forecariah
2:Dubreka/Boffa

Benin
3: South-Benin

Burkina Faso
4: Batie, 5: Loropeni, 6: Bobo

Antibodies against certain immunogenic tse-tse salivary proteins can be used as biomarkers of exposure to the trypanoma

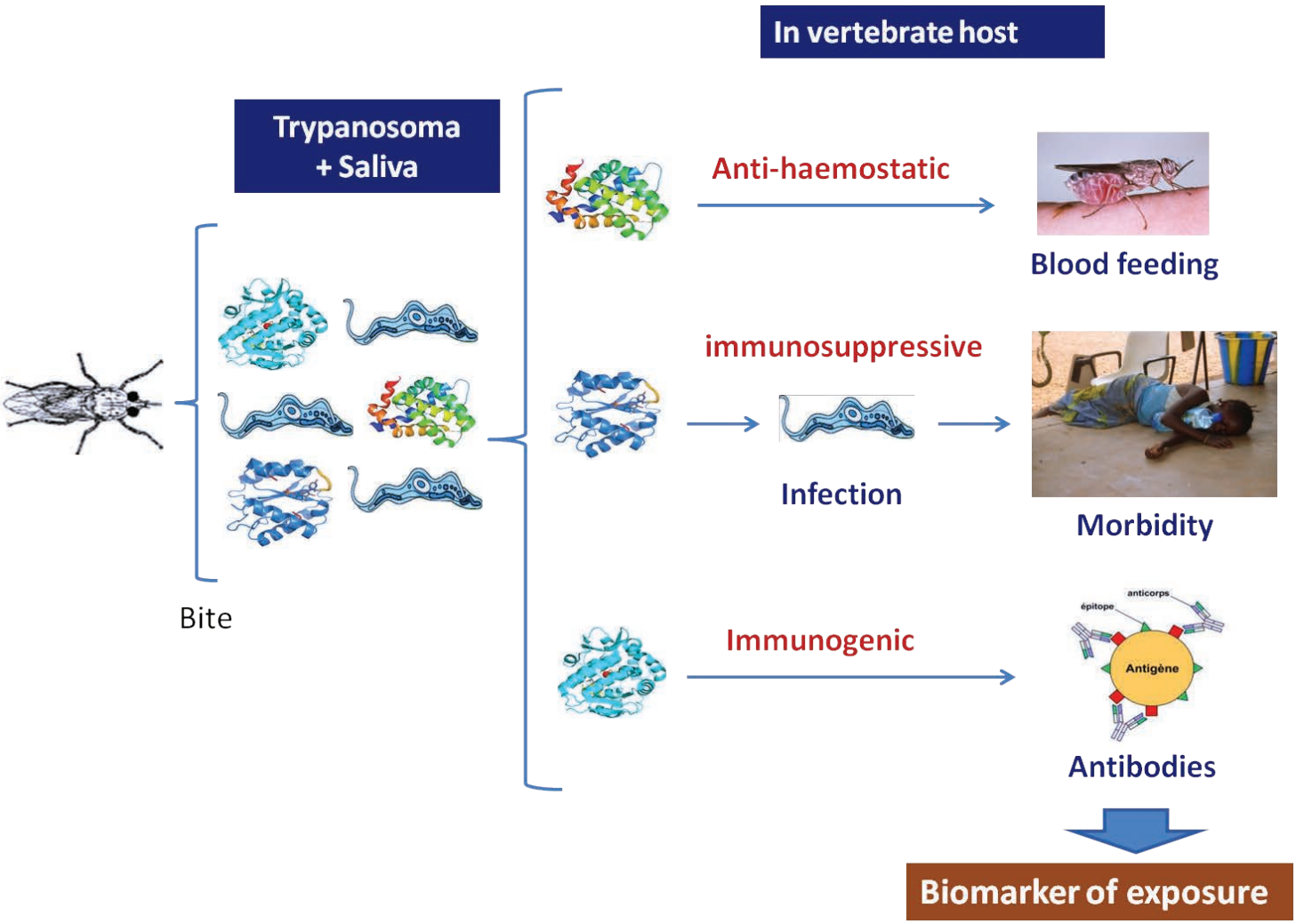


Photo 1: A technician performing the HAT LAMP test at Lwala Hospital in Uganda

Photo 2: Performing the HAT LAMP test at Makerere University in Uganda

C. Molecular test kit developed by Eiken and FIND shows great performance in diagnosis of *Trypanosoma brucei rhodesiense* sleeping sickness in Uganda

Matovu E, Ojom J, Edielu A, Kitibwa A, Bieler S and Ndungu J

Makerere University and Lwala Hospital in Uganda reported excellent performance of the Loopamp™ *Trypanosoma brucei* Detection Kit developed by FIND and Eiken Chemical in Japan to detect *T.b. rhodesiense* patients. This novel test uses the loop-mediated isothermal amplification (LAMP) technology to amplify parasite DNA with high sensitivity and specificity. The kit is supplied as dried down reagents in empty tubes that can be stored at room temperature for at least one year (Photo 1). The equipment used is simple and can be operated using solar power by technicians with no training in molecular biology.

Blood samples were obtained from human African trypanosomiasis (HAT) patients and endemic controls. After lysis with SDS, fresh samples were used to perform a LAMP assay in the field at Lwala hospital, where the equipment is operated using solar power (Photo 1). The remaining SDS treated blood was spotted on ordinary Whatman filter paper, while non-SDS treated blood was spotted on FTA cards. All of them were stored individually on silica gel at room temperature, and subsequently tested at Makerere University in Kampala by both LAMP assay and SRA PCR (Photo 2).

The sensitivity of the Loopamp™ *Trypanosoma brucei* Detection Kit when performed on fresh blood diluted 10 times and on filter papers was excellent, and the specificity was 100%. The kit was superior to SRA PCR, which missed a significant number of cases. This work has improved the prospects of one day being able to perform routine HAT diagnosis in remote endemic areas using simple field-applicable tools.

D. Uganda uses novel approaches to accelerate the control of *Trypanosoma brucei rhodesiense* human African trypanosomiasis

Matovu E, Mugasa C, Waiswa P, Kitibwa A, Boobo A, Kazibwe A and Ndungu J

Latest records indicate that the incidence of human African trypanosomiasis (HAT) continues to decline, and the WHO has included it on the list of diseases for which elimination is being pursued. A project led by Makerere University in Uganda hopes to accelerate this process by systematically screening and treating both livestock and humans. Screening is accompanied by control of the tsetse fly vector. The target is to achieve elimination of HAT by incorporating state of the art diagnostics to guide interventions that will wipe out trypanosomes from humans and domestic animal reservoirs, while at the same time reducing transmission. The project has incorporated iLED fluorescence microscopy and detection of parasite DNA using a loop-mediated isothermal amplification (LAMP) test (Loopamp™ *Trypanosoma brucei* Detection Kit) for targeted screening of people in Kaberamaido district, eastern Uganda.

Blood is collected on microscopy slides from patients with persistent malaria-like symptoms at health centres level III-IV, and sent to Lwala hospital where it is examined by LED fluorescence microscopy and LAMP test, before sending results back to the centres. Domestic animals are actively screened for

trypanosomiasis at three-month intervals. They are treated with isometamidium chloride, and insecticide pour-on is applied to control tsetse flies.

One case of HAT was detected using this approach over a 3-month period. Livestock trypanosomiasis is a serious problem in the project area (Photo 1). A significant drop in the overall prevalence of livestock trypanosomiasis was also observed at first follow-up. Furthermore, the proportion of cattle with anaemia (low packed cell volume - PCV) due to trypanosomiasis and other haemoparasitic diseases (mainly tick-borne) decreased. Blood microscopy revealed that babesiosis, anaplasmosis, and theileriosis are important contributors to low PCV in livestock in the district, thereby confirming the need to deliver a complete control package addressing the key problems affecting the livelihoods of the communities and livestock in endemic areas. This project is providing proof of concept for an innovative approach to HAT elimination.

Photo 1: Cattle in Eastern Uganda act as reservoirs of T. b. rhodesiense*, exhibiting symptoms that are similar to those observed in the human disease.*

E. Improving diagnosis of human African trypanosomiasis (HAT) around a conservation area in Malawi

Biéler S, Lemerani M, and Ndung'u J

Malawi is endemic for *Trypanosoma brucei rhodesiense* sleeping sickness or HAT, which presents in a more chronic form in this region than in eastern African countries. According to the WHO, only 22 cases of HAT were reported in Malawi in 2011. Most cases of HAT reportedly come from Kasungu, Nkhotakota, and Rumphi Districts, originating from conservation areas, and are essentially detected passively in the 2nd stage of the disease.

In 2012 and 2013, most cases came from Thunduwike and Malidade Health Centres in Mzimba North District, Bolero and Katowo Rural Hospitals, as well as from Mwazisi and Chisimuka Health Centres in Rumphi (Figure 1). Unlike the Rumphi District Hospital, which is approximately 60 km from the Vwaza Marsh Game Reserve, these health centres are located within nearby villages, closer to the Reserve. The labs, however, do not have the necessary facilities to diagnose HAT; this causes a major delay before confirmatory diagnosis can be done at Rumphi District Hospital.

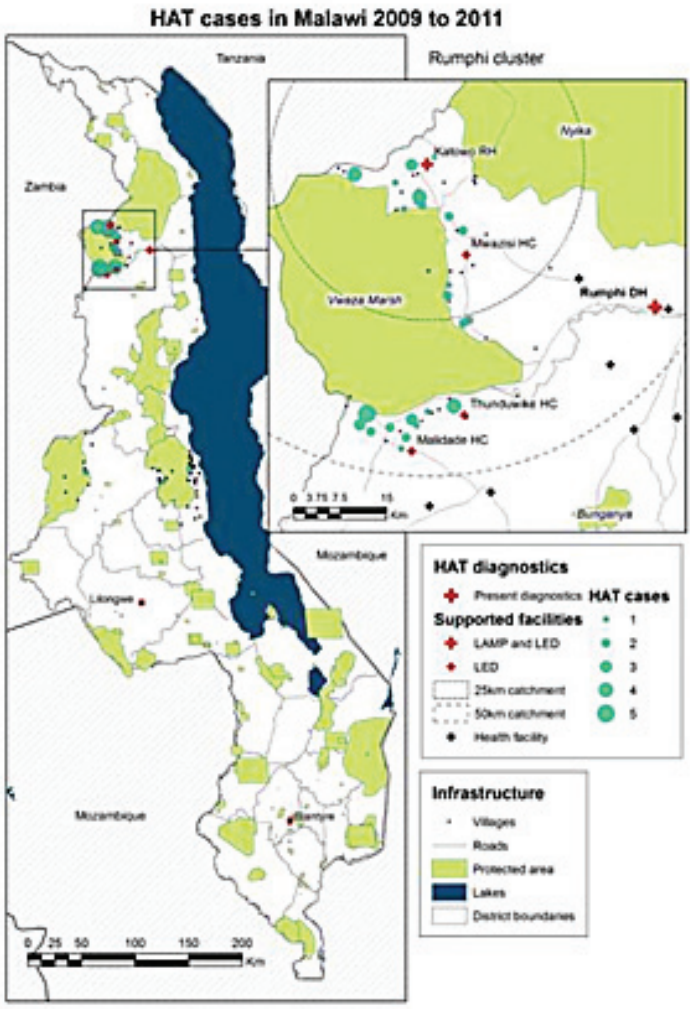


Figure 1: *Map of Malawi, showing the location of the Vwaza Marsh Game Reserve, including adjacent health centres (boxed). Diagnosis and treatment of HAT cases is currently done at the Rumphi District Hospital, about 60 km away from the reserve.*

The Ministry of Health of Malawi, with support from FIND, is strengthening the capacity of health centres around the Vwaza Marsh Game Reserve to detect HAT cases by providing novel diagnostic tests and appropriate training. This will reduce the delay between infection and confirmatory diagnosis, thereby increasing the chances of detecting early-stage HAT, when treatment is safer and more effective. It will also reduce the burden on patients in terms of time and costs of travelling to and from Rumphi District Hospital for diagnostic services. The project will complement other projects planned by the government of Malawi, focusing on the livestock reservoir and the tsetse fly vector in support of the PATTEC initiative.

FIND and its partners have developed new tests to screen communities for HAT, to confirm the disease, and to stage cases before treatment. Among the new tests is a robust LED fluorescence microscope developed by FIND and Carl Zeiss GmbH that can be used for both bright field and fluorescence imaging. The microscope does not require a dark room and can be operated using solar power. The sensitivity of parasite detection with this microscope is greatly improved when blood samples are stained with acridine orange and examined using fluorescent light. The microscope was approved for routine use by the Ministry of Health of the Democratic Republic of the Congo (DRC) in December 2012. In addition to the DRC, it has been introduced in 13 sites in north-western and central Uganda and Nigeria. Another diagnostic tool is a simple molecular method known as LAMP test, that detects parasite DNA in blood samples and was developed by FIND and Eiken Chemical, Japan. The Loopamp™ *Trypanosoma brucei* Detection Kit, which has been evaluated at multiple sites in the DRC and Uganda, can be used in a simple laboratory by technicians who have no training in molecular biology. Individuals who are found positive by this method are considered to be strong suspects, and have to undergo parasitological confirmation. The LAMP equipment can also be operated using solar energy, with blood samples that are dried and stored on filter paper.

Finally, the Ministry of Health of Malawi and FIND are introducing HAT diagnostic services around the Vwaza Marsh Game Reserve by providing equipment for routine and LED fluorescence microscopy, and LAMP tests. Patients who are suspected of HAT at Mwazisi, Thunduwike and Malidade health centres will be tested by microhematocrit centrifugation test (CTC) and LED fluorescence microscopy. If they are found negative, a blood sample will be dried on a filter paper and transported by motorcycle to Katowo Diagnostic Centre, where the LAMP test will be performed. If this is found positive, the patient will be referred to Rumphi District Hospital for parasitological confirmation, staging and treatment.
The project includes refurbishing health facilities and equipping them to diagnose HAT and other diseases prevalent in the area, as well as training laboratory personnel on LED fluorescence microscopy and LAMP test, both locally and at Makerere University.

F. Two rapid tests to screen for sleeping sickness are now commercially available

1. SD BIOLINE HAT developed by FIND, ITM Antwerp, and Standard Diagnostics

On 6 September 2013, FIND, the Institute of Tropical Medicine (ITM) in Antwerp, Belgium, and Standard Diagnostics, Inc. (SD) of the Republic of Korea announced that a rapid test to screen for human African trypanosomiasis (HAT) is now available for upscaled roll-out. The test was launched in December 2012 in Kinshasa, Democratic Republic of the Congo (DRC), after study results showed that it had the potential to dramatically change the management of this disease.

The announcement was made following the signature of an agreement among the three partners, under which ITM is producing and supplying parasite antigens that are being used by SD to manufacture and roll out the rapid test, in collaboration with FIND and other stakeholders. This is exciting news for people at risk of the disease and is an important step in the roll-out of this diagnostic tool. The new test, named SD BIOLINE HAT, is an immunochromatographic rapid test that detects antibodies against *Trypanosoma brucei gambiense*, the parasite responsible for more

than 90% of sleeping sickness cases. It is cheap (US$ 0.50 per test), very simple to use, and can be performed by health workers with minimal training, using fresh blood from a finger prick. Results are obtained after only 15 minutes. Individuals who are found positive by this test will have to be confirmed as sleeping sickness cases by other methods. Yet this test is unlike any screening tool in use today, as it is stored at ambient temperature (up to 25 months at 40°C) and does not require specialized equipment or electricity, which means that it can be used in very remote settings where most of the infected people are found.

The SD BIOLINE HAT test can be ordered from Standard Diagnostics (sales@standardia.com) for a price of US$ 0.50 per test. It is also available as a kit containing 25 tests, including accessories (alcohol pads, lancets, plastic capillary pipettes and assay diluent).

Development of the rapid test for sleeping sickness has been a joint effort of FIND, ITM, MicroCoat Biotechnologie GmbH (Germany), the International Livestock Research Institute (Kenya), the Institute of Tropical Neurology (France), Médecins sans Frontières (Spain), the DRC National HAT Control Programme (PNLTHA, DRC), the Central African Institute of Agronomical Research (ICRA, Central African Republic), the World Health Organization and SD. This work is supported mainly by the Bill & Melinda Gates Foundation, the Department for International Development (DFID) of the United Kingdom, and various Belgian authorities.

2. Test developed by ITM Antwerp, INRB Kinshasa, and Coris BioConcept

This article has been forwarded by the following authors: For ITM Antwerp: Philippe Büscher and Marleen Boelaert; for INRB Kinshasa: Dieudonné Mumba and Pati Pyana; for Coris BioConcept: Pascal Mertens, Quentin Gilleman, and Thierry Leclipteux.

By the end of the 20th century, gambiense HAT was ravaging several west and central African countries. Thanks to the activities of national HAT control programmes, bilateral cooperation agencies, non-governmental organizations, and the Word Health Organization (WHO), less than 10,000 new cases were reported in 2012. Today, it is considered possible to eliminate HAT as a public health problem. As a consequence of the steadily decreasing prevalence of HAT, budgets for active screening of the population at risk are being reduced, and the role of the primary healthcare centres in HAT patient management as well as in HAT surveillance becomes more prominent. However, the diagnostic tools should be adapted, and the development of a highly specific individual rapid diagnostic test (RDT) that is stable at ambient temperature and that can be performed after minimal training, is considered a research priority. Recently, two novel rapid diagnostic tests (RDTs) for *gambiense* sleeping sickness, called HAT Sero-Strip and HAT Sero-K-SeT have been co-developed by Coris BioConcept, a Belgian medium-size company specialised in developing and producing diagnostic tests, and the Institute of Tropical Medicine of Antwerp. Both tests were designed to be performed on plasma as well as on whole blood with the target antigens, a mixture of *T.b. gambiense* variant surface glycoproteins LiTat 1.3 and LiTat 1.5.

The first evaluation of the new RDTs, carried out on plasma and reconstituted blood of *gambiense* HAT patients and endemic controls, demonstrated the diagnostic potential of both RDT formats in comparison with immune trypanolysis. Subsequently, a diagnostic accuracy study was designed as a Phase II or case-control study on clinical samples from well characterized cases and endemic controls in the Democratic Republic of the Congo (DRC), in comparison with an existing antibody detection test used in routine screening (CATT whole blood) and a sophisticated antibody assay used in reference laboratories (immune trypanolysis). The study was conducted on approximately 500 samples in Bandundu Province, where a 0.18% prevalence was reported amongst 606,968 persons examined during active screening. Also in this study, trypanolysis was used as the reference test for specific antibodies against *T.b. gambiense* VAT LiTat 1.3 and LiTat 1.5. This study confirmed the excellent diagnostic potential of the HAT Sero-K-SeT. A manuscript on the obtained results is being submitted for publication.

HAT Sero-Strip and HAT Sero-K-SeT are commercially available worldwide in a strip or a cassette format, with or without added sampling material.

Orders and pricings are available by sending an email to: sales@corisbio.com

The test and the present study were supported by the NIDIAG network (Collaborative Project) of the European Commission in the 7th Framework Programme.

This test has been reported in a letter recently published: Büscher P, Gilleman Q, and Lejon V. (2013) Rapid Diagnostic Test for Sleeping Sickness N Engl J Med 368;11. doi: 10.1056/nejmc1210373

G. SCYX-7158 (AN5568): CNS Exposure Predicted from First-in-Human Clinical Studies Indicates a Single Oral Dose Treatment is Possible for Sterile Cures of Stage 2 Human African Trypanosomiasis POSTER (#LB-2117)

Stephen Wring,1 Eric Gaukel,1 Robert Jacobs,2 Sanjay Chanda,2 Virginie Gualano,3 Eric Evène,3 Yves Donazzolo,4 Mathilde Latreille,4 Robert Don,5 Charles Mowbray,5 Antoine Tarral5

Affiliations:
1. Scynexis Inc, Research Triangle Park, NC, USA
2. Anacor Pharmaceuticals Inc, Palo Alto, CA, USA
3. PhinC Development, Evry, France
4. Eurofins Optimed, Gières, France
5. DNDi, Geneva, Switzerland

Abstract:
SCYX-7158 (AN5568), an orally bioavailable benzoxaborole for the treatment of stage 2 (CNS) Human African Trypanosomiasis (HAT), is currently progressing through first-in-human single ascending dose studies in healthy subjects.
The purpose of this interim sub-analysis of plasma SCYX-7158 concentration data following single oral doses (20, 40, 80, 120, 160, 200 mg) is to estimate the likely therapeutic dose required for sterile cures following a single dose treatment, based on maintenance of a target free drug exposure in CNS tissue.

In humans, SCYX-7158 was well-tolerated and demonstrated excellent dose dependent exposure in plasma. The geometric mean value for half-life across all completed treatment groups is 325 hr / 13.5 days (range, 259-402 hr / 10.8-16.8 days) - consistent with a single dose treatment.

A single dose regimen is desirable to mitigate treatment failures from potential poor compliance with multi-day therapy. The efficacy target for free drug exposure in brain tissue is a CNS AUCu0-24hr of 5.8 μg.hr/mL for >5 days, as determined by in vitro time-kill and reversibility studies with T. b. brucei, and efficacy studies in a murine model of stage 2 HAT. Values for CNS AUCu0-24hr were calculated from the human concentration versus time data for SCYX-7158 in plasma, using the in vitro ratio of binding to human plasma proteins (concentration dependent fu 1.3-3.0% for 1-10 μg/mL SCYX-7158) and cynomolgus monkey brain tissue (fu 6.4% for 0.5-10 μg/mL SCYX-7158) in conjunction with free plasma/brain ratio from efficacious doses in murine studies.

Predicted CNS AUCu0-24hr on the first day of treatment increased proportionally with dose, and exceeded the target exposure following a single 160 mg dose (CNS AUCu0-24hr 6.5 μg.hr/mL). Following a 200 mg dose, the predicted CNS AUCu0-24hr exceeded the target on a daily basis for 3 days, and for 5 days based on average CNS AUCu0-24hr measured over 120 hr. The predicted single dose required to exceed the target CNS AUCu0-24hr on a daily basis for ≥5 days is ~280 mg.

H. Evaluation of rapid diagnostic tests (RDTs) combined with clinical and laboratory predictors for the diagnosis of tropical neglected diseases in patients with persistent fever (>1 week) in Cambodia, Nepal, DRC and Sudan

NIDIAG (IMT.A)

Since antiquity, fever has been a major diagnostic problem. Nowadays, despite the availability of good diagnostic capacities, undifferentiated febrile illness is still a challenge for physicians. In developing countries, shortage in qualified staff and lack of adequate laboratory equipment complicate the differential diagnosis of febrile illness.
Consequently, clinicians often base their diagnosis and treatment on empirical approaches relying on the syndrome, which may result in over- or under-estimation of the frequency of certain diseases.
Tropical neglected diseases contribute largely to the burden of febrile syndromes persisting for more than a week. Even though they have a major impact on mortality and morbidity rates in tropical areas, they are rarely diagnosed in primary healthcare centres.
The objective of this multicentre study is to improve the diagnosis of tropical neglected diseases. It started in April 2013 and is expected to last 18 months. The study's inclusion criteria is a fever lasting longer than a week in patients aged 5 years or over.

I. Fexinidazole

In our previous newsletter (n°13), we announced DNDi's commitment to open four new study sites to increase the rhythm of inclusions. Three new sites have been opened in Mushie in the Province of Bandundu, Katanda in the Province of East Kasai, and Isangi in the Eastern Province, and all are functional to the same standards as the first five sites. At the end of December 2013, 207 patients have been included in the 9 study sites.

Obituary

Dr Augustin Kadima Ebeja

Dr ALLELUIA MUWANGA TEBE, died on 28 September 2013 at the age 41, in Vanga, DRC.

It is in difficult times that we know who are true friends are. Among the many expressions of sympathy we received, I would like to share with you the spontaneous message from Dr Didier Kalemwa.

« I last saw Dr Alleluia during my monitoring visit with Stefan at the beginning of September 2013. Although he was supposed to be on sick leave at home, Dr Alleluia was present at both our meetings at the beginning and the end of the monitoring visit. He still bore his habitual smile, although it was slightly weaker due to his illness. I remember our conversation when I told him he should leave Vanga for a while once his treatment was finished. But he said that he could not leave because his wife was due to give birth very soon. He was so keen to see his newborn child but now he will never see her. Death, unfair, undiscerning death struck this young couple. Death took away a husband and a father. I was so sure Dr Alleluia would recover his health and resume his activities in the hospital and within the Fexi team. The news struck us all like a thunderbolt in a clear sky during our initiation session in Mushie. It was such a shock to us all. The Fexi team in Vanga has lost a Co-Investigator who loved his job and carried out his duties with unfailing efficiency. Dr Alleluia was the real right hand man of the Investigator.

May the death of Dr Alleluia be the occasion for all in the Fexi Team, in Vanga and elsewhere, to strive even harder to excel at all times as Dr Alleluia excelled at his work. I shall always remember him as a brilliant researcher with a huge heart. I would like to offer my condolences to the Vanga health centre, the Fexi Team in Vanga and the whole Fexi family, and may God help them carry on with the study. I would also like to extend my deepest condolences to Dr Alleluia's widow, and may God bring her strength and solace.»

Welcome to our new members

Dr Lucia WILLIAM KUR, BDS, Msc
Department of NTDs
Directorate of Preventive Health Services
Ministry of Health-RSS
Juba, South Sudan

My name is Dr Lucia William Kur Chol. I am currently working as Director of Neglected Tropical Diseases at the Ministry of Health, Republic of South Sudan. I am a specialist in applied/field epidemiology and fond of research work. I am skilled in programme management, including planning, budgeting, implementation, and monitoring and evaluation. I have worked in health and nutrition programme management with UNICEF, the WHO, and the Ministry of Health in South Sudan for 12 years. I have been managing the onchocerciasis and trachoma control programmes in South Sudan since 2007, and I also managed the South Sudan eye-care services from 2010 to 2013.

Dr Pierre-Marie DOUZIMA
Coordinator of the national
HAT control programme (PNLTHA)
Ministryof PublicHealth,
Population and AIDS
Control Bangui, CAR

Prior to his current appointment, Dr Pierre-Marie Douzima worked for several years as an expert in monitoring & evaluation for the Sexually Transmitted Infections, AIDS and Tuberculosis Control Programme.

We are also happy to announce the arrival of four newcomers into the world, four babies born to families of physicians working in the Provinces of Bandundu, Kasai and Oriental Province. We wish to thank God in particular for the birth of Allege, the little daughter of the late Dr Alleluia.

1. **Allege Muwanga**, born on 14 October 2013 in Vanga
   Father: The late Dr Muwanga Alleluia
   Mother: Gertruide Benatsuna

2. **Clément Nyembua**, born on 13 December 2013
   Father: Léwis Kaninda
   Mother: Francine Ciasa

3. **François Botalema**, born on 02 December 2013 in Isangi
   Father: Franck Botalema
   Mother: RachelleNgalia

4. **Bénédicte Jeannette Ntumba**, born on 09 December 2013
   Father: Mélchias Mukendi
   Mother: GiseleNkankolongo

5. **Joyeuse Nganzobo**, born on 27 November 2013 in Bandudu ville
   Father: Pathou Nganzobo
   Mother: Bibiche Mvuntha

ABOUT THE TSETSE FLY

Extract from the PATTEC course on
« Tsetse Flies & Trypanosomiasis »

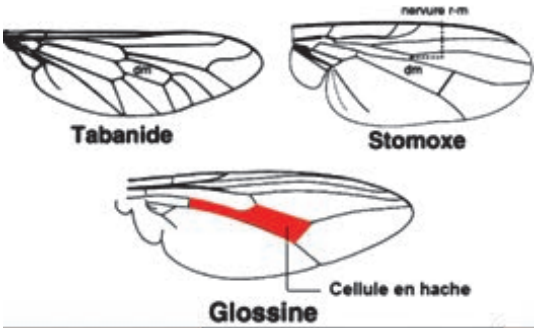
DESCRIPTION

Glossina, commonly known as tsetse fly, is an insect of the Diptera order (one pair of wings) brown or dark coloured, with a long slender silhouette. Its length (without the proboscis) ranges from 6 to 16 mm depending on the species, and its mouthparts, or proboscis, lie horizontally pointing forward.

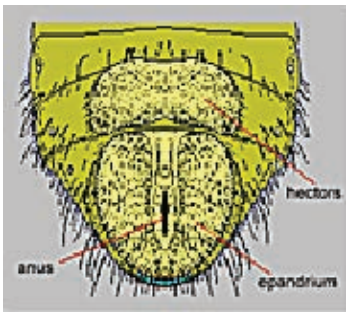
The colour of tsetse flies varies from one species to another from a dull dark grey to light brown. Tsetse flies are never metallic in colour. They are easily recognisable at rest, with the two wings lying one on top of the other over the back of the abdomen (instead of resting at an angle with the body), like scissor blades.

Tsetse fly at rest© Robert

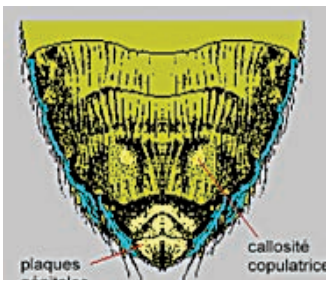
- The head is very characteristic. In addition to compound eyes, a proboscis (maxillary palps, labium, labrum and hypopharynx) and antennas, it has a thin line between the two eyes called the ptilinal suture.
- The thorax carries one pair of wings, three pairs of legs and one pair of halters.
- Tsetse wings are very characteristic: the central cell, shaped like a meat cleaver or hatchet, is used to identify the genus *Glossina*, and particularly to distinguish them from the family of *tabanidae* and the genus *Stomoxys*. The wing cells in tsetse flies form a characteristic pattern:
  - Vein 1 is very long.
  - Veins 2 and 3 are very close together throughout their length.
  - Vein 4 has a strongly curved basal part, before it meets with the anterior cross vein. This causes the cell (area of wing enclosed by veins) immediately after vein 4 to take on a peculiar shape; it is known as the 'hatchet' cell.
  - With its clearly homologous veins and intersections, tsetse wings provide morphometric data with multiple applications: taxonomy, gene flow study, and identification of isolated populations for vector control (Solano et al., 2010a; Kaba et al., 2012).



Characteristic venation of tsetse wing (hatchet cell)



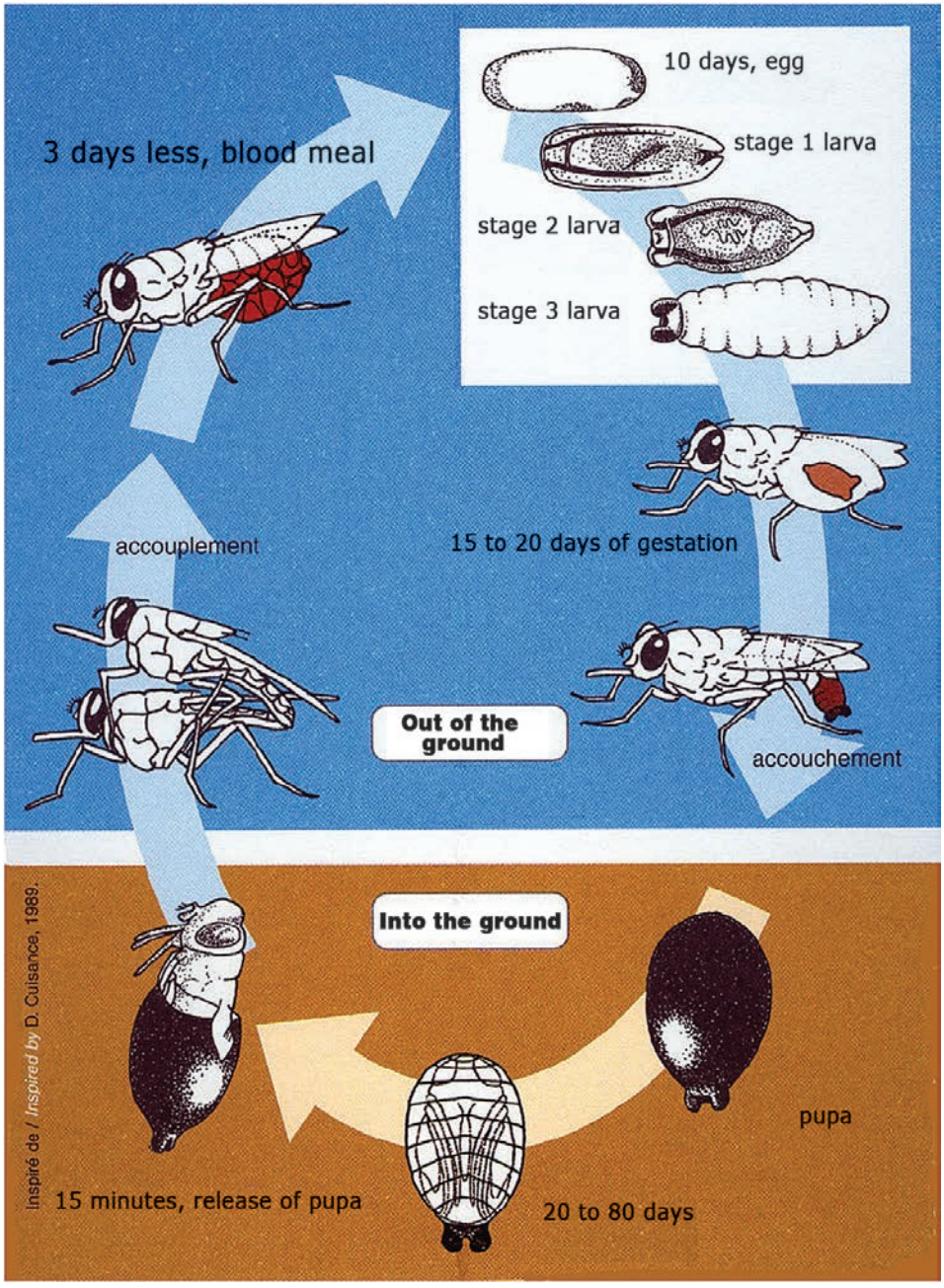
Abdominal extremity (ventral view) in male *Glossina*



Abdominal extremity (ventral view) in female *Glossina*

Genital structures are used for the classification of species and subspecies.

The external genitalia is found at the posterior end of the abdomen. Male genitalia includes a rounded structure called hypopygium (at rest, the mating organs are folded twice to fit against the inside of the seventh abdominal segment), whereas female genitalia is limited to plates located at the tip of the seventh visible segment.



In Launois et al., 2004

Reproductive cycle of the tsetse fly

Bioecology

Glossina of both sexes suck blood. Their mode of reproduction is specific: females are fertilized only once in their lifetime, and produce eggs which hatch into larvae inside their body. After approximately 10 days of gestation, the fully-grown stage-3 larva (L3) is expelled by the female and dropped in a shady area. The larva is mobile and buries into the ground where it will turn into a pupa; its tegument becomes opaque and hard and it changes to a dark brown colour.

The duration of the pupal stage varies according to the soil's temperature and humidity, as well as the species and sex. The young adult fly emerges from the puparium through a circular outlet. Its cuticle becomes chitinous and it is then able to fly and look for a host and its first blood meal. From the time the fly emerges to the taking of its first meal, the young fly is called a teneral fly.

It is during this period that the fly is most receptive to infection by *Trypanosoma sp*. if it feeds on an infected host. Mating also occurs in the first few hours following its emergence. The first ovulation occurs between day 18 and day 20. Larviposition occurs thereafter at regular intervals, approximately every 10 days.

The reproduction rate of *Glossina* is relatively low compared to other Diptera.

The life span of *Glossina* varies depending on species, habitat and season. It is optimum in the rainy season. Breeding sites are generally areas where females go to rest during daytime, mostly shady and sufficiently humid to allow for pupal emergence. There are four determining factors for tsetse survival: heat (temperature between 25° and 30°), humidity, shade and food. However, each species also has its own specific requirements.

Tsetse flies spend most of their time resting in humid and dark areas, for digestion or gestation. Their normal flight goes backwards and forwards, interspersed with pauses, over a limited area and for short periods, i.e. 5 to 30 minutes per day. Tsetse flies travel on a straight line over a distance which rarely exceeds 300 metres, with maximum dispersion during the rainy season and minimal dispersion during the dry season when all stay in sites which are still humid. They can also disperse passively by following the movements of herds and/or vehicles. This dispersion capacity explains the reinvasion of treated areas and dissemination of trypanosomes.

THE VOICE OF HAT HEALTHCARE WORKERS

A ENRICHING EXPERIENCE OF PEER SUPPORT

Based on the report from the Bandundu team in charge of the support MISSION, and which included the principal investigator Dr. NGANZOBO Pathou, the head nurse YULU Jean-Pierre, and the laboratory technician MUKANKEN Antho.

DNDi decided to open new sites for its multicentre clinical trial project DNDiFEX004, including one in Mushie, and to designate a support team to help the new sites. The Bandundu team was chosen for this role, due to its experience of over one year since the actual launch of their activities, i.e. since the beginning of the inclusions.

The mission benefited from the technical and logistical support of PNLTHA north coordination (Dr Florent Mbo and Martin Mulunda).

The main objective was to ensure the successful launch of inclusions at the Mushie site, and specific targets were identified for the three main categories of actors:

Investigators

- Review the Investigator File, explain the importance of each one of its sections, and how to maintain it properly
- Learn to interact with the various study stakeholders to solve problems (cardiabase, Cardinal system, IT DNDi, project coordination, etc.), while ensuring that the sponsor remains blinded to the study data
- Helping (but not replacing) the site investigators with every aspects of the procedures, from informed consent to treatment initiation, ECGs and other tests
- Helping the site investigators with the daily management of patients included in the study:
  - Daily evaluation of hospitalised patients
  - Active detection of adverse events

- Adverse event reporting
- Handling of serious adverse events, if any
- Preparation of patient follow-up

- Review of stock management, especially of sensitive inputs, such as finances, drugs, Piccolo discs, etc.
- Promote social peace and open collaboration with all the personnel involved in the study.

Laboratory technicians

- Review the laboratory procedures relevant to the study
- Ensure that the equipment has been properly set up/ configured (Piccolo, microscope, centrifuge, etc.)
- Draw the team's attention to the correct maintenance of source documents
- Help the team with the various tests
- Draw the team's attention to the management of sensitive inputs and temperature taking
- Universal standard precautions and different aspects of waste management
- Compliance with biosafety measures
- Compliance with the HAT diagnosis tree as directed in the study protocol

Nurses

- Review of the study procedures (flow chart)
- Help the team with the study's daily activities
- Help the team with the management of study drugs, and filling-in of the various *ad hoc* documents
- Draw the team's attention to the importance of reporting any event observed in patients
- Universal standard precautions and different aspects of waste management.

After 13 days spent working together, the supporting team declared that "Overall, the new team members had, each in their own field, the required knowledge, perquisites and skills to help our support mission, i.e. willingness to learn, availability, patience, sacrifice, assiduity and enthusiasm".

The teams worked together and under the supervision of the investigators, showing a spirit of cooperation, respect and readiness to listen in an atmosphere of mutual trust and confidence. Each point mentioned in "the terms of reference" was reviewed, discussed and clarified for everyone, and practical exercises were done to reinforce learning.

From a logistics point of view, equipment and infrastructures were verified on site. Missing items were notified to the logistician of the DNDi project Coordination and to the site's principal investigator, who found the appropriate solutions.
From a technical point of view, identified deficiencies were corrected and mentioned for a special follow-up by the local investigator and team of supervisors.

To conclude, the support team declared that "Overall, we believe we have reached our objectives as defined in the reference manual and described above. We thank warmly the investigator and his whole team for having made our stay so easy and enjoyable, in spite of the amount of work to be done, the pressure and overlapping activities. We believe that the site is now ready for the DNDiFEX004 adventure."

RECENT HAT PUBLICATIONS

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11. *Büscher P, Gilleman Q, and Lejon V. (2013) Rapid Diagnostic Test for Sleeping Sickness N Engl J Med 368;11. doi: 10.1056/nejmc1210373*

12. WHO (2013) Control and Surveillance of Human African trypanosomiasis WHO Technical Report Series (TRS 984). Un comité d'experts réunis par l'OMS du 22 au 26 Avril 2013 a finalisé le "livre bleu", récemment publié en anglais et disponible sur : http://apps.who.int/iris/bitstream/10665/95732/1/9789241209847_eng.pdf Ce manuel très complet remplace le rapport produit lors d'une réunion en 1995. La prise en charge de la THA a beaucoup évolué depuis, notamment grâce à l'apparition de nouveaux outils diagnostiques et thérapeutiques, à l'engagement des pays à éliminer la maladie, et à la mise au point d'approches individualisées en fonction de la prévalence locale de la maladie.

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