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EANETT/HAT PLATFORM

JOINT SCIENTIFIC MEETING IN

KINSH/AS/A

From 17 to 19 september 2014, Kinshasa, DRC

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Democratic Republic of the Congo

Calendar of 2015 scientific events

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Editorial

s promised in our previous Newsletter $(N^{\circ}15)$, we bring to you this time a special issue on the scientific event of 2014 for our HAT Platform, organised jointly with EANETT.

As we cannot give a full account here, we present some of the highlights of this vast forum promoting exchanges and mutual enrichment.

The many parallel meetings, unofficial discussions and few late nights in Kin by night boosted our objective of sleeping sickness elimination.

The event was attended by over 160 participants from 22



Dr Augustin Kadima Ebeja ; Coordinateur Plateforme THA

countries, including 16 HAT endemic countries, and a large number of scientific partners and

This issue is also special because it gives us the opportunity to thank all our partners who support us and help the development of our HAT Platform.

Special also because it is the last time I shall act

as the editor of this Newsletter, as I have been called to other responsibilities. I pass on the torch and wish long life to the HAT Platform, and particularly to this Newsletter, which is a highly appreciated communication tool.

Happy reading.

2. Extract of the opening speech of the Minister of Public Health of the Democratic Republic of the Congo



Directeur Malaba Le représentant du Ministre de la Santé Publique.

llow us first of all to express, on behalf of the President of the Democratic Republic of the Congo, his Excellency Mr Joseph Kabila Kabange, our gratitude as well as that of the Congolese people to the organisers of this scientific meeting.

We wish to thank the entire scientific community member of EANETT (Eastern Africa Network for Trypanosomiasis) and of the Human African Trypanosomiasis Platform for having chosen the city of Kinshasa, and more specifically the wonderful setting of Hôtel Béatrice, to host the 3rd EANETT/HAT Platform joint meeting. We wish a warm welcome to Kinshasa to all the participants from Africa and elsewhere. [....]

Dr Constantin Miaka Mia Bilenge, Honorary General Secretary of the Ministry of Public Health, and Dr Victor Kande Betu Kumeso, former Director of the National HAT Control Program, played a decisive role in the creation of the HAT Platform.

We would like to ask you to observe a minute's silence in memory of the Honourable Miaka Mia Bilenge, a monument in the history of sleeping sickness in the DRC.

Following the success of NECT (Nifurtimox-Eflornithine Combination Therapy), now included in the WHO Essential Medicines list for the treatment of stage 2 HAT, the HAT Platform is focusing mainly on finding solutions to the administrative and regulatory challenges, and on strengthening the capacities of clinical studies on HAT diagnosis and treatment

Over 600 people have been trained in various fields of clinical research (Good Clinical & Laboratory Practice, Ethics in Research, Pharmacovigilance, etc.); hospitals and laboratories have been renovated and fitted with state-of-theart equipment; and the list goes on. The HAT Platform is also involved in sharing information and strengthening the links between endemic countries.

In the Democratic Republic of the Congo, trypanosomiasis is still a major public health issue. Over the past five years, 253 out of the 515 health zones reported at least one case of THA. Based on WHO estimations, approximately 30 million inhabitants (almost half the DRC population) live in former trypanosomiasis foci and are exposed to the risk of infection.

In 2013, over 5,000 new cases of sleeping sickness were reported in the DRC. The population coverage ranges between 15% and 20%. Consequently, the current number of individuals already infected is probably about five times higher, and in the absence of effective control measures on a sufficient scale, transmission may rise considerably in the near future, and thus hinder the elimination objective advocated by the WHO.

In terms of HAT control, significant results were achieved in endemic areas of the provinces of Equateur and Lower Congo, where the prevalence is currently the lowest in the country. However, special attention should be given to new endemic areas currently not or inadequately covered, such as Province Orientale.

The National HAT Control Programme (PNLTHA) is responsible for organising the control of sleeping sickness throughout the country, as well as for HAT research. For many years, PNLTHA has been involved in clinical, entomological and diagnostic studies.

Thanks to this commitment, PNLTHA contributed to the latest progress which led to the inclusion of NECT onto the WHO Essential medicines List, and the adoption of the Rapid Diagnostic Test SD Bioline for human African trypanosomiasis screening. PNLTHA is currently participating in the studies on fexinidazole as oral treatment for stage 2 HAT, as well as in the evaluation of the LAMP test to screen and confirm HAT.

Since the objective announced by the London Declaration on Neglected Tropical Diseases in January 2012 and that expressed by the WHO to eliminate certain neglected diseased by 2020, numerous breakthroughs have been especially where human observed. African trypanosomiasis is concerned. In this context, both organisations considered it necessary to share these results and make them available to the control programmes and those in charge of their implementation, so they could be included in their disease control strategies.

In 2014, the meeting was held in Kinshasa, capital city of the Democratic Republic of the Congo (DRC).

We hope that the 3rd EANETT/HAT Platform joint meeting will take place in a spirit of constructive dialogue.

During this meeting, we will review the progress recorded in terms of knowledge and research on human African trypanosomiasis. We will certainly issue recommendations on new lines of research to hasten the elimination of sleeping sickness.

We are convinced that the results will be sufficiently shared among the scientific community so as to help direct research on HAT.

For our part, we guarantee that the Ministry of Public Health shall spare no effort to implement the conclusions drawn from the present meeting.

We would like to finish by wishing you all a wonderful stay in Kinshasa. Don't forget to pay a visit to the city's tourist areas, by day or by night.

Thank you.



3. Keynote address - WHO Strategy for Elimination of HAT: A Situational Overview by José Ramón Franco Minguell



Introduction

y 2009, the number of reported new cases of human African trypanosomiasis (HAT) had fallen below 10,000, then down to 7,216 in 2012 and to 6,314 in 2013, with an estimated number of infections of around 20,000. Currently, gambiense HAT (g-HAT) cases represent 98% of all HAT cases, rhodesiense HAT (r-HAT) accounting for the remaining 2%. Recent trends in new HAT cases are promising, but figures should be interpreted with care as the disease occurs mainly in remote rural areas where health infrastructures are weak.

Cases are not always recognized, which results in significant under-detection and under-reporting.

An estimated 70 million people live at different levels of risk of HAT infection. Of those, 57 million (81%) are at risk of g-HAT, and this population is distributed over an area of approximately 1.38 million km² in 14 of the 24 g-HAT endemic countries. Over

2 million people live in areas classified as high to very high risk of g-HAT.

Research and development play an important role in the elimination of HAT, to cross roadblocks, fill research gaps and introduce needed tools. The main challenges that need to be overcome to eliminate HAT include:

- Knowledge gaps on the geographical distribution of the disease (grey areas), mainly in old foci lacking appropriate surveillance, and in regions with difficult accessibility or affected by security constraints. The epidemiological situation in these areas needs to be clarified. Adapted and adequate sensitive tools will help assess these areas and fill the mapping gaps.
- The epidemiological role of asymptomatic, seropositive human carriers with undetectable parasitaemia. The

occurrence of seropositive aparasitaemic human cases and healthy carriers is well described, and these people could play a role in the persistence of disease transmission. Further studies are needed to clarify their epidemiological significance, and to develop appropriate strategies for their management.

- The epidemiological role of animals as reservoir of gambiense HAT. The presence of T.b. gambiense in animals has been widely described. The role they could play as reservoirs maintaining the transmission of gambiense HAT needs to be elucidated.
- Under-detection and under-reporting: gambiense HAT is a rural disease, occurring in remote areas not always easily accessible. Under-detection and under-reporting are a reality, and they have been estimated in different ways. Additional indicators and modelling tools to estimate the location and abundance of undetected cases must be developed.
- The risk of reintroducing the infection after elimination of a focus. There is a risk of reintroducing HAT after its elimination, and therefore surveillance activities must be maintained even after HAT has been eliminated from a focus. Studies on the risk factors of HAT reintroduction are encouraged, to ensure sustainable elimination.
- The integration of control and surveillance into existing health systems.
- Low attendance rates at healthcare facilities, lack of preparedness of staff and sometimes staff overloading in gambiense HAT endemic areas. Operational research is needed to improve the integration of control and surveillance of gambiense HAT into the existing healthcare systems.
- The lack of skills of healthcare staff on gambiense HAT control and surveillance. Experienced and committed staff presently involved in HAT control and surveillance is progressively retiring, and prospects for appropriate replacement are limited. Approaches to engage a new generation of health staff on HAT control need to be implemented.
- The lack of awareness among people at risk. When the
 disease becomes rare, local knowledge of the disease among
 the affected populations is progressively lost. Campaigns
 and tools to maintain gambiense HAT awareness among
 the populations in endemic areas have to be developed and
 implemented.
- Xenomonitoring for assessing gambiense HAT elimination.
 The feasibility of monitoring T.b. gambiense infections in vectors should be further explored as a potential tool for assessing HAT elimination programmes.
- Screening, diagnosis and staging serological tests must be

ensured. The introduction of simple, individual serological tests can help the integration of *gambiense* HAT control and surveillance into the healthcare system, which will be critical to achieve the elimination goal.

Tremendous efforts have been made during the past ten years, thanks to the partnerships between involved actors from different fields. However, we still need to work together to overcome identified challenges and fill the gaps in order to achieve HAT elimination as targeted.

Goal of HAT elimination

The goal as defined in the WHO NTD Roadmap is "to eliminate gambiense HAT as a public health problem" by 2020. This is an intermediate step, defined as < I new case in 10,000 inhabitants in at least 90% of foci, with < 2,000 cases reported annually for the whole continent.

In compliance with the recommendations of the WHO strategic and technical advisory group for NTDs, the final goal of WHO, endorsed by disease endemic countries, is "to stop gambiense HAT transmission" by 2030. This is a sustainable final step, defined as reducing to zero the incidence of infection caused by gambiense HAT in endemic countries. However, continued actions will be required to prevent the re-emergence of the disease.

Gambiense HAT elimination strategy and methods

Typically, HAT control involves four approaches:

- Active screening through mobile teams
- Passive screening integrated in fixed healthcare facilities
- Vector control to reduce tsetse population
- Management of detected cases

The appropriate combination and "dosage" of each approach in each particular focus must be based on the intensity of transmission, the epidemiological conditions (including geographic and demographic data), the accessibility and capabilities of existing healthcare facilities, vector knowledge (including the sites where vector control must be applied and appropriate methods based on human-vector interactions), and the security situation. The strategy must be flexible and dynamic enough to be adapted to the disease progress, changes affecting the local healthcare services, new tools and research results.

Active screening is highly effective in areas with a high risk of transmission. Its frequency will depend on the level of risk. In low risk areas, screening needs to be properly targeted, reactive and highly focused on areas where cases are being found. It must be determined in each village in the risk area.

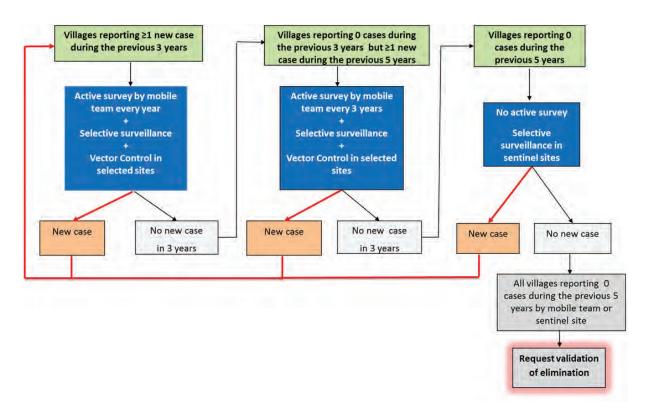
Passive screening needs to be integrated into the routine activities of healthcare services. New RDTs may simplify this integration. Places to do these tests shall be selected according to staff competencies and covered population. Screening ability must be adapted stepwise in each chosen centre, based on the number

of clinical cases detected, serological positives and parasitological confirmation of cases. Passive screening complements active screening in areas at high risk of transmission, but in low risk areas it becomes an essential tool to maintain epidemiological surveillance.

Vector control is an efficient and necessary tool whose use will depend on the results of medical interventions. It can play a

role to quickly reduce transmission in high prevalence areas or in areas where transmission remains stagnant despite repeated medical interventions. Vector control activities need to be focused on the areas of transmission and must use the most adequate and effective methods depending on local conditions. Interventions are planned at the village level, based on its own epidemiological status.

General algorithm of interventions:



Progress toward elimination will be measured by two primary indicators updated annually:

- Number of reported cases
- Number of foci reporting less than I case per 10,000 inhabitants

Secondary indicators, assessing the quality and extent of elimination activities include:

- Geographical spread of the disease
- Populations and areas at different levels of risk
- Populations at risk covered by control and surveillance activities

Conclusion

Much progress has been made in the fight against *gambiense* HAT. The sustainable elimination of HAT looks like a challenging but reachable objective. Coordination of the interventions is crucial to reach the proposed objective, but the road is not easy and the finish line is not in sight just yet.

4. Round tables

a) Needs to achieve a lasting elimination of sleeping sickness

Five speakers participated in this round table, chaired by Dr Pere Simarro from the WHO, Geneva.



Dr Abdoulaye Diarra, HAT medical officer at WHO / AFRO



Challenges, gaps and needs to support HAT elimination

The prevalence of new cases reported in West Africa and Central Africa has fallen. The populations and geographical areas at risk have dropped, but HAT often develops in remote rural areas where the quality of healthcare services is very poor.

The elimination of HAT faces the following challenges:

- Lack of epidemiological knowledge
- Role of asymptomatic but HAT seropositive patients
- Role of domestic animals as reservoirs of T.b. gambiense
- Under-detection and under-reporting of cases due to weaknesses in the public health systems

- Risk of re-emergence of HAT from within a foci
- Inaccessibility to foci for various reasons (social and political instability, poor road conditions, etc.)
- Poor knowledge on the disease by the populations at risk
- Lack or ageing of qualified personnel to screen patients

2. Dr Crispin Lumbala, Director of PNLTHA, Kinshasa, DRC



Challenges of the National HAT Control Programme

The national HAT control programmes face various challenges regarding active and passive screening in healthcare facilities, diagnostic methods, treatment, and vector control (example of the programme in the DRC).

Active screening:

- o Primary strategy for early detection of the disease
- Cheaper in conditions of low prevalence (Province de Equator, Bas Congo, etc.)
- Risk of re-emergence once active screening is stopped (from 1968 to 1998)
- Accessibility problem for mobile teams in certain risk areas
- Lack of mobile teams
- Passive screening in healthcare facilities
 - o Requires motivation
 - In most healthcare facilities in remote areas, the use of CATT is difficult (the 50-dose presentation requires a cold chain and electrical energy)
 - Very low rate of use
- Diagnostic methods
 - Based on the visualisation of trypanosomes under a microscope
 - Requires trained personnel
 - But loss of skills or lack of motivation always occurs once patients become rare in healthcare facilities
 - The cost of the mini anion exchange centrifugation technique (most sensitive method) is €5

Treatment

- Examination of the patient by the mobile team at the healthcare centre
- Patient treated on site or referred
- How to make sure that each patient diagnosed with stage 2 is treated at the hospital
- Need to increase coverage (number de healthcare facilities capable of treating stage 2 disease, availability of treatment in remote areas, etc.)
- o Easy treatment to administer (oral drug)
- o Definition of a cure

Vector control

- How to get the healthcare personnel committed to lasting control activities (economic interest)
- Monitoring and evaluation

3. Prof Philippe Buscher, director of the laboratory of parasitology, IMT/Antwerp, Belgium



Challenges and prospects in terms of diagnosis

The diagnosis is carried out in several stages:

- Suspicion of infection (clinical examination, serology, or molecular evidence)
- Confirmation of infection (visualisation of the parasite under a microscope)
- Staging of the disease (examination of cerebrospinal fluid)

The clinical symptoms of trypanosomiasis are not pathognomonic, even at stage 2.

The clinical presentation may complement a serological suspicion, but microscopy confirmation will remain necessary as long as the treatment is toxic, expensive and difficult to administer. Serological mass screening (active screening) is performed with a CATT, a rapid and cheaper test, but which requires a cold chain and a source of energy.

New rapid tests have become available, cheaper and requiring no special equipment or energy source:

- SD BIOLINE HAT developed by Standard Diagnostics, South Korea, with the financial support of FIND. This test has a sensitivity of 99% and a specificity of 87%.
- HAT Sero K-SeT developed by Coris BioConcept and IMT/ Antwerp with the financial support of the European Union as part of the NIDIAG project. This test is provided in a field-portable format. It has a sensitivity of 98.7% and a specificity of 88.1%.

Presentation of microscopy diagnostic methods for parasites:

- Capillary Tube Centrifugation (CTC)
- Mini Anion Exchange Centrifugation Technique (mAECT)
- Trypanolysis
- Molecular methods (DNA amplification)
- Methods identifying biomarkers of the invasion of the nervous system (neopterin and CXCL10)

4. Dr Wilfried Mutombo, Investigator of the Fexinidazole clinical trial, DNDi



Treatment challenges

Contrary to other diseases, clinicians have very few tools to treat sleeping sickness:

- There is only one drug available to treat the early stage (pentamidine).
- Until the '90s, there was only one drug, toxic and very difficult to administer, to treat the late stage (melarsoprol).
- Eflornithine is one of the new options, but it is very restricting and there is a risk of resistances.
- The revolution came with the Nifurtimox-Eflornithine Combination Therapy (NECT).

There is an urgent need for easy to administer, oral treatments (on-going studies on fexinidazole and oxaborole).

As the treatment of the stage 2 disease must be administered in a hospital setting, it faces logistics problems to transport the treatment equipment (large volumes, poor road conditions, etc.).

5. Dr Mathieu Steele of the Bill & Melinda Gates Foundation



Challenges and prospects for HAT elimination

There are three main challenges:

- Changes associated with the switch from disease control to disease elimination.
- Identification of rational and effective drug combinations, proven tools, people and procedures.
- Improved cooperation between donors for a more effective allocation of funds.

To switch from control to elimination, the following points must be taken into account:

- Control is difficult to measure and varies depending on the location
- Elimination is easier to measure directly but difficult to achieve.
- The reduction to zero requires a combination of interventions taking into account the local heterogeneity of the disease and knowledge of the dynamics of the transmission.
- The elimination must have the same meaning to the relevant

- people in different countries.
- Progress must be measured geographically in the same way.
- Populations at risk must be identified in terms of number and disease burden.
- The reduction of the disease must occur at both national and provincial levels, and verified every year.
- It is essential to establish a partnership between countries affected by HAT to ensure a concerted action, because the disease crosses borders.

The following measures must be taken to increase the chances to eliminate trypanosomiasis in Africa:

- Create a direct international partnership based on a common plan aligned with the individual plan of each country;
- Use a combination of plausible interventions, and recruit other donors to amplify and scale up the impact.

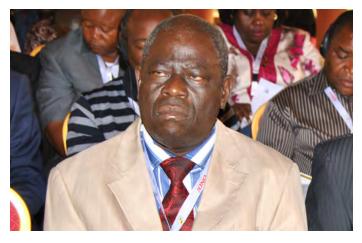
Following the discussions generated by these presentations, Dr Pere Simarro, chair of the round table, summarised the situation and declared that we should learn lessons from the past and not give up now, when efforts are about to pay.

Elimination is achievable, and we must capitalise on all our strengths and current opportunities.

a) Research ethics in sub-Saharan Africa

A round table on research ethics in sub-Saharan Africa was organised during this scientific forum. It was based on three presentations by the following specialists:

Prof Félicien Mundayi Mulopo (President of the National Bioethics Committee in the DRC)



His intervention entitled « Ethics in human research in Africa » was guided by two questions: how is the biomedical or behavioural research subject perceived from an ethical point of view, and is this perception of the person the same in an African research setting?

After a brief review of the history of ethics worldwide, Professor Mundayi explained that research ethics is a new topic in Africa.

Biomedical or behavioural research in Africa is not yet based on its own standards and on African tradition. Instead, it is based on European standards with little or not contextualisation.

Individuals participating in research are vulnerable, with a low capacity to exercise their autonomy and act freely without undue influence from others. They often belong to economically and medically disadvantaged groups, highly exposed to diseases. These persons are also sometimes illiterate and almost invariably have little medical knowledge, which exposes them to a risk of abuse

Such vulnerability disrupts the capacity to accept consciously to participate or not in a study.

In Africa, we believe that any research protocol involving humans must be submitted, prior to its implementation, to the local or national ethics committee. We also believe that it is urgent to introduce a course on research ethics in medicine and pharmacy studies to create a culture of compliance with these principles. Researchers have a duty to protect vulnerable persons and not exploit them.

2. Prof Josaphat Ndelo-di-Phanzu (President of the Bioethics Committee in Central Africa)



His intervention was entitled « Clinical trials in sub-Saharan Africa: review, challenges and future prospects ». Clinical trials are designed to provide evidence that a medical intervention is beneficial for patients, whether it is a drug, surgery, diagnostic tool, ultrasound equipment, public health strategy (circumcision against AIDS), etc. Such evidence is based on the efficacy, side effects, and especially the benefit/risk ratio of the intervention. Clinical trials help build medicine based on evidence rather than on subjective opinions.

Review

As in the industrialised world, the history of clinical trials in Africa is fraught with errors and scandals (Trovan in Nigeria 1996, 2001; Tenofovir in Cameroun and Nigeria 2005; Ivermectine in Cameroun; study on meningitis in Niger 1957-1960; polio vaccine tested in one million subjects in the DRC who were told it was a candy).

In the Western world, such errors are things of the past but in Africa they are still a reality. The speaker mentioned authors such as Jean-Philippe Chippaux (2004), Sonia Shah (*Cobayes* humains: le grand secret des essais pharmaceutiques), and John Le Carré (The Constant Gardner).

Multiple reasons explain these scandals: pressure from endemic diseases (AIDS, malaria, tuberculosis); pressure from epidemics and fear of death (ethical abuses surrounding Ebola are a current example); pressure from pharmaceutical companies in the North; pressure from subcontractors; pressure from ignorance (rulers, intellectuals, population); cultural and media pressure; legal failures (lack of appropriate laws); organisational failures; ethical failures (rulers, intellectuals, population), lack of partners; poverty and cultural issues.

However, efforts are currently being deployed. Several clinical trial centres are being set up in various black African countries in partnership with institutions of the North: the European Union, CDC Atlanta and the European and Developing Countries Clinical Trials Partnership (EDCTP). Answers are provided for diseases occurring in sub-Saharan Africa (AIDS, tuberculosis, malaria and neglected infectious diseases), and multicentre projects are coming to light, combining clinical trials, strengthening capacities and networking. In addition, Regional Centres of Excellence have been set up in West Africa, East Africa, Central Africa and in South Africa.

Challenges

Several targets have been identified to improve the ethics of research in Africa:

- Researchers: their number is rising but it is important to continue to generate interest and motivation and to provide better training. The number of trainers must be increased, with greater commitment and motivation. The spectrum of training topics must be broadened (GCP, GLP, bioethics, writing clinical trials and SOPs). The selection of field teams must be improved, with more motivation and better follow-up.
- The population must be better informed on ethics to improve the management.
- Ethics committees: their number is insufficient, and they need independence, greater means and improved organisation. National ethics committees must be created with good partnerships.
- Supervisory authorities must be involved at various levels.
 Advocacy is needed.
- Scientific partnerships: local and international partnerships must be increased.
- Means: greater means of communication (Internet), as well as legal and financial means.

Future prospects

Clinical trials are essential and their number will increase in Africa.

Africans must take responsibility at various levels, to meet the numerous challenges they are facing: researchers, authorities, population, and partners.

Ethics must be vulgarised and better organised, the operating of ethics committees improved and partnerships improved.

3. Dr Samba Cor Sarr, vice-president of the African Vaccine Regulatory Forum and coordinator of the Senegalese national ethics committee



The third speaker talked about « the standards and specificities of ethical review in multi-site and multi-country projects ».

A multi-site research project is carried out in several sites, involving several organisational entities, and is generally reviewed by several ethics committees. It is led by several primary investigators, but with a single protocol. Data collected in the different sites are pooled and analysed together, producing a single report based on all the data from all the sites.

On the other hand, a research project conducted in various locations of a single entity and reviewed by one single ethics committee is not a multi-site project (e.g. a project carried out

by Institut Pasteur in Dakar in its various sites, and covered by the Senegalese national ethics committee).

Multi-site or multicentre projects have numerous advantages, such as:

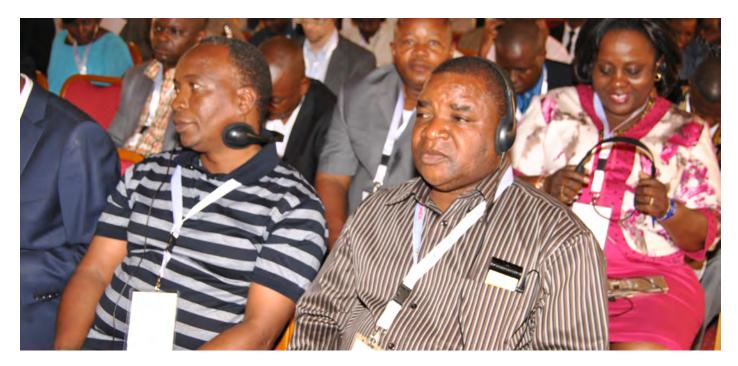
- Large number of participants or events, faster recruitment than with a single site.
- Research under different conditions, diversity of participants and greater representativeness of the source population.
 Research results can be widely generalised.
- Resources and participant expertise can be pooled.
- A comparison between sites is possible, based on determinants and results.

Challenges faced by multi-site projects include:

- The complexity of the organisation, management and logistics
- Communication and coordination
- Standardisation of the protocol and procedures
- Variations in legal and insurance requirements
- Differences between sites in terms of scientific procedures, ethical review and ethical monitoring of studies, subject to different policies, regulations, and social and cultural settings.

The lessons learned to promote a single ethical review include:

- Promote the development of common polices, processes, forms and orientations for an integrated research application system;
- Identify relevant fields of ethical expertise among the regional economic communities; consider competence modules for ethical review; consider the use of electronic databases and document sharing; setting up systems of national certification; create a register of establishments certified for the ethical review of multicentre research.



5. Sessions

a) Diagnosis

Theme: Screening and diagnosis tools

President: Enoch Matovu

Reporter: Pierre-Marie Douzima

This theme included six oral presentations, two on basic research and four on the evaluation of screening tests/ rapid diagnostic tests (RDTs).

I. About basic research

Miss Dawn Maranga presented neopterin as a biomarker which may help post-treatment follow-up, instead of the current very heavy strategy of lumbar puncture.

Mr Kennedy Mochabo explained that recombinant proteins based on *Trypanosoma congolense* could be used for the early diagnosis of animal African trypanosomiasis due to this species.

2. About screening tests/rapid diagnostic tests

Useful RDTs

Crispin Lumbala, Thierry Leclipteux, Paul Bessel and Mariam Camara presented the RDTs seen as useful tools after various evaluations: i) in fixed facilities for screening and passive surveillance of HAT, and ii) in the field for mass screening, instead of CATT in areas where the latter is impractical due to technical constraints.

There are various RDTs currently available and prototypes being improved and expected to be launched in 2015:

- SD-Bioline RDT
- HAT Sero-k Set (Coris)
- Rec HAT sero-strip (2015)
- SD-Bioline second generation

Lessons on RDTs from West Nile, Uganda

Jennifer Palmer, Fred Kansiime, Enoch Matovu, Charles Wamboga, Sylvain Bieler & Joseph Ndungu

Through a partnership with FIND, Uganda is the first country in Africa to integrate rapid diagnostic tests (RDTs) for *gambiense* human African trypanosomiasis (HAT) into primary healthcare services. Here, health workers have been asked to only use RDTs when they strongly suspect HAT, based on symptoms.

At the HAT Platform-EANNET meeting in September, we presented preliminary findings on how RDTs had been used by health workers over the first nine months of the programme. Below are four key lessons we learned from our experience, which HAT programmes in other countries might consider as RDTs are rolled out there:

1. Most health workers were new to HAT.

Before RDT training in Uganda, two-thirds of clinicians (68% of medical/clinical officer and nursing staff) had never before suspected HAT in a patient, based on symptoms. Health workers also had incomplete knowledge of HAT symptoms.

While almost all health workers associated malarialike symptoms with HAT, fewer associated behavioural symptoms, enlarged lymph nodes and severe neurological signs, which are key to targeting RDTs to HAT suspects. Future trainings should therefore focus on ensuring that health workers are confident in recognising syndromic cases before they leave with RDTs. A memorable way to do this could be to share stories about the symptoms which led trainers to diagnose true cases in the past, or to have participants act out key symptoms of the disease in a memory game.

2. RDTs were appreciated in front-line facilities.

According to interviews with health workers, HAT RDTs have not substantially increased facility workloads. In fact, health workers believed RDTs ease the burden of differential diagnosis, particularly in front-line facilities where opportunities to rule out diseases other than malaria are limited because of the small number of tests typically available in rural environments.

There was little indication that HAT RDTs were being over-used. In interviews about decisions involved in testing 47 patients with HAT RDTs, malaria was 'ruled-out' first 87% of the time, and decisions largely matched the criteria for targeting tests, which were taught during training. (Continued on p.16)





























3. Patients can reinforce health worker suspicion of HAT.

Two ongoing challenges to the use of RDTs in Uganda appear to be that, (i) health workers do not always suspect HAT using the full range of characteristic symptoms (such as behavioural signs), and (ii) within facilities, only some of the health workers who could be using RDTs actually do. Both of these challenges mean that true cases could be missed.

On review, it appeared that facilities with higher rates of RDT use by health workers were also the facilities where the highest rate of 'self-referral' by patients who wanted to be tested for HAT with a RDT, so these two behaviours may be mutually reinforcing.

One fifth of health worker decisions to use HAT RDTs were prompted by requests from symptomatic patients, so patient suspicions about their illnesses could be important in sustaining or even building health worker vigilance for HAT. This is especially important in an era

of elimination. There are several ways health workers and programme managers can encourage HAT self-referral behaviour among populations. These include communicating to village health committees who can refer suspects and communicating to patients via outreach, education at facility outpatient departments or via radio.

4. Review records regularly to identify problems early on.

While this may seem obvious, it is easy to forget the importance of regular monitoring by local supervisors to ensure that potential cases are not being missed because health workers have developed bad habits related to HAT RDTs. Simply reviewing testing registers to identify months when no RDTs are used, or days when many more tests are used than expected, can suggest key implementation problems such as stock-outs or tests being offered without syndromically screening first. Each of these problems sends inconsistent messages to communities whose help we need to sustain RDT services for HAT control.





b) Treatment

Theme: Clinical research on new treatment options (7 presentations)

1. DNDi strategy to treat human African trypanosomiasis (HAT)

This theme was presented by Antoine Tarral. He presented the on-going projects of DNDi on the research, development and implementation of new molecules for the treatment of HAT.

Regarding the oral treatment expected as of 2016, two molecules are currently at the clinical trial stage:

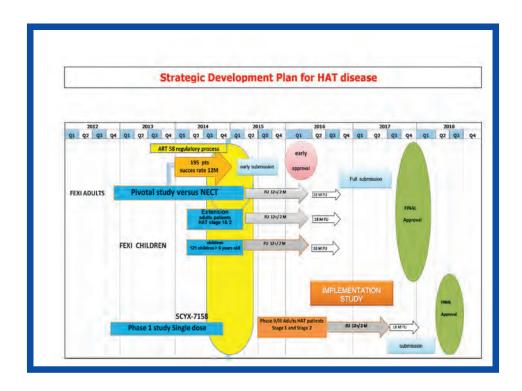
- Fexinidazole: promising oral treatment, taken once a day for 10 days, currently at phase II/III of its clinical development in the DRC and CAR
- SCYX-7158, a new molecule for single-dose oral treatment, at the end of phase I; Phase II/III expected in 2015

Some of the objectives de DNDi regarding the WHO roadmap for HAT elimination by 2020 include:

- Participating in the detection of the disease in all foci
- Provide two new oral products in 2017-2018 for both stages of HAT
- Promote access to the products in the HAT foci

After describing the DNDi development plan for HAT molecules, Antoine Tarral presented the different study sites in the DRC and the role of DNDi in the improvement of these sites.

In conclusion, DNDi considers that it is possible to change the history of sleeping sickness, based on the promising results of the new diagnostic tools and on-going treatments.



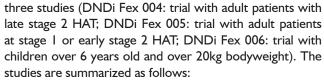
2. Implementation and coordination of a multicentre clinical trial on THA: challenges and lessons learned

This theme was presented by Wilfried Mutombo (coordinating investigator of the DNDi study on fexinidazole). He described the current difficulties faced by the fight against sleeping sickness, and the need for simple

diagnostic tools and appropriate treatments to reach the objective of disease elimination.

He then described the requirements and challenges associated with clinical trials on sleeping sickness, before presenting the different steps in the implementation of phase II/III studies on fexinidazole. After a review of the various steps, he explained the lessons learned from these





- It is possible to carry out quality clinical trials in remote areas
- Their cost is high (in terms of investments, renovation and equipment) and they require major logistics.
- The ethics committee/regulatory authorities' response times when submitting a file for review vary (two weeks to two months in the DRC).

The fexinidazole project has led to the creation of a network of centres, which have qualified personnel and are able to conduct any clinical trial.

3. Implementation and daily management of a clinical trial on the site of Masi Manimba (DRC)

The theme was presented by Willi Kuziena (local investigator for the Masi Manimba fexinidazole study site). He presented the hospital of Masi Manimba, with the HAT treatment ward, the hospital's total capacity and human resources. He explained that data transfer on electronic case report forms (e-CRF) is a complex procedure and that paper CRF are easier to use.

He then described the patients included in the study and their follow-up in the different studies on fexinidazole (Fexinidazole 004, 005 and 006), after reviewing the strengths, weaknesses and constraints associated with the study. In conclusion, he praised the study's success based on strengthened capacities, improved patient management and post-treatment follow-up.

4. Clinical trial on children with THA at the Mushie site This study was presented by Guylain Mandula (local

investigator at the Mushie fexinidazole study site). The study



was performed at the hospital of Mushie. He presented successively the preparation of the site (renovation and equipment), health worker training, and inclusion of children in the study, which started in May 2014. Following a review of the different study parameters, he concluded that clinical trials with children is an enriching but difficult experience, which requires specific adaptations, but that it is not impossible if the determination to succeed is there.

5. Clinical study on fexinidazole in conflict zones: experience of the collaboration between MSF and DNDi in Batangafo (Central African Republic)

This study was presented by Laurence Flevaud. She described the history of the MSF project in Batangafo, and the inclusion of THA in its health programme in 2007.

She reviewed the collaboration between DNDi and MSF which led to the initiation of the Fexinidazole study in 2013. She then presented the site preparation, training in GCP and GLP, and the collaboration with PNLTHA to contact the ethics committee and obtain the authorisation to import products for the study. Following the inclusion of the first 12 patients in the study, the armed conflict caused severe damage to healthcare facilities, which led to the suspension of inclusions. From then on, the study focused on the follow-up of the 12 patients already included.

In such a difficult setting, the challenge was to find those 12 patients and define a strategy for the monitoring visits. In spite of the conflict and ensuing difficulties to carry on with the study, the Fexi team in Batangafo did not give up. Laurence Flevaud concluded by saying that in a conflict zone, it is sometimes necessary to innovate and develop new strategies to reach the objectives set by the clinical trial.

6. Challenges for the surveillance of HAT clinical trials with electronic case report forms

This study was presented by Aita Signorell. She described the

importance of the management of clinical data to preserve the quality of the study. She then showed the feasibility of using eCRF and paper CRF, before presenting the advantages and disadvantages of these data management tools.

7. Post-treatment follow-up of patients with human African trypanosomiasis: challenges to be met



This study was presented by Esperant Bolimbo. In his introduction, he presented the context in which treated patients must be followed for 2 years before declaring a cure. Treated patients generally do not present themselves spontaneously to the post-treatment follow-up visit.

c) Entomology and vector control to help HAT elimination

The session entitled "The role of entomology and vector control in HAT elimination" included five presentations followed by a session of questions and discussions:

- Three presentations on HAT epidemiology and *T.b.* rhodesiense animal trypanosomiasis in Uganda and Tanzania, with a special focus on vector species, trypanosomes and vector control. The main vectors for the transmission of trypanosomes in areas of social, economic and touristic importance (Serengeti National Park) are *Glossina fuscipes fuscipes*, *Glossina swynnertoni* and *Glossina morstans*, as well as *Glossina pallidipes*. These tsetse flies act as hosts to trypanosomes potentially dangerous to humans and animals, i.e. *Trypanosoma brucei sp.* and *Trypanosoma congolense*.
- A communication on trials for a new tsetse fly trap whose characteristics (size, etc.) may improve vector control in terms of cost, workload, covered area, etc.
- A communication on the interaction between Glossina pallidipes and Sodalis glossinidius, a symbiotic bacteria.

A campaign for the active search of treated patients was launched in 2013 to find out why they are not coming to the control visit. The results of this study showed that the fear of lumbar puncture and the absence of clinical signs are the two main causes for the non-compliance with prescribed post-treatment follow-up. He ended his lecture by saying that post-treatment follow-up in HAT is still relevant, but that the series of tests to be carried out needs to be reexamined. With the promising success of new molecules, it would be advisable to abandon the systematic use of lumbar puncture for the follow-up of patients.

After this series of presentations, a number of questions were asked, including on the use of a camera on microscopes for studies, post-treatment follow-up, solutions for studies carried out in conflict zones, and management of clinical data on electronic media (eCRF).

Regarding the first question, the speaker said that cameras are useful for educational and control purposes, but they do not help visualise the parasite. Furthermore, although post-treatment follow-up is not compulsory outside clinical trial settings, it becomes essential in the presence of HAT warning signs. Regarding the management of clinical data, the choice of electronic (eCRF) or paper (CRF) case report forms depends on the context in which the study takes place.

For safety reasons, it is not easy for patients to travel for follow-up visits in the CAR. It is currently difficult to identify an area in which patients can travel safely, knowing that it needs to be close to MSF's area of intervention, currently reduced to a 5 km radius.

There seems to be a correlation between tsetse infection with trypanosomes and the presence of this bacteria. This means that *Sodalis glossinidius* could be used in a strategy for the biological control of trypanosome development in tsetse flies.

The participants then focused on the following points:

- The methodology of the use of live tsetse flies to determine the rate of infection.
- Seasonal variations of the apparent density per trap per day of tsetse flies. The dry season seems to be the most suitable for vector control because tsetse flies then congregate around watering holes.
- New small-sized screens could reduce the apparent density
 of tsetse flies, reduce their rate of infection beneath a given
 threshold, so that in the long-term, they will no longer
 transmit sleeping sickness, similarly to what happened for
 malaria in Europe.

6. Steering committee meeting

The only meeting of the HAT Platform steering committee in 2014 was held on 16 September 2014 in the offices of DNDi in Kinshasa. All member countries as well as partners were present.

The objectives of this meeting included:

- A review of the activities of the HAT Platform during the first three quarters of 2014
- Sharing the progress of on-going studies with the HAT Platform partners
- Proposal of activities for 2015
- Proposal of new members

Expected results:

- The strengths and weaknesses of the activities over the first three quarters of 2014 were presented and analysed.
- The progress of on-going studies in all HAT Platform countries was communicated to all the members and partners.
- The objectives and activities of the HAT Platform were redefined.
- The Republic of Guinea and the University of Edinburg were admitted as new members of the HAT Platform.

Strengths were presented by the different country members:

- The ICAT6 training, at which most French-speaking countries participated
- The evaluation and 2014 planning of the DRC with the help of the HAT Platform
- Training of the personnel involved in HAT control in Chad
- All endemic countries use NECT as first-line treatment for stage 2 infection caused by T. brucei gambiense; support was given to the ethics committees (DRC)

Weaknesses (mainly associated with the organisation of HAT control and not with the achievement of certain objectives outside the studies):

- Lack of operational resources with low coverage of active screening
- Fear of lumbar puncture and of stigmatisation
 Ageing of personnel and lack of interest of young health workers for HAT

workers for HAT
Slow roll-out of rapid diagnostic tests and for certain

countries limited access to more sensitive parasitological tests (mAECT)

• Lack of researchers and research means

The progress of on-going studies was presented in details during the three scientific days which followed this steering committee meeting.

The HAT Platform has three main lines of activities: strengthening of capacities, training and support to ethics committees, and activities targeting solely sleeping sickness. The question of broadening its action to other neglected diseases was raised, as the number of cases is dropping and there is a risk of funding no longer being available. Nevertheless, this proposal was rejected because the work on HAT is currently reaping success with the discovery of new diagnostic tools and oral treatments. Therefore, it is advisable to remain focused on HAT for another 3 to 4 years and move progressively thereafter towards other zoonoses. A total of 6 objectives were formulated again:

- Strengthening of capacities to broaden research
- Improvement of research environment
- Communication
- Operational research: regulations, RDTs and others, new diagnostic tools
- Fund raising
- Seeking partnerships

The following recommendations were made:

- The HAT Platform must have a president with a one-year mandate to help the coordinator
- Share all HAT research with all the Platform members
- Develop a communication plan
- A committee was set up to produce a base document outlining the HAT Platform's strategic and functional planning, and produce follow-up activity reports. The committee is composed of Dr Kande, Dr Lumbala, Dr Ebeja and Dr Mbongo. The Republic of Guinea and the University of Edinburg have been accepted as members of the HAT Platform.

7. Calendar of 2015 scientific events

Event date	Deadline for abstract submission	Deadline for registration	Location	Event name
Jan 12-16			San Francisco	33rd JP Morgan Annual healthcare conference http:// sternir.com/ailec_event/j-p-morgan- 33rd-annual-healthcare-conference/
Jan 23			London, UK	RSTMH: Topics in Infection
Feb 11-15	15 June 2014		Kolkata, India	I4 th World Congress on Public Health: Healthy People-Healthy Environment http://www.I4wcph. org/
Feb 23-26	Ist October 2014 (late breaker Dec 2-Jan 8 2015		Seattle, WA, USA	CROI 2015 http://www. croiconference.org/
March 2-5			Hyderabad, India	ICID 2015 International conference on emerging infectious diseases http://www.isid.org/icid/welcome.shtml
March 8-13		Application by Feb 2015	Galveston, TX, USA	Gordon Research Conference: Tropical Infectious Diseases - Challenges, Opportunities and Successes https://www.grc.org/ programs.aspx?id=13985
March 13			Geneva, Switzerland	Philanthropy and Intellectual Property: The case of access to drugs for developing countries - Geneva University http://swissfoundations.ch/de/cycle- philanthropie

March 15-20	Discounted abstract: Nov 17 2014; Abstract Dec 16 2014	Discounted registration: Jan 14 2015	Ouro Preto, Brazil	Keystone conference: Co- infection: A global challenge for disease control http://www. keystonesymposia.org/15C6#utm_ source=2014email&utm_ medium=emaillink&utm_ campaign=2015globalhealth
March 17-18	Symposium: 21 July 2014; Posters: I November 2014	lst Feb 2015	Oslo, Norway	GLOBVAC: 9 th conference on Global Health and Vaccination Research http:// www.forskningsradet.no/ prognett-globvac/Annual_ Conference/1253954270899
Apr 25-28	30 Oct 2014		Copenhagen, Denmark	ECCMID European Society for Clinical Microbiology & Infectious Diseases http://www.eccmid.org/ eccmid_2015/
May 2015			Toronto, Canada	Ist Canadian conference on NTDs
May 5-7			Seattle, USA	2015 Global Health Product Development Forum
June 10-12			Boston, USA	WPC 2015: World Pharma Congress
Aug 25-27			Manila, Philippines	COHRED Forum «People at the centre of research & innovation for health» http://www.cohred.org/global-action/
Sept 6-10	Opens early 2015; early rate by 29 April; late from 16 July	April 9 2015	Basel, CH	9th ECTMIH - European Congress on Tropical Medicine and International Health http://www.festmih.eu/Page/ WebObjects/PageFestE.woa/wa/ displayPage?name=ectmihbasel2015
September 2015?				33rd International Scientific Council for Trypanosomiasis Research and Control (ISCTRC): http://www.au-ibar.org/isctrc
Oct 25-29			Philadelphia, USA	64 th ASTMH http://www.astmh.org/Future_Meetings.htm

8. Obituary

(in memory of Dr Nicolas Mbongo)

nce again, death struck our large family of the HAT Platform, and this time it is one of our most active and endearing members of the steering committee, Nicolas Mbongo, affectionately known as Nico, who left us in the prime of his life.

The HAT Platform coordination received

many messages de condolences, a few of which are shown below:

This is really sad my dear Nicolas. What happened? You were in top form in Kinshasa, you liked to tease, and in return I called you a rebel. Lately you had been working hard on HAT control, with many field trips of which you showed me photographs. Alas, death has just taken you from us. Did God want this? I am in tears, we shall miss you a lot, you and your radical positions during our coordination

meetings, which I criticised often, and to which you replied that that was how you are. So, such is life.

Dr Louise Mariette DETHOUA

Goodbye dear brother of the Malebo Pool. We shall miss you, because at each of the HAT Platform meetings, we always exchanged a few words in lingala. Hindoubil

May your soul rest in peace!

Dr Médard ILUNGA

Dear all.

Sad news. Nicolas was more than a colleague. He was a brother but more importantly a friend. He visited the service whenever he came to Kinshasa. The last joke we shared with him at the Cercle Elais in Kinshasa

after the Platform meeting, with Prof Enoch and Dr Andrew from Uganda and other colleagues, was about the expression *Meh* used by a waitress of the restaurant to explain to our English-speaking friends that we also had goat meat on the table.

May his soul rest in peace.



Dr Stomy Karhemere Bin Shamamba

This is very sad and happened so soon! We exchanged emails with Nicolas just last week. May his soul rest in peace.

Enoch

It is an unexpected and sad new. We will keep in our memory the time passed with him

Jose Ramon

This is really very sad; we had talked of common projects in Kin during the Platform meeting. May his soul rest in peace and may God look after his family. Amen.

Dr Diarra

This is hard to believe. He was full of life and teasing during our last meeting in Kinshasa 3 weeks ago. May his soul rest in peace.

Mumba Dieudonné

What sad news from our friend Nicolas! All my thoughts go to his family, his

friends and all of you.

Els

This has been shocking. Our condolences go to the family, relatives and friends of Nicolas. May God give them strength during these difficult times.

Joseph

This is really very sad news! He seemed so full of energy and ideas. The Swiss TPH team wishes great strength and courage to his family during these difficult times.

Christian

I am sad and shocked. Words fail me. My condolences to his family, and the HAT Platform team. Rest in peace Nicolas.

Aline OKOKO

I was out on prospection when I received a call telling me this sad news.

With Nicolas, Péka and Dr Olaf, we had worked late into the night on the 16 and early morning on the 17 September to draft the new focuses of the Platform in Kinshasa. Nicholas had distributed the roles on this occasion.

My dear Nicholas, you kept us so often in suspense...Rest in peace.

Dr Pierre-Marie DOUZIMA

9. Births

Name of the child: Loïs Madiya Date of birth: 6 October 2014

Sex: female

Mother: Brigitte Kamuanya Father: Jose Dinanga

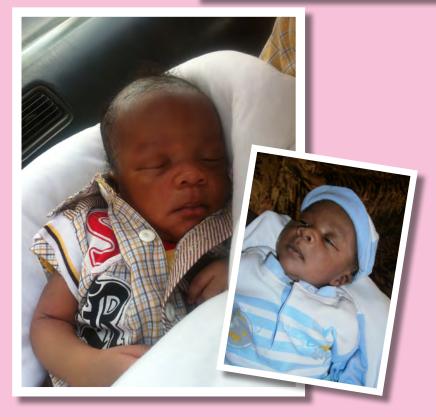


Name of the child: Israel Tschowa Kalengela Date of birth: 24 September 2014

Sex: male

Father: Dr Adonis Mwembia Kalengela

Mother: Dr Julienne Tschowa



10. Voice of HAT patients and caregivers

a) A life saved thanks to NECT

Esperant Bolimbo
PNLTHA supervisor, Isangi



The decision was made to administer the Nifurtimox-Eflornithine combination treatment, generally known as NECT, with symptomatic treatment to help his general condition.

During his stay in hospital, the medical personnel, physicians and nurses paid him a visit every morning before getting to work. Our patient was bed-ridden and needed constant care (massages, talcum, catheters, flexion exercises).

Once he finished the trypanocidal treatment, physiotherapy sessions were given three times a day at first, and then more often.

On the morning of the fourth day, Fiston decided to wake up and walk alone.

Emotions were running high in the room: cries of joy, praise, and prayers were heard throughout the ward and all the hospital staff came running to see this event, comparable to a resurrection. Today, Fiston is back with his community. Congratulations to PNLTHA and its partners.

Mr Fiston Amisi Lilufi

To reach the objective of the elimination of sleeping sickness, scientists set up a close surveillance system, with the help of the personnel of the health centre Yaselia/ZS Yakusu/Province Orientale/DRC.

When Mr. Fiston Amisi Lilufi, aged 33, from the Yalungu village, came to the consultation in a very weak condition, the personnel suspected trypanosomiasis.

Given the absence of equipment, the personnel decided the patient should be transferred to the Isangi mobile unit in the neighbouring health zone of Lusambila. The diagnosis of sleeping sickness was confirmed with the very first lymph node aspirate sample examined under a microscope.

The patient was referred immediately to the Isangi HGR hospital for appropriate treatment. His prognosis was unfavourable, he was unconscious, he did not speak.

b) Contribution of clinical trials in the integration of sleeping sickness control activities in general ward; case of the Mushie rural health zone

Dr Digas NGOLO TETE
Assistant Coordinator Fexinidazole



Sleeping sickness, or human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense*, is one of the common and impoverishing diseases which affects communities in this rural health zone, located in the north of the Bandundu province, as well as in most of the Democratic Republic of the Congo.

Several years ago, the National HAT Control Programme (PNLTHA) in the DRC set up a functional mobile unit (MU) for the screening, treatment and follow-up of patients in this health zone (ZS). This MU worked alone without the help of the health zone supervising team (ECZ), even though the MU is only acting as support to the health zone.

One year ago (20 November 2013), the Fexinidazole study was launched at the Mushie HGR Hospital. This was a first for the personnel of this hospital, which had never been used to conduct a clinical study.

Given that PNLTHA and DNDi had chosen this hospital to be one of the Fexinidazole study sites, and even though he was not an investigator for the study, the coordinator of this ECZ set the tone to ensure that activities went according to plan, with a close collaboration between the MU and the hospital general ward.

Within a year, many things changed:

- The Physician Head of the Zone, coordinator of the ECZ, now signs authorisations for the MU to go on field trips.
- The head of the MU after each field trip writes a report for the health zone central office and ECZ.
- The community facilitator of the health zone, during his supervisions, raises the population's awareness on their commitment to sleeping sickness control.
- The head of the MU is part of ECZ and now sits on the meetings if he is present in the area at the time.
- Situation and epidemiological analyses are performed during these meetings, and also address various aspects of HAT.

H

- In the health zone, 6 out of the 51 structures perform serological screening, and clinical research is performed in all the structures.
- 5 registered nurses are being trained with the MU to learn new sensitive techniques.

We found the effort to involve communities in sleeping sickness control worthwhile.

As we know, information to rural communities is essential, and is only the

first step of a process aiming to improve their participation in sleeping sickness control. While the Mushie HGR continues to include patients in the three studies (DNDi Fex004, DNDi Fex005 and DNDi Fex006), during supervisions in the health zones, the ECZ speaks with the communities about what they should do to fight HAT.

Regarding the progress of HAT, we believe that its elimination by 2020 is feasible, but it does raise the following questions: is it achievable if the communities affected by the disease are not involved (low coverage); and how can we achieve this if HAT control remains poorly integrated in healthcare facilities?

The DNDi Fexinidazole study in Mushie restored some balance in the health zone (integration of HAT control activities). However, we should not expect the same results on sleeping sickness control in fixed healthcare facilities and with mobile units, as these two approaches have different but complementary dynamics.

Complementary characteristics of fixed healthcare facilities (passive screening) and mobile units (active screening)

Fixed healthcare facilities (passive screening)	Mobile units (active screening)	
Secondary prevention	Secondary and primary* prevention	
Competencies +++	Competencies +++	
Geographical accessibility +	Geographical accessibility +++	
Resources +++	Resources ++	
Confidence / acceptability ++	Confidence / acceptability ++	
Care centred on the patient « curative medicine »	Public health / Cleaning ¹ « Preventive medicine »	
Polyvalence	Specialisation	
Long term accessibility +++ « Permanent »	Long term accessibility + « Periodic »	

^{*}Targeting explicitly the reduction of transmission.

II. RECENT HAT PUBLICATIONS July 2014 – November 2014

PreparED BY Aita Signorell

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- Ministry of Foreign and European Affairs (MAEE) / FRANCE

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