



HAT

REGIONAL PLATFORM FOR CLINICAL RESEARCH

Platform

Special Edition

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4th Joint Scientific Meeting

HAT Platform - EANETT

20-22 September 2016, Conakry, Guinea

**Elimination of Human African trypanosomiasis :
a same objective for both research and control**

Partners



Others partners

International and national research groups : INRB, CDC, TRC-KARI, University of Makerere...



Dear all,
HAT coordination wishes you
a good and happy year 2017
Success in your projects



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EDITORIAL



Dear Readers,

The 18th HAT Platform Newsletter focuses on the activities of the 4th Joint Scientific Meeting HAT Platform-EANETT which was held from 20 to 22 September 2016 in Conakry, Guinea. The meeting's theme was "Elimination of Human African trypanosomiasis: a same objective for both research and control ". Over 80 participants coming from endemic countries, African and foreign research institutions, and the health sector attended the meeting. A total of 60 abstracts were submitted for oral presentations and posters, of which 46 were selected. We summarised a few of the presentations for you in this issue. For full presentation transcripts, please contact the HAT Platform coordination.

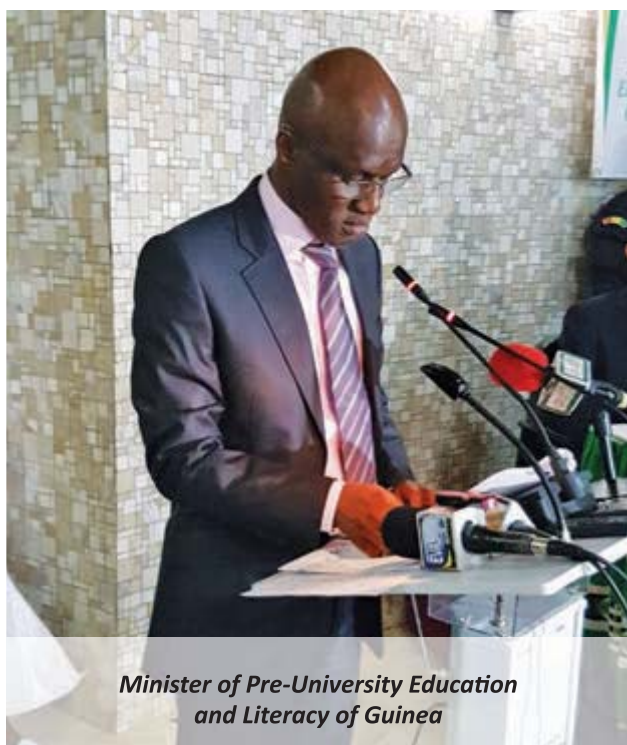
**Elimination of
human African
trypanosomiasis:
a same objective for
both research and
control ».**

The WHO recommends that the fight against different neglected tropical diseases (NTDs) affecting the same populations be integrated. In that spirit, this special edition is going to look to the efforts of our partner, DNDi, to develop a macrofilaricidal drug against filariasis, neglected tropical diseases that affect in Africa, and are co-endemic with HAT in some HAT foci. We should consider how NTDs research can be steered towards meeting that WHO objective.

Happy reading.

Dr. Florent Mbo Kuikumbi

Summary of the 4th Joint Scientific Meeting HAT Platform-EANETT, 20-22 September 2016, Conakry, Guinea



*Minister of Pre-University Education
and Literacy of Guinea*



Dr. Florent Mbo, HAT Platform Coordinator

1. Opening ceremony

The President of the Special Delegation of Ratomata, the HAT Platform Coordinator, the EANETT Coordinator and the Chair of the Scientific Committee gave introductory speeches, before the opening address by the Minister of Pre-University Education and Literacy of Guinea.

On behalf of the committee's internal and external members, the Chair of the scientific committee thanked all the eminent HAT experts and participants present at the 4th Joint Scientific Meeting HAT Platform-EANETT (Eastern Africa Network for Trypanosomiasis).

The meeting's theme was "The elimination of human African trypanosomiasis: research and control share the same objective". A total of 60 abstracts were submitted, of which 46 were accepted for oral presentations or posters. However, only 33 abstracts were presented due to funding difficulties. The scientific meeting was divided into 7 sessions:

1. Roundtable on the situation of human African trypanosomiasis
2. Update on the epidemiological profiles of endemic countries
3. Operational research for the elimination of HAT
4. Research on new treatment options
5. Roundtable on the role of ethics committees, regulatory authorities and pharmacovigilance systems for research
6. Vector control for HAT elimination
7. Basic research for HAT elimination

2. Description of the sessions

Session 1: Roundtable on the situation of Human African Trypanosomiasis



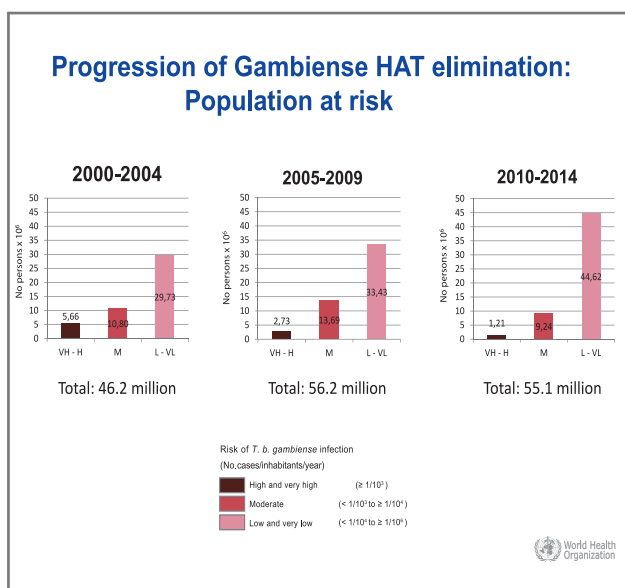
The WHO representative reviewed the strategies implemented to eliminate HAT as a public health concern by 2020, and interrupt the transmission of *gambiense* Human African Trypanosomiasis by 2030, as set out by the WHO roadmap.

He stressed the following key strategies:

Support to endemic countries to ensure access to diagnosis and treatment for people at risk.

Strengthening the surveillance through data collection and analysis to plan and monitor interventions, as well as document and track disease trends.

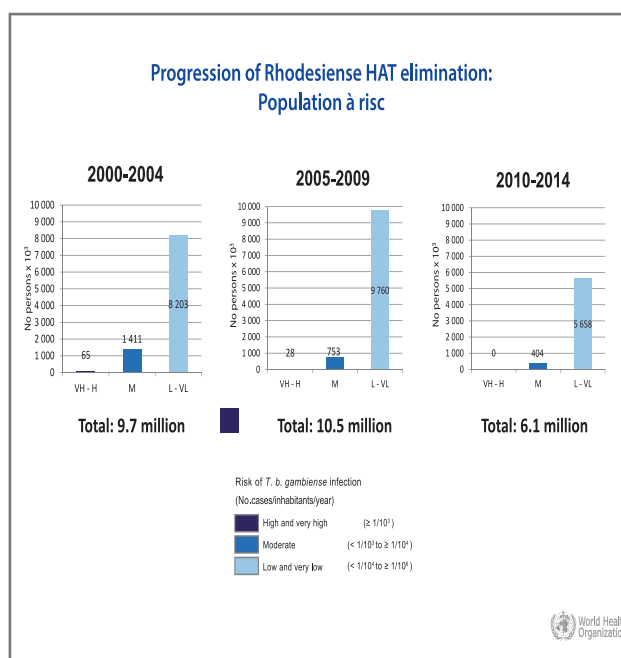
Coordination of the action of stakeholders involved in HAT elimination as set out by the WHO roadmap.



The WHO representative indicated that the number of diagnosed cases dropped from 26,574 in 2000 to 2,804 in 2015. He presented the geographical dis-

tribution of *gambiense* HAT foci (2010-2014) and *rhodesiense* HAT foci (2008-2012), as well as the progress achieved in the elimination of *gambiense* and *rhodesiense* HAT within the population at risk.

A total of 56,410,611 people are currently at risk of contracting HAT in Africa, but only 2.8%, i.e. 1,603,176 people, are covered by active screening activities. The most affected country is the Democratic Republic of Congo (DRC) with 36,569,039 people at risk, i.e. 64% of the total population at risk, and Angola is in second place with 5,852,950 people at risk, i.e. 10.4% of the total population risk.

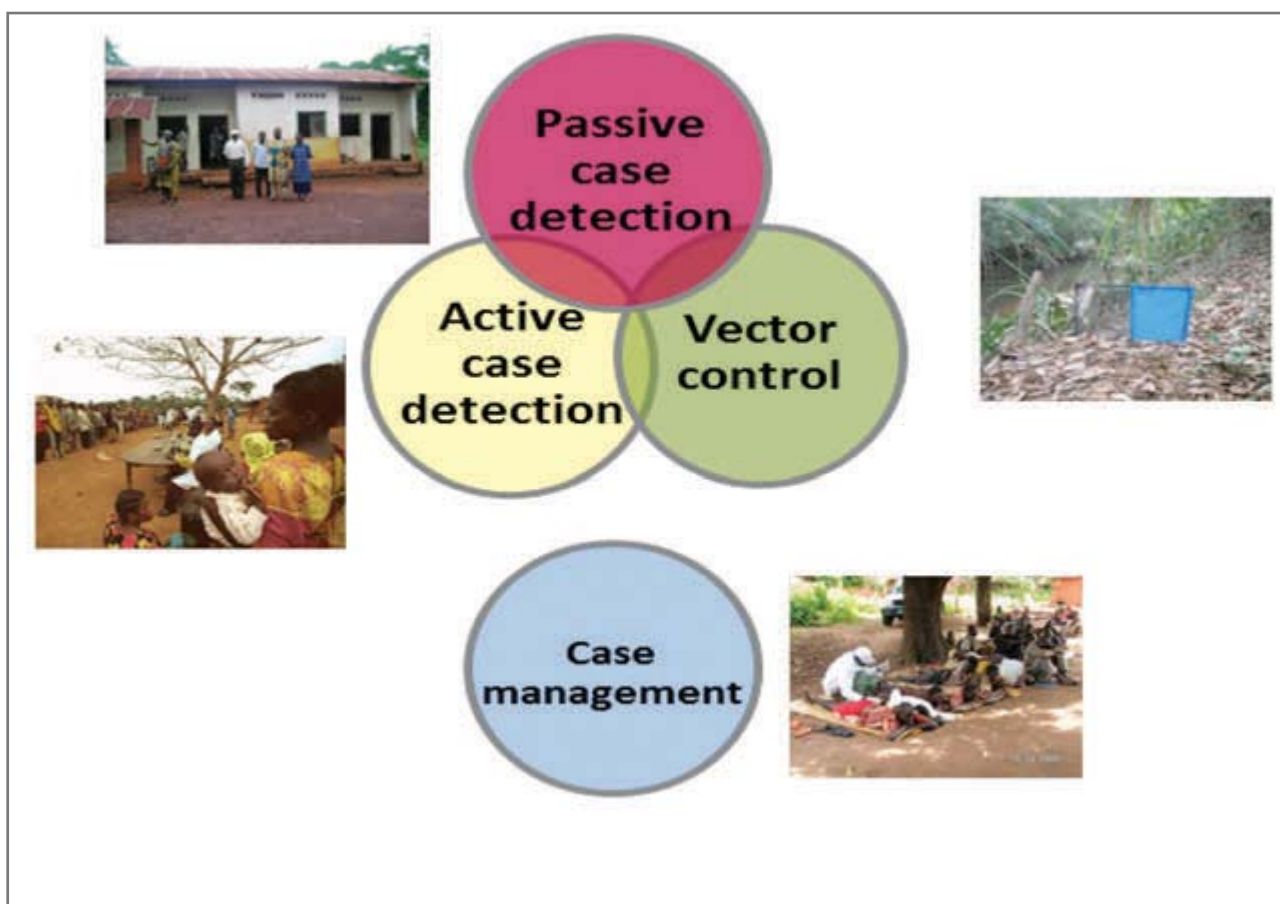


Diagnosis and treatment health facilities in endemic countries

The number of fixed health facilities able to diagnose HAT in endemic countries increased from 622 in 2013 to 879 in 2016. Currently, 89% of the population at risk lives 5 hours from a health facility able to diagnose THA, versus 87% in 2013. And yet, the number of health facilities able to treat HAT increased from 495 in 2013 (180 using NECT) to 516 in 2016 (224 using NECT).

A total of 203,198 HAT cases have been entered in the Atlas of human African trypanosomiasis database, including 191,222 (94%) mapped in the villages.

HAT elimination strategies



Session 2: Update on the epidemiological profiles of endemic countries

Following his review of the current situation, the epidemiological data of endemic countries were presented by their focal points.

Kenya has not reported a single case since 2014. The actions implemented to reduce the number of cases and prevent a resurgence of the disease are sustained passive surveillance in hospitals, training of primary care workers in some regions like Busia/Teso, and participation in regional activities by various governmental agencies attached to the Ministry of Health, as well as national and international research institutions.

As a result of its HAT elimination program, **Ivory Coast** reported only 3 new cases in 2015, in the endemic foci of Bonon and Sinfra. HAT is no longer a pu-

blic health issue in Ivory Coast, but enhanced passive surveillance must be maintained to eliminate HAT and prevent its re-emergence.

In 2015, the **Central African Republic** reported 147 new cases including 92 serological cases and 55 parasitological cases. This country is emerging from a conflict, and a return to safer conditions in the foci of Nola, Lobaye and Ombella-Mpoko, as well as the resumption of screening activities may improve the coverage of the population at risk, as well as the new case detection rate.

South Sudan reported 45 new cases in 2015, and 39 new cases in the first half of 2016, despite the conflict which caused nearly a million refugees to flee to neighbouring countries, such as the Democratic Republic of Congo, Uganda, Kenya and Ethiopia. The conflict prevents any active screening in the country, but is also raises the question of implementing active or passive surveillance of the refugees in neighbouring countries, followed by proper management after a diagnosis.

Guinea remains one of the countries most affected by human African trypanosomiasis in West Africa. A total of 29 new cases were diagnosed in 2015 and 43 new cases in the first half of 2016. Sleeping sickness is endemic on the coast, the major foci being in Boffa and Dubreka. This country is recovering from an Ebola epidemic, which led to the breakdown of healthcare services. THA control activities are suspended, except for passive screening at the Dubreka centre.

Chad reported 47 new cases in 2015. The disease is concentrated in the south of the country in the Mandoul focus. The use of combined approaches helped reduce the number of cases (on average, 100 new cases were reported per year between 2002 and 2013).

Congo reported 35 cases in 2015 and 8 new cases in the first half of 2016. Most active foci (Ngabe, Mossaka, Loukolela, Mpouya and Makotipoko) are located along the Congo River, which separates the country from the Democratic Republic of Congo.

In **Angola**, a third of the population is at risk. In 2015, 34 cases were reported, and a further 17 new cases were diagnosed between January in September 2016, out of a total of 14,073 people examined by passive screening. No active screening was conducted in 2016.

The **Democratic Republic of Congo** reported 2,339 new cases in 2015, out of a total of 2,102,547 people examined by active or passive screening.

The population at risk (exposed) in the DRC is estimated at 35 million by the WHO and 12,6 million by the National HAT Control Program. After a stagnation between 2011 and 2013, the number of new cases dropped between 2013 and 2014 while the coverage increased by 48%, in spite of a reduction in the number of mobile units from 34 to 30 between 2011 and 2015. The infection rate dropped from 0.39% down to 0.11%.

Uganda is the only country where the two forms of human African trypanosomiasis (*T.b gambiense* and *T.b rhodesiense*) coexist. In 2015, a total of 32 new cases of both *gambiense* and *rhodesiense* HAT were reported. Among those, only 5 cases were due to *T.b gambiense* (a further 2 were reported between January and September 2016) in a population at risk estimated at 10 million people. For *rhodesiense* HAT, 25 new cases were detected by passive screening, and 3 by active screening. Active screening was funded by

the Liverpool Tropical Medicine School in July-August 2015 and by the WHO in January 2016, but no new cases have been diagnosed. Uganda is currently facing an influx of South Sudanese refugees from endemic areas. In the absence of any screening, these people may cause a resurgence of HAT in the areas they have fled to.

C. Session 3: Operational research for HAT elimination

1. Combined approach to HAT control: the Mandoul focus in Chad

Peka Mallaye and al.

As of 2014, the National HAT Control Program set up a combined approach with the WHO, FIND, IRED and the CIRDES/IRD/MTSL group, which includes:



NSSCP CHAD

Passive case detection by deploying Rapid Diagnostic Tests (RDTs) in 10 health centres located in the HAT transmission area within the focus;

Active case detection by a mobile team traveling by car using CATs to sort suspected cases in villages accessible by car;

Active case detection by a mobile team traveling by motorcycle using RDTs to detect suspected cases in villages accessible and not accessible by car, followed by a referral system for parasitological confirmation;

Tsetse control using insecticide-impregnated screens in locations favourable to contacts between humans and tsetse flies.

The combination of these control approaches contributed to the decrease in the number of new HAT cases in 2015. Out of 47 new diagnosed cases, 22 (47%) were reported by the 10 health facilities during passive screening, 19 (40%) by the mobile team traveling by car during active screening, and 6 (13%) by the mobile team traveling by motorcycle. Only 4 flies were captured out of 8 entomological evaluations conducted between March 2014 and May 2016, using 44 sentinel traps every time.

In light of these results, in spite of the substantial contribution of RDTs in the passive detection of cases in fixed health facilities, it is important to focus on active screening by mobile teams traveling by car and motorcycle, as well as on vector control. These measures will help speed up the process of HAT elimination as a public health issue by 2020, as set out by the WHO roadmap.

2. Study on integrated HAT control in the Bonon focus in Ivory Coast

Kaba Dramane and al.



*Institute Pierre Richet
Ivory Coast*

The general objective was to understand the geographical, entomological, and parasitological factors that characterize an active HAT focus in an Ivorian forest area, to target control efforts. In the Bonon focus, the researchers set up untargeted vector control activities with the deployment of 1,880 insecticide-impregnated tiny targets, combined with medical supervision. In the Sinfra focus, they combined targeted vector control using tiny targets, with pour-on insecticidal treatments of the village pigs and cattle, medical surveys, and passive HAT surveillance in the health centres. A preliminary assessment at 3 months showed an overall reduction in apparent parasite density of 94.4%.

3. Integration of HAT control in the primary healthcare system in South Sudan

Angelique Mumbo and al.



*Malteser International
SOUTH SUDAN*

In 2014, the government of South Sudan launched a program with the Foundation for Innovative New Diagnostics (FIND), Malteser International and the WHO, as well as other partners, to intensify HAT control in the Maridi and Yei Counties, by integrating screening

into the primary healthcare system. The viability and profitability of this new strategy combining three diagnostic tools will be determined.

All 61 health facilities present in both counties were characterized, and the strategic centres will be upgraded to provide confirmatory diagnoses of HAT by microscopy or loop-mediated isothermal amplification (LAMP) test. The health workers were trained by experts from the Makerere University, Uganda. Screening of patients suspected of HAT started in May 2015. Out of the 10,609 people suspected of HAT screened since May 2015, 16 HAT cases were diagnosed and treated successfully. This approach has improved dramatically the coverage of the population at risk, and could be a sustainable way of controlling the disease.

4. Contribution of “the HAT Atlas” in the planning of active screening activities by mobile teams in the DRC

Shampa and al.

Given the lack of material and financial resources and accessibility issues in certain villages, it is important to target the villages properly based on epidemiological evidence. The Atlas was used in the DRC to identify the endemic villages to visit.



NSSCP DRC

This tool outlines the activities as well as active and passive screening results in the endemic villages.

The planning of villages to visit was based on the following criteria:

At least one case reported over the past three years

Absence of cases over the past three years, but at least one case reported 4 to 5 years ago

The villages which reported no new cases over the past 5 years were excluded from active screening.

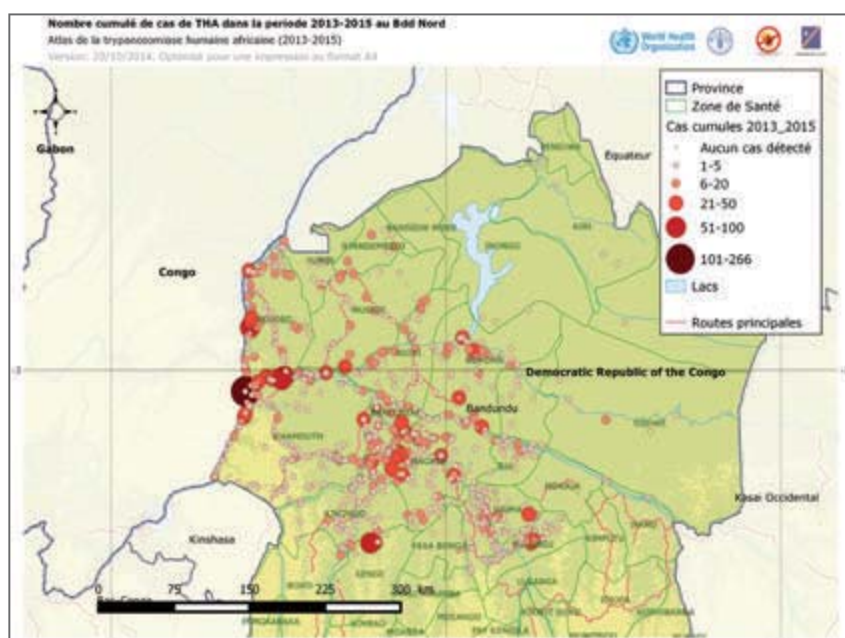
The planning of active screening was based on the following criteria:

- The epidemiological status of the village, based on reported cases
- The size of the population to examine, based on the capacity of the mobile team

- The most appropriate time to visit based on the constraints imposed by seasons
- Road conditions

The planning of active screening in the DRC was decided during a seminar with officials from the endemic provinces. A total of 3,907 endemic villages were selected (population estimated at 3,765,455), of which 2,772 were programmed (population estimated at 2,759,620).

Identification of axes



Prior to August 2013, only 4 HAT diagnostic centres were covering a population of 2.2 million people at risk within the *gambiense* region. The average distance between these 4 facilities and infected people was 25.1 km. Since then however, 212 facilities have been equipped with RDTs, thereby increasing the passive surveillance coverage, and 12 were upgraded to perform parasitology testing by LED fluorescence microscopy, and 3 by LAMP test. By the end of 2014, the number of participating facilities was reduced to 125, due to changes in the geographical distribution of cases.

In 2015, the number was increased back to 149 to include selected private clinics and health facilities serving refugee camps near the border with the Adjumani district, South Sudan. In May 2016, 18,095 people were tested with HAT RDTs. Out of 460 positives, 16 were confirmed as HAT cases. Nine of these cases were confirmed in 2014, 4 in 2015, and only 3 in 2016.

This strategy was successful in detecting HAT cases passively in low-prevalence and resource-limited settings, such as in northwest Uganda. However, the lack of diagnostic confirmation of 23.2% of the suspected cases is a challenge that must be addressed.

5. Passive surveillance of *gambiense* HAT using a new diagnostic algorithm in a low prevalence setting in north western Uganda

Charles Wamboga and al.



Ministry of Health
UGANDA

active surveillance with mobile teams very expensive.

The authors developed a new diagnostic algorithm targeting three levels of the health system to improve access to *gambiense* HAT diagnosis. The prevalence of HAT has been declining over the past few years, making case detection through

6. Improved access to *rhodesiense* HAT diagnosis in a conservation area in Malawi helped early case detection and reduced mortality

Sylvain Bieler and al.

Authors reported a project to improve passive screening signed in 2013 between the Ministry of Health of Malawi and FIND. The capacity to confirm the diagnosis was strengthened in 5 centres, through technician training and laboratory upgrading to include parasitological diagnosis, using centrifuges



FIND
Geneva, SWITZERLAND

and LED fluorescence microscopy. One facility was upgraded to perform LAMP tests. Between August 2014 and July 2016, 55 HAT cases were diagnosed out of 1,349 suspected using this new strategy. Among these 55 cases, 19 (35%) were diagnosed by parasitology testing in centres unable to do so previously, while 36 (65%) were diagnosed in the former Rumpfi sites.

Between August 2014 and July 2016, only 35% of cases were diagnosed in the new centres. Therefore, the proportion of cases diagnosed in the new centres increased from 21% in 2014 to 63% in 2016. However, the project does not seem to affect the stage of diagnosis. Nearly 80% of cases are diagnosed as stage 2 HAT, whether before or after the implementation of the project. The availability of diagnostic services located closer to infected people may promote early case detection, improve prognosis and reduce mortality.

7. Demonstration of innovative methods to improve HAT screening in two health districts in the DRC, the TRYP ELIM-project

Yves Claes and al.



*Institute of Tropical medicine
Antwerp, BELGIUM*

A 3-year operational pilot study (2016-2018) is under way in the Mosango and Yasa Bonga health zones in the Kwilu Province of the DRC, to evaluate the feasibility and cost-effectiveness of these innovative methods, and their perception by the communi-

ties, and to define the means required for up-scaling. Active screening is organized with mini mobile teams traveling by motorbike, to perform door-to-door serological tests and collect electronic data. This strategy is flexible and helps rationalise planning.

An electronic platform connected to a geo-referenced database generates maps and lists to help plan active screening. This electronic platform also helps control the quality of the performed diagnostic tests (parasite video) and data. According to preliminary results, 6 screening agents examined 24,962 people, with an average of 90 people/day/agent, and 4 new cases were diagnosed. One year after the first intervention, vector control with impregnated small screens (tiny targets)

reduced the density of tsetse flies by 90% in the intervention area, and by 60% in the area of non-intervention. However, it is too early to draw conclusions.

8. Diagnostic tools for HAT elimination and clinical trials: DiTECT-HAT

Veerle Lejon and al.

The objective of the DiTECT-HAT project is to evaluate the accuracy and feasibility of new diagnostic tools and design algorithms to diagnose gambiense HAT in three situations: passive case detection in peripheral health centres, post-elimination monitoring to detect any re-emergence of the disease, and early cure test in clinical trials. For passive case detection, the project will determine the performance and cost of rapid diagnostic tests (RDTs) in clinical suspects identified in peripheral health centres performing HAT diagnosis and treatment, as well as in sites performing serological testing in the DRC, Ivory Coast and Guinea.



*IRD
FRANCE*

These RDTs will be combined with serological and/or molecular tests on dried blood spots performed in reference centres. The cost-effectiveness of different algorithms with high positive predictive values will be determined to treat suspected cases without parasitological confirmation. For post-elimination monitoring, the feasibility and cost of diagnostic algorithms based on RDTs, and of high-speed serological and molecular tests will be determined.

Blood samples will be collected on filter paper during door-to-door visits in low-prevalence foci. An appropriate warning level will be established to send mobile teams in areas at risk, minimizing the number of false alarms. Finally, the accuracy of neopterin and of the presence of parasitic RNA as markers of early cure will be determined in a clinical trial. The availability of a reliable early marker should help accelerate the development of new drugs to treat HAT and improve the management of relapses. The DiTECT-HAT project will focus on low-prevalence areas in the DRC, Guinea, Ivory Coast and Burkina Faso. Regional reference centres in the DRC (National Institute for Biomedical Research) and in Burkina Faso (CIRDES) will perform the reference tests: ELISA, trypanolysis, RT-PCR, LAMP, SL-RNA and neopterin.

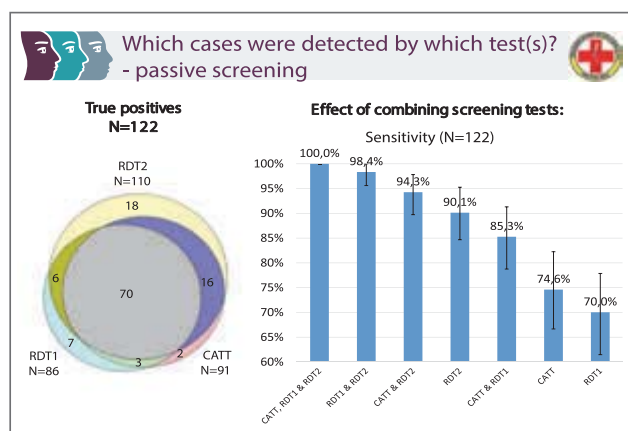
9. Prospective evaluation of a rapid diagnostic test for *gambiense* HAT based on recombinant antigens in the DRC

Crispin Lumbala and al.



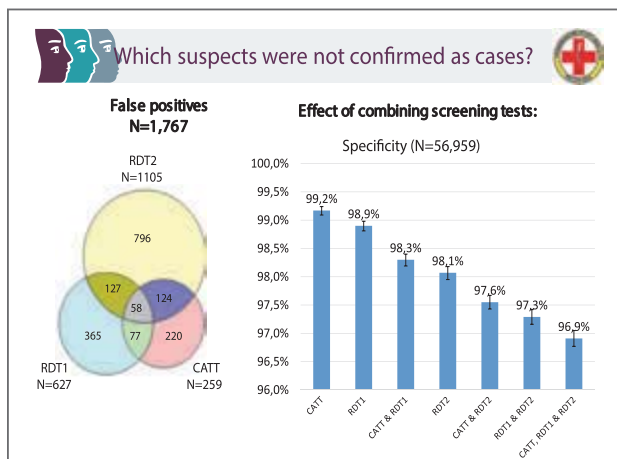
NSSCP DRC

Serological tests are used as input data in diagnostic algorithms for *gambiense* human African trypanosomiasis (HAT). Until recently, the Card Agglutination Test for Trypanosomiasis (CATT) was the only screening tool used routinely to screen for HAT. This test has several limitations, which have been partially addressed by the recent introduction of rapid diagnostic tests (RDTs). However, current RDTs, such as the SD BIOLINE HAT, require the production of native antigens, which is expensive and difficult.



An RDT using recombinant antigens (SD BIOLINE HAT 2.0) was evaluated in 10 health facilities and by 5 mobile teams in the DRC. A population of 57,632 individuals, including 260 confirmed HAT cases, was screened using CATT, SD BIOLINE HAT and SD BIOLINE HAT 2.0. When results of passive and active screening were combined, the sensitivity of screening tests was 62.5%, 59.0% and 71.2%, and the specificity was 99.2%, 98.9% and 98.1%, respectively. Sensitivity results were lower than previously reported, as some HAT cases were detected by only one test. Passive screening sensitivity (74.6%, 70.0% and 90.1%) was higher than that of active screening (51.8%, 49.2% and 54.8%). The difference may be attributed to variable antigen expression by parasites over time, causing the host to develop immune res-

ponses to numerous antigens as the disease progresses. While the sensitivity of the tests was already high in passive screening, combining SD BIOLINE HAT with SD BIOLINE HAT 2.0 increased the sensitivity (98.4%).



This effect was more pronounced in active screening, where the sensitivity of all 3 tests was low, and where combining both RDTs greatly improved sensitivity (83.0%). While the cost-effectiveness of algorithms including several screening tests should be investigated, this study demonstrated that using two or more tests to screen for HAT greatly improves sensitivity.

The authors suggested that the development of a 3rd generation RDT combining several antigens may be of interest to improve sensitivity.

10. Evaluation of rapid diagnostic tests in passive or active HAT detection in Guinea

Oumou Camara and al.

The objective was to evaluate the potential of SD BIOLINE-HAT in Guinea and its use in various diagnostic approaches:



NSSCP GUINEA

1. A passive diagnosis system with RDTs deployed in peripheral health centres and outposts;
2. Active door-to-door screening in villages;
3. Active screening targeting the families and neighbourhood of former patients or seropositive individuals. The initial analyses carried out on a bank

of plasma samples showed a sensitivity of 99.6% and a specificity of 87.9%. The test's specificity was higher under field conditions, at around 97% for each of the strategies used, suggesting that the use of frozen plasma samples is not optimal for the evaluation of the test characteristics.

In a non-biased population sample (general population screening), the positive predictive value of the test was extremely low (13%), but it varied greatly according to the screening strategy and the disease prevalence, and was up to 62% with active screening in high-prevalence areas. Therefore, the use of RDTs seems interesting in the various diagnosis strategies used to eliminate HAT in Guinea.

11. The immune trypanolysis test: an accurate serological marker to manage elimination of *gambiense* HAT

Emilie Dama and al.



CIRDES
BURKINA FASO

Post-elimination surveillance is required to ensure that the transmission of human African trypanosomiasis (HAT) remains nil and to avoid any re-emergence due to the presence of *T.b gambiense* reservoirs in animals and/or humans.

There is no tool currently available to attest or validate HAT elimination. The serological immune trypanolysis test is increasingly used in decision algorithms to characterise CATT- or RDT-positive cases unconfirmed with parasitology tests.

To confirm the high specificity of immune trypanolysis, the authors tested samples from domestic animals in a tsetse-infested area in Ethiopia, a country devoid of *T.b gambiense* but where bovine trypanosomiasis is prevalent. They then tested cattle and human samples from southwestern Burkina Faso, a historical *gambiense* HAT focus that still harbours tsetse populations and animal trypanosomiasis. Lastly, they tested human samples from active foci in Ivory Coast and Guinea. Their results showed a total absence of positive trypanolysis in animals from Ethiopia,

whereas in the historical HAT foci in Burkina Faso, 4.89% (14/286) of cattle were trypanolysis positive. In humans, none of the 729 samples were trypanolysis positive in Burkina Faso, while the percentage of positives was 3.77 (44/1166) in Guinea, including 7 new cases diagnosed during the sampling, and 1.3% in Ivory Coast (8/598). According to the authors, trypanolysis, whose very high specificity has been confirmed in humans, could potentially be used to confirm HAT elimination in a given area. However, further studies on the specificity of trypanolysis in *gambiense* diagnosis in animals should be carried out.

12. Use of RDTs in an integrated HAT elimination program in Uganda

Jennifer Palmer and al.

The authors used the theories of the psychologist Kahneman on fast and slow thinking to discuss the unexpected complications that arose 2 years after the introduction of rapid diagnostics tests (RDTs) into Uganda's Integrated Sleeping Sickness Elimination Programme, and the coping strategies devised by primary healthcare staff, district supervisors and patients. They interviewed 20 RDT-positive suspects on their knowledge, experiences and perceptions of RDTs, and program supervisors on the information system, support for the implemented strategy and problems encountered.



University of Edinburgh
UNITED KINGDOM

They also organized 14 focus groups with communities close to RDT centres, including refugees, to discuss their knowledge of RDTs. They concluded that RDTs offer a quick way to identify potential HAT cases when traditional active screening is no longer attractive for economic or ideological reasons. This study raised interesting contradictions, perhaps related to the study design. Personal interactions with supervisors seem to play an important role to overcome healthcare quality problems in the care centres, but communication on the usefulness of the test is complicated by the population's poor understanding

of RDTs. RDTs also raise new challenges, whose costs and social implications must be recognised. A slower diagnostic approach may be preferable, not only aims to confirm the biomedical diagnosis, but also to ensure that it is socially understood and activates appropriate health care responses. The program must also meet the needs of all health personnel and patients. It is essential to take into account these considerations to achieve the elimination objectives.

13. Knowledge, attitudes and practices related to HAT among communities in Yei County, South Sudan

Salomé Bukachi and al.



University of Nairobi
KENYA

The authors conducted a basic social survey to collect relevant information for the development of effective information, education and communication (IEC) channels targeting populations in endemic areas. The specific objectives of this survey are to identify:

Knowledge about the causes of HAT, symptoms, management, seeking treatment

Attitudes and practices regarding the diagnosis and treatment of HAT

Preferred channels and sources of information for African human trypanosomiasis

This cross-sectional survey was conducted in the Yei County using questionnaires, interviews of key informants and group discussions with key people. The survey included 603 people (55% of men and 45% of women), mostly farmers and 58% had completed primary school. Most responders (63% to 99%) had some knowledge on HAT causes, prevention and cure, and community perception.

However, for 1% to 37% of them, prevention, cure and perception of the disease evoked mosquitoes & environment or dirty water, mosquito nets & vaccination, and stigmatization, respectively. The symptoms named included headaches, sleep disorders, itching, and other signs such as memory loss.

The main reasons for non-consultation at health centres were transportation difficulties and the cost of care. Preferred sources of information included radio, health personnel and village elders. The authors concluded by stressing the need for an appropriate communication strategy to eliminate existing myths and misconceptions, and raise awareness on specific information using identified communication structures. The results were used to develop a strategic communication plan for health services in Yei County. These findings will also help communicate information effectively on public health interventions that are crucial to achieve the WHO objective of HAT elimination by 2020.

Session 4: Research on new treatment options

1. Improving efficiency and quality in clinical trials in sub-Saharan Africa

Christian Burri and al.

The authors investigated difficulties met in clinical trials to optimize the efficiency of processes in Sub-Saharan Africa while maintaining quality. Their working hypothesis were:

How can time be saved while maintaining quality in clinical trials in sub-Saharan Africa?

What are the advantages and challenges raised by the Good Clinical Practice (GCP) guidelines, and how must they be applied to clinical trials in sub-Saharan Africa?

How can the relevance of the clinical trial protocols be improved in sub-Saharan Africa?

The authors combined several exploratory methods. A total of 60 members of the clinical trial staff, with various professional capacities, were asked questions on the quality, guidelines, challenges, and inefficiencies of clinical trials in two English-speaking countries (Kenya and Ghana) and two French-speaking countries (Senegal and Burkina Faso). The interviews were analysed to identify recurring themes based on settings and positions.



University of Bale
SWITZERLAND

They also conducted an online survey of the staff working on clinical trials in Sub Saharan Africa, to investigate protocol suitability based on the main themes. The results highlight two problems limiting the efficacy of the studies: study planning (mainly described as poor and not suited to the context) and site organization (mainly staff turnover and workload).

These two problems are of particular relevance since they relate only to sponsors and sites and are therefore independent of external conditions (e.g. lengthy approval processes and population issues). The online survey confirmed the necessity to adapt trial protocols to local settings by early involvement of the sites and careful consideration of local capacity, systems and conditions.

According to the authors, the efficiency of clinical trials could be improved by in-depth site assessment, appropriate and coherent planning, clear task allocation, and strengthening of management capacities. The involvement of study sites in the development of the protocol was perceived as beneficial.

2. Evaluation of trypanocidal drugs used in HAT to treat *Trypanosoma lewisi* infection

Mariette Dethoua and al.



University of Bangui
CENTRAL AFRICAN REP.

According to the authors, trypanosomes that are pathogenic for animals are also potentially pathogenic for humans. Several cases of human infection by *Trypanosoma lewisi*, a parasite found in rats, have been reported, and the number of these infections is possibly under-estimated. Cases of self-cure have been described but other cases require treatment with drugs used in human African trypanosomiasis. The efficacy of several of these drugs, including fexinidazole, a new oral drug candidate, has been evaluated *in vitro* and compared to their efficacy against *T. brucei gambiense*.

All had comparable activities against both parasites, except for suramine, which is not effective. Trypano-

cidal drugs were then evaluated *in vivo* in rats immunosuppressed with the administration of cyclophosphamide.

The highest efficacy was obtained with fexinidazole and pentamidine (15 mg/kg), a cure being achieved in 7 and 10 days, respectively. Rats receiving nifurtimox-eflornithine combination therapy (NECT) were cured after 28 days, while melarsoprol was only weakly active. At the dose of 4 mg/kg recommended for the treatment of HAT and pneumonia, pentamidine was not active but its efficacy was demonstrated at a higher dose of 15 mg/kg.

Even if cases of self-cure have been reported in humans infected with *T. lewisi*, the conclusions of this study will be very useful to treat *T. lewisi* infections extending to the cerebrospinal fluid. The identification of effective drugs with reduced toxicity will help improve the management of new cases of atypical trypanosomiasis.

3. Impact of clinical trials for trypanocidal drug development on efforts towards disease elimination

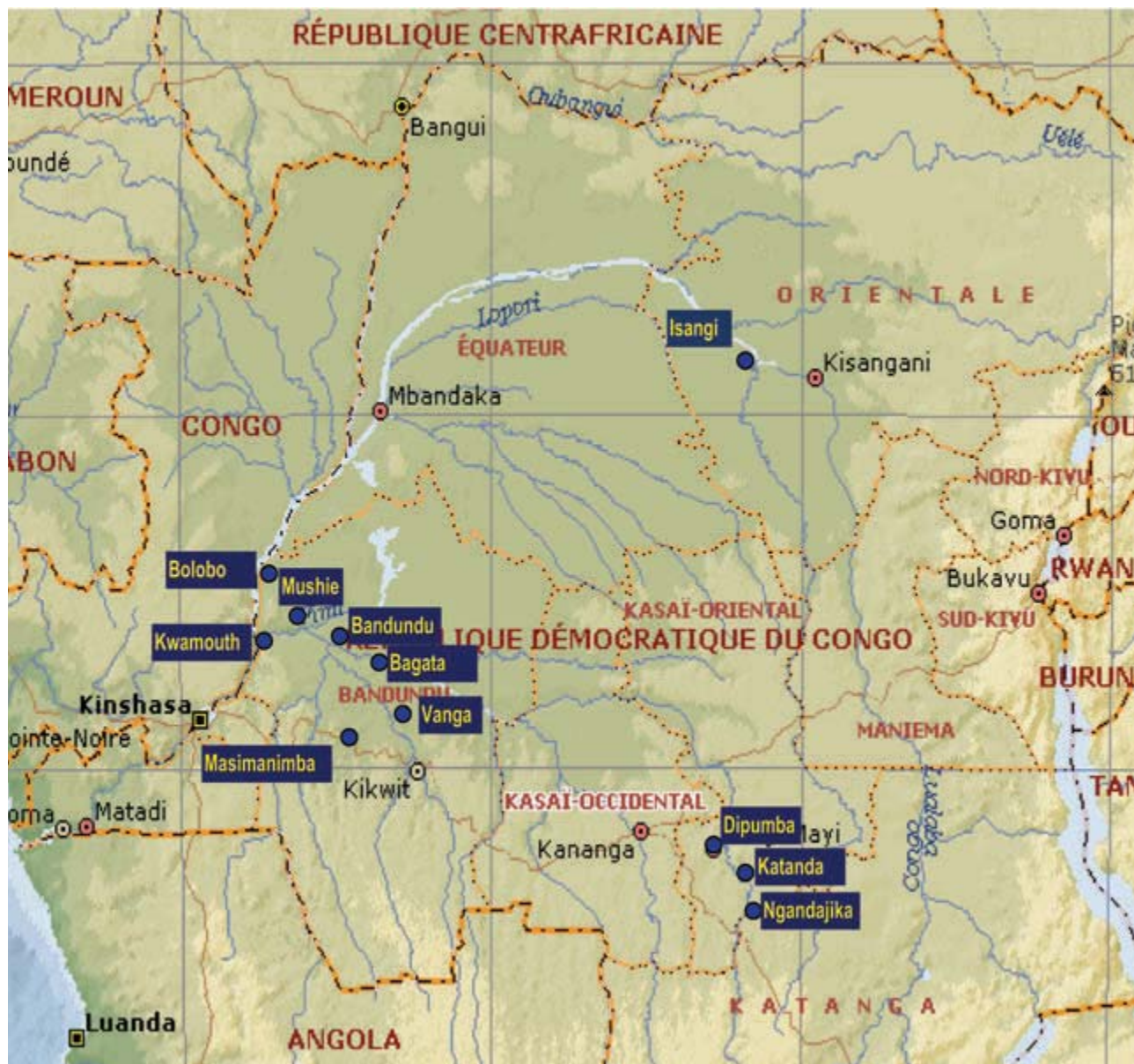
Olaf Valverde and al.

DNDi performs clinical trials to develop new treatments for human African trypanosomiasis (HAT) in disease-endemic countries, mainly in the Democratic Republic of Congo (DRC) but also in the Central African Republic (CAR). Thus through intensive screening of populations at risk to identify patients to be included in clinical trials, DNDi contributes to HAT control and elimination. In 2015, mobile teams of the National HAT Control Programme (NSSCP), supported by DNDi, examined over 25% of the 2.1 million people screened throughout country.



DNDi
SWITZERLAND

In addition, health infrastructures, equipment, and training have been upgraded to meet the international standards for clinical trials. These measures improved the general environment of care in health



Sites of Clinical trials of DNDi in DRC

structures and strengthened capacities for staff involved in clinical trials. Three ongoing clinical trials are currently testing a new oral drug for HAT (fexinidazole) in nine reference hospitals in the DRC, and two more are expected to start in 2016. Sites are selected after a multidisciplinary assessment including a review of the case detection rate.

Together with the HAT Platform, DNDi has contributed to strengthening capacities in endemic countries by training researchers, monitors, and practitioners in Good Clinical Practice, laboratory diagnosis,

pharmacovigilance, and HAT patient examination techniques, including those specific to the trials. Due to a decline in the number of new cases, recruitment into the fexinidazole trials in the DRC is problematic.

The support of active screening by mobile teams will be complemented by strengthening of the current passive surveillance network, set up by NSSCP in areas of ongoing clinical trials. This measure is expected not only to help identify additional candidates for the clinical trials, but also to establish a passive surveillance system for sustainable elimination.

4. Phase I data on SCYX-7158 – a single dose treatment for HAT

Antoine Tarral and al.



DNDi
SWITZERLAND

The number of cases of human African trypanosomiasis (HAT) dropped significantly over the last decade, mainly due to improved case detection and access to treatment. The current first-line treatment for second stage *gambiense* HAT

with the nifurtimox-eflornithine combination therapy (NECT) is a vast improvement over previous treatments, but it requires staging of the disease and hospitalization during intravenous administration. Two other oral treatments for HAT, fexinidazole and SCYX-7158, are currently under clinical development by DNDi.

SCYX-7158, a single dose treatment, the former is a particularly interesting treatment tool to promote sustained elimination in rural areas with few health structures and where HAT is prevalent.

Oxaborole compound discovered by Anacor Pharmaceuticals, SCYX-7158 is the first new chemical entity generated from DNDi's lead optimization programme. Preclinical studies in an animal model showed that SCYX-7158 was safe and efficacious to treat stage 2 HAT, as it is able to cross the blood-brain barrier. First-in-man studies started in 2012 with a total of 128 subjects included in a Phase I single ascending dose study evaluating its safety and tolerability. PK results showed that SCYX-7158 was quite rapidly absorbed and that levels remained steady for at least four days.

This long half-life means that SCYX-7158 could be used as a single-dose treatment. Its clinical safety profile revealed no problem with doses ranging from 20 to 1200 mg. The therapeutic dose of 960mg selected for the pivotal trial is associated with a 90% probability of achieving pharmacologically active concentrations of the free compound in the CSF. No significant dose-related adverse event was detected in the human volunteers.

5. Phase IIIb open-label, multicentre clinical study evaluating the use of fexinidazole in outpatients and special populations

Christelle Perdrieu and al.

The primary objective of this prospective, multicentre, open-label cohort study is to evaluate the efficacy of fexinidazole administered to adult and paediatric HAT patients (all stages of the disease) either in hospital or at home. Three research sites in the DRC



DNDi
SWITZERLAND

are expected to recruit 174 patients. Success or failure is assessed 12 and 18 months after treatment completion. The secondary objectives of the study are to evaluate the safety, adherence to treatment and feasibility of patient self-management from admission to treatment, acceptability of the proposed packaging and understanding of the instructions for use. The pharmacokinetic parameters of fexinidazole and its main metabolites in the blood are measured in hospitalised patients only. The dose regimen is based on the weight of the patient: < 35 kg or ≥ 35 kg.

Eligible patients are adults and children aged 6 and over, irrespective of the stage of the disease, with or without concomitant diseases. Pregnant women (beyond the first quarter), breastfeeding women, and low-bodyweight patients are also eligible.

To be eligible for home treatment, patients must have a Karnofsky index > 50%, and a clear understanding of the treatment instructions. Pregnant or breastfeeding women, and patients with neurological symptoms or medical or psychiatric contraindications to the treatment cannot be treated at home. Patients must be reachable and reside near the study centre during the treatment period.

A carer or responsible person must be with the patient during the treatment period to remind him/her to take the treatment, help him/her with meals, etc. He/she will **also** be responsible for calling the investigator in case of AE/SAE, or for any question. Patients unable to continue their treatment at home

will be admitted to hospital. An interview is conducted on the day of treatment dispensation using a specific questionnaire designed with Sanofi, industrial partner, to verify that the patient and the carer have a clear understanding of the instructions for use. Another interview is conducted at the end of treatment to verify treatment compliance, determine the acceptability of the packaging insert and the instructions, and record any adverse event and concomitant medication taken by the patient.

Session 5. Roundtable on the role of ethics committees, regulatory authorities and pharmacovigilance systems in research

Before giving the floor to the participants, the chairman of the session highlighted the challenges faced by the ethics committees, regulatory authorities and pharmacovigilance systems. Among the 6 regulatory functions, he insisted on the evaluation and registration of the product or drug, as well as on the follow-up of adverse events.

The challenges faced by regulatory authorities are the officials' qualifications, the lengthy process to review the protocols, and often the lack of interest of certain authorities for clinical trials. He reiterated the 7 principles of ethics committees for clinical research, and he insisted on the importance of good clinical practice (GCP) and informed consent procedures, which must be adapted to clinical trials with limited resources.

1. Ethical considerations on research in sub-Saharan Africa

Félicien Munday



University of Kinshasa
DRC

the community (religions and independent groups)

The study protocol must be comprehensive and rigorous (methodology, objective, etc.);

The ethics committee includes experts (physicians, researchers, lawyers, statisticians, pharmacists), and lay persons representing

who play a role before (approval), during (verification of interim reports) and after (verification of final report) the study. The ethics committee and researchers pursue the same objective (good quality research);

The ethics committee applies the ICH GCP guidelines, with a right to monitor the well-being, safety and rights of research subjects. The ethics committee is also responsible for the education of its members. It must comply with the standard operating procedures. Following the review of a study protocol, ethics committees may issue an approval/favourable opinion, a conditional approval or a rejection.

2. Clinical research during the Ebola outbreak in Guinea

Younoussa Sow

With 3,558 cases confirmed on 20 March 2016, the Ebola outbreak practically destroyed the health system in Guinea, but it also triggered a strong mobilisation against the disease.



Ethics Committee
GUINEA

The National Ethics Committee for Health Research (CNERS) in Guinea was founded on 29 October 1998 and developed between 2012 and 2014 with the support of the European & Developing Countries Clinical Trials Partnership (EDCTP) to renovate the building, enhance documentation, create a database, etc.

In 2016, this ethics committee was further strengthened with the support of the WHO. The speaker talked about the review of protocols by the ethics committee during the Ebola outbreak. In 2015, the Guinea ethics committee reviewed 76 protocols. In 2016, 29 research protocols on Ebola and 18 non-Ebola protocols were reviewed.

However, Guinea currently has no regulatory guidelines regarding intellectual property, biological sample banks, and community participation. Furthermore, the ethics committee's standard operating procedures do not provide for emergency situations such as the Ebola outbreak. However, in 2016, the

members of CNERS were trained by the WHO on ethical considerations in a situation of emergency and on the management of biological sample banks. The frequency of the ethics committee meetings was increased during the Ebola outbreak.

3. Experience of the National Pharmacovigilance Centre of the DRC

Ntamabyaliro Nsengi



University of Kinshasa
DRC

The efficacy but the also the safety of a medicinal product must be demonstrated before it is granted a marketing authorisation. Medicinal products such as melarsoprol and eflornithine are associated with numerous side effects. A total of 677 moderate adverse events associated to NECT have been reported to the National Pharmacovigilance (PV) Centre of the DRC, and to the centre in Uppsala, of which 665 were reported by MSF. The speaker explained that the PV centre in the DRC has issued no national guideline, and communication between the national PV centre and treatment sites is difficult. Consequently, notifications are rare. A solution could be the creation of regional PV centres, or the submission of PV reports by telephone.

A pilot study is currently testing this latter solution with the National Malaria Control Programme in the DRC. Further development of the PV centre in the DRC is difficult and funding is lacking.

This roundtable led to exchanges on notifications from health facilities to the pharmacovigilance centre, the destruction of samples, the approval of study protocols by an institutional or local ethics committee, and the influence of the amount of the compensation offered to the study participants.

Two main conclusions were drawn: a pharmacovigilance system should be set up to monitor all HAT treatments in all endemic countries, and the ethics committees in endemic countries should be encouraged to harmonise the evaluation processes of HAT studies, to support joint reviews.

Session 6. Vector control for HAT elimination

1. Reducing contacts between humans and tsetse flies using impregnated screens increases the efficacy and HAT screening campaigns

Moise Kagbadouno and al.

The authors combined vector control activities with medical interventions in the Boffa focus in Guinea, and they measured the impact of this approach on the control of endemic sleeping sickness. The focus was divided into two separate areas on either side of the Rio Pongo: screening/treatment in the west and screening/treatment and vector control in the east. A population census was carried out and basic entomological data were collected in both areas at the beginning of the study. Then 4,673 insecticide-impregnated screens were deployed only in the eastern area (13 screens/km², i.e. 1 screen per 4 inhabitants). Medical prospections were carried out in both areas in 2012 and 2013.

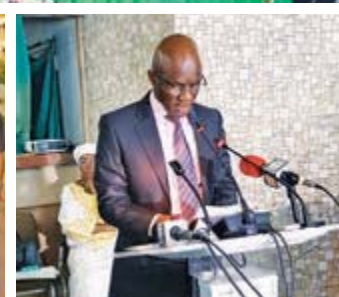
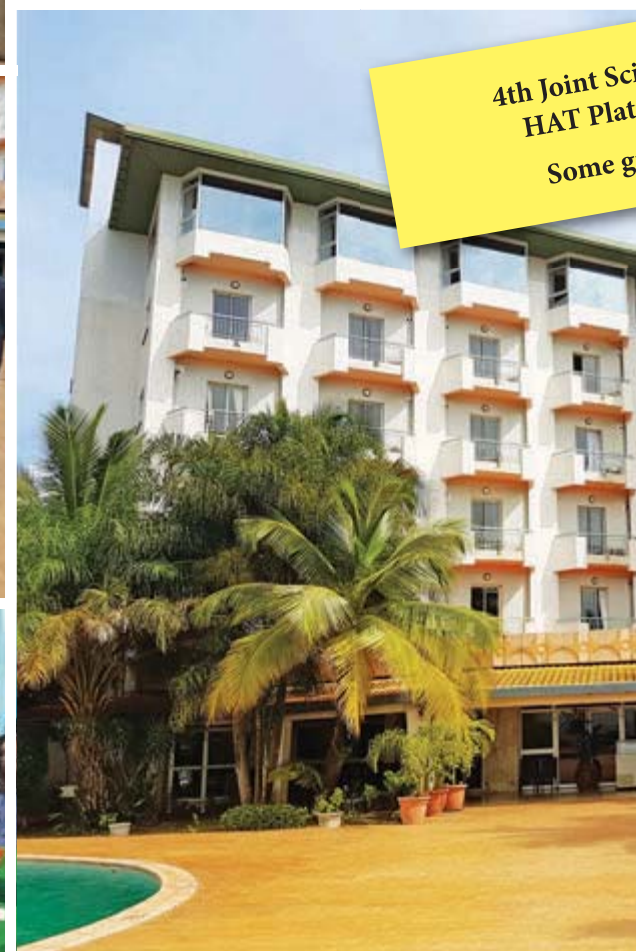


NSSCP
GUINEA

In the vector control area, this strategy resulted in an 80% reduction in tsetse density, a significant reduction in human-vector contacts, a reduction in the disease's prevalence (from 0.3% to 0.1%; $p=0.01$), and an incidence of new infections close to zero ($<0.1\%$).



Inversely, the incidence was 10 times greater in the western area with a slight increase in disease prevalence (from 0.5 to 0.7%; $p=0.34$). These results show that the combination of vector control and medical control had a major impact on transmission and helped accelerate the process of HAT elimination. Although active screening activities had to be





Scientific Meeting
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discontinued during the Ebola outbreak, vector control interventions were able to continue. The analysis of the distribution of HAT cases (2014-2016) in the Boffa focus shows that, even in the absence of active screening, vector control interventions protected the population in areas covered by screens, whereas HAT prevalence increased sharply in areas not covered by screens.

2. A molecular method to discriminate between mass-reared sterile and wild tsetse flies during eradication programs using the sterile insect technique -

Sophie Ravel and al.



IRD
FRANCE

The Government of Senegal launched several years ago a project aiming to eradicate *Glossina palpalis gambiensis* from the Niayes area to manage animal trypanosomiasis. The elimination of animal trypanosomiasis would help develop more efficient livestock produc-

tion systems. The project was implemented using an area-wide integrated pest management strategy where the sterile flies used for the sterile insect technique (SIT) component were derived from a colony originating from Burkina Faso.

To monitor the efficacy of mass-reared sterile male releases it was necessary to discriminate between wild and sterile male *G. p. gambiensis* sampled in monitoring traps. Before being released, sterile male flies were marked with a fluorescent dye powder. The marking was however not infallible, as some sterile flies were only slightly marked or some wild flies got contaminated with a few dye particles in the monitoring traps.

Trapped flies can also be damaged due to predation by ants, making it difficult to discriminate between wild and sterile males using a fluorescence camera and/or a fluorescence microscope. They developed a molecular technique based on the determination of cytochrome oxidase haplotypes of *G. p. gambiensis* to discriminate between wild and mass-reared sterile males. DNA was isolated from the head of flies

and a portion of the 3' end of the mitochondrial gene coding for subunit I of cytochrome oxidase was amplified and finally sequenced. Their results indicated that all mass-reared sterile males from the Burkina Faso colony displayed the same haplotype and systematically differed from wild male flies trapped in Senegal and Burkina Faso. This allowed 100% discrimination between sterile and wild male *G. p. gambiensis*. This tool might be useful for other tsetse control campaigns with a SIT component included in the Pan-African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) and, more generally, in other vector or insect pest control programs.

3. Control of *G. fuscipes fuscipes* in the Mandoul HAT focus (southern Chad), using tiny targets -

Jean-Baptiste Rayaisse and al.

The Mandoul focus is an area of endemic sleeping sickness inhabited by a significant cattle population, exposing humans to the risk of contracting animal African trypanosomiasis. This is why a vector control campaign was initiated, whose primary objective was to eliminate host-vector contacts. An awareness campaign was first conducted, followed by a population census.



CIRDES
BURKINA FASO

A baseline entomological survey was then carried out, followed by the initiation of a vector control campaign using tiny targets impregnated with deltamethrin at the dose of 300mg/m². The awareness campaign led to the establishment of 39 target-monitoring committees in the 111 villages bordering the river, an area inhabited by 38.674 people. The baseline entomological investigation revealed the presence of *Glossina fuscipes fuscipes* with an average density of 0.67 tsetse/trap/day, ranging from 0 to 26 tsetse/trap/day depending on the site.

Over 2,600 tiny targets were deployed in January 2014, thereafter replaced annually with new ones. Monitoring of the 44 sentinel traps showed that tsetse densities dropped sharply (> 99%) which in turn

reduced the incidence of HAT. This is evidence of the effectiveness the tiny targets in tsetse control. A simultaneous follow-up of trypanosome prevalence in animals would provide additional indicators of the impact of this vector control campaign.

Session 7. Basic research for HAT elimination

1. Research into immunological markers of latent or on-going HAT in seropositive suspects with negative parasitology

Mamadou Camara and al.



NSSCP
GUINEA

The authors present the results of several studies conducted in Guinea and Ivory Coast to analyse the expression of immunological markers in patients and seropositive individuals not confirmed parasitologically and monitored over several years.

Although certain individuals maintain high antibody levels over long periods (>2 years), others develop the disease within months following the initial diagnosis. The seropositive individuals, strongly suspected of being carriers of latent infections, are generally not treated and may play a role in maintaining transmission in spite of control efforts. In Guinea, high plasma levels of IL10, TNFα and HLA-G were predictive of a rapid development of the disease.

Inversely, high levels of IL8 were observed in individuals with decreasing antibody levels, considered as potentially undergoing a spontaneous recovery. In Ivory Coast, an INFγ response during stimulations on whole blood was observed only in seropositive individuals maintaining a strong serological response over time. This response was lost in individuals who became seronegative, and it was absent in patients in the active stage of the infection or after their recovery. These preliminary results suggest that such markers, predicting an on-going or latent infection, could be used to develop new diagnostic tools targeting seropositive cases to improve their detection and management.

2. Study of host genetics factors involved in resistance or susceptibility to *Trypanosoma brucei gambiense* infection in Guinea

Justin Kaboré and al.

Human African trypanosomiasis (HAT) or sleeping sickness is a disease of sub-Saharan Africa caused by two trypanosome sub-species transmitted by tsetse flies, *Trypanosoma brucei gambiense* (in West and Central Africa) and *Trypanosoma brucei rhodesiense* (in East and southern Africa), *T.b. gambiense* being responsible for over 95% of all HAT cases. Long considered as invariably fatal, observations are increasingly indicating that infection by *T.b. gambiense* can result in a wide range of clinical outcomes in humans.



CIRDES
BURKINA FASO

Indeed, *T.b. gambiense* in West and Central Africa is characterized by a broad clinical diversity, ranging from asymptomatic to acute infections, and cases of spontaneous cure have even been reported. Moreover, individuals with high responses to the card agglutination test for trypanosomiasis (CATT), individuals positive for the highly specific *T.b. gambiense* immune trypanolysis test (TL), and individuals negative for parasitology test results have been reported in several endemic foci in West Africa.

The determinism of this clinical diversity is still unclear but it could be due to the host's genetic factors. The objective of our study is to determine the genes involved in the susceptibility or resistance to the disease caused by *T.b. gambiense*. We selected 10 genes based on their involvement in the clinical diversity of HAT or other parasitic diseases as described in the literature: APOL1, HPR, HLA-G, HLA-A, IL10, IL8, IL6, IFNγ, MIF and TNFα. The polymorphisms of these genes were then genotyped across all samples. The preliminary results provided 476 DNA samples, representing 251 cases, 73 seropositive individuals and 152 controls. These samples are used for the candidate genes study and these results are currently being analysed.

Reading of the final communiqué and selection of the best poster

At the end of this session and after lunch, a final communiqué on the scientific meeting was read and adopted by the participants in the presence of the Secretary General of Health of Guinea.

1. Coverage of the population at risk must be improved, using the following tools and strategies:

The Atlas of the human African trypanosomiasis for an effective planning of active screening

Screening performed by mini-teams in hard-to-reach areas

Integration of HAT monitoring and control in the existing health system

2. The performance of a combination of serological screening tests needs to be evaluated. The most sensitive parasitology tests are recommended to detect cases.

3. The participants welcomed the progresses achieved in on-going clinical trials on new oral drugs to treat HAT, such as fexinidazole and oxaborole (SCYX-7158), as these drugs could revolutionise the treatment of sleeping sickness and contribute to its elimination.

4. The participants highlighted the role and independence of ethics committees in the approval and monitoring of clinical trials.

The ethics committees on HAT in the endemic countries must be encouraged to harmonise the evaluation procedures of clinical trials on HAT to promote the joint evaluations of international projects.

5. The participants identified the need for an effective pharmacovigilance system.

6. The participants welcomed the on-going elaboration of WHO protocols to validate HAT elimination.

7. Regional collaboration must be strengthened in cross-border regions, particularly in areas receiving displaced populations, with the support of the WHO. Evidence of *gambiense* and *rhodesiense* vector hybridisation in northern Uganda singles out this area as particularly at risk.

8. Develop mechanisms to monitor unconfirmed RDT-positive subjects.

9. Vector control is an important component which, combined with medical control, will contribute to the elimination of HAT.

10. Increase interactions between basic research and the actors of HAT control.

Before reading the final communiqué, the chairman of the scientific committee asked the participants to elect the best poster of this 4th scientific meeting. The winner was the poster entitled “Transfer of tsetse control activities at the community level in the Boffa human African trypanosomiasis focus, Guinea”.

Phoebe Mukiria, Grace Murilla and Florent Mbo



Report of the regional HAT Platform steering committee meeting, 19 September 2016, Conakry, Guinea

HAT Platform activities of last three months of 2015 and January to September 2016

- Publication of Newsletter N°17
- Training in South Sudan
- On-going HAT Platform steering committee meeting and 4th joint scientific meeting EA-NETT-HAT Platform
- HAT Platform support to the two member countries, with practical training of 3 technicians of South Sudan in the DRC, and training support for the technicians of the 33 mobile units in the DRC
- Monitoring visit from Dr Mariame Camara in Guinea following training on the management of human African trypanosomiasis
- Participation in the investigator meeting of Fexinidazole (Fexi 004, Fexi 005 and Fexi 006) clinical trials and explanation of the oxaborole (SCYX-7158) study protocol
- Printing of the DRC National Ethics Committee brochures on health research
- Participation of the coordinator to international conferences (Innovation & Access, DNDi partners meeting in Rio de Janeiro, June 2016)

Activities scheduled for the last three months of 2016 and 2017:

- Prepare Newsletter N°18 (December 2016) and the next two Newsletters for 2017
- Organise HAT training in Angola in 2017 (draft completed)
- Organise the HAT Platform steering committee meeting at the same time as the next ISCTRC conference
- Organise the participation of the HAT Platform to the next ISCTRC conference
- The HAT Platform report was followed by presentations by the countries and then by the partners.

Recommendations

At the end of the day, the HAT Platform steering committee meeting made the following recommendations:

1. The legal status of the HAT Platform must be adopted during the next steering committee meeting
2. The countries' HAT Platform must be strengthened with activities in each countries
3. Visit to the member countries once a year (priority to those not visited in 2016)
4. Support the training of the new national coordinator of Congo-Brazzaville in the DRC
5. Support the HAT Platform coordinator to monitor the countries
6. Provide equal activities in the countries and advocacy to the partners to support technician training in the countries
7. Advocacy efforts to obtain mAECT kits at a lower price for the national control programs
8. Integrate clinical research training in Angola in the 2017 action plan

The reporters

*Pierre Marie Douzima, Erphas Olema
and Florent Mbo*



Members of HAT Platform Steering Committee

Training on Good Clinical and Laboratory Practice for HAT

A. Technicians of the mobile units in the DRC



A total of 143 laboratory technicians working with the 30 mobile units and national structures of the NSSCP DRC were trained between 26 January and 2 February 2016 in Kinshasa on the diagnosis of HAT, malaria, and filariasis. Training was organised jointly with the NSSCP DRC, DNDi, INRB, IMT-Antwerp and IRD, to update personnel's knowledge on trypanosomiasis diagnosis. The instructors suggested that additional refresher courses be organised within 2 to 3 years, as well as training courses for the provincial supervisors, to improve their technical expertise and train them on supervision and evaluation, as well as on the improvement and standardisation of standard operating procedures.

Florent Mbo

B. Practical training of laboratory technicians from South Sudan in the DRC

This training supported by the HAT Platform with the help of DNDi, INRB and NSSCP DRC, was organised in two stages.

1st stage: Training at the DRC National Biomedical Research Institute (INRB)

This training focused on three modules, covering serology, parasitology and elements of laboratory bio-safety. The trainees were given a lot of time to practice the various parasitology techniques, CTC, mAECT and counting WBCs in the CSF.

2nd stage: Practical training for the mobile unit and the Masi Manimba Hospital in the DRC

The three trained technicians spent 10 days with the Masi Manimba mobile unit performing active screening activities in endemic villages, with two supervisors of the NSSCP DRC laboratory.



In the Masi Manimba Hospital, the 3 south Sudanese technicians improved their skills in screening, diagnosis, lumbar puncture, and post-treatment follow-up.

C. Training of the laboratory technicians of Congo-Brazzaville and Angola

In anticipation of the implementation of the new screening strategy initiated by FIND in Angola and Congo-Brazzaville, 20 technicians of the screening and treatment centres in these two countries were trained in HAT diagnosis techniques in

Kinshasa, DRC: capillary tube centrifugation (CTC), mAECT, LED fluorescence microscopy and LAMP molecular test.



Technicians of Congo Brazza

These technicians were accompanied by a team of instructors from INRB DRC, NSSCP DRC and the University of Makerere in Uganda. This training was financed by Find in collaboration with National Institute of biological research Kinshasa, NSSCP DRC and University of Makerere.

Simon Kayembe and Florent Mbo



Technicians of Kinshasa

D. Training of investigators and site initiation visits in anticipation of clinical trials SCYX-7158 (OXA002) and FEX-09-HAT in the DRC

DNDi in collaboration with NSSCP DRC launched the FEX-09-HAT study, which will be conducted in three sites in the DRC, of

which two in the Kwilu province (Bandundu General Reference Hospital and Bagata General Reference Hospital) and one in the Mai Ndombe province (HGR General Reference Hospital).



Personnel of clinical trial site of Mushie

Prior to the launch, a meeting was held between the investigators and site personnel (physicians, nurses and laboratory technicians), followed by initiation visits for site personnel.



Personnel of clinical trial site of Bagata

The training seminar for the personnel of the sites of the phase IIb clinical trial on oxaborole (SCYX-7158) in the DRC was held in Kinshasa on 23-25 May 2016. A total of 30 people (investigating physicians, laboratory technicians and nurses), from the hospitals of Masi Manimba, Dipumba, Isangi, Katananga, N'gandajika, Kwamouth and Bolobo, attended these seminars. The primary objective was to train all the personnel on compliance with SCYX-7158 clinical trial protocol, as well as on good clinical and laboratory practice. This seminar was followed by initiation visits.

Wilfried Mutombo, Digas Ngolo and Florent Mbo

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Aita Signorell

International meetings scheduled for 2017

- 29-30 March: 19th International Conference on Tropical Infectious Diseases (ICTID 2017) – Singapore
- 3-7 april: 15th World Congress on Public Health – Melbourne, Australia
- 16 – 17 May: ISNTDD3 - The International Society for Neglected Tropical Diseases (ISNTD) – London, United Kingdom
- 34th International scientific council for trypanomiasis research and control: expected in September 2017, place to be defined
- 16 – 20 Octobre: 10th European Congress on Tropical Medicine and International Health (ECTMIH) - Antwerp, Belgium
- 5 – 9 Novembre: 66th American Society of Tropical Medicine and Hygiene (ASTMH) – Baltimore, USA
- 30 Novembre: 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) - Vienna, Austria

Visits and meetings

DNDi executive Director and Swiss TPH Director visited DNDi and Swiss TPH offices at Kinshasa and sites of HAT clinical trials in Maindombe and Kwilu provinces, DRC.



Work meeting of two Directors with staff of NSSCP DRC



Visit of health centre with HAT activities

Exploratory visit of the HAT Platform coordinator with a delegation of partners (DNDi, FIND, WHO, Swiss TPH) at the sleeping sickness diagnosis and treatment centre in Dubreka and at the Dubreka General Hospital 50 kilometres from Conakry in Guinea on 24-28 April 2016 and 23 September 2016



Visit of diagnosis and treatment centre of Dubreka, Guinea

Participation of the HAT Platform coordinator to the 40-year anniversary of the launch of onchocerciasis control in Ouagadougou



*Demonstration of community-directed treatment with ivermectin (CDTI)
in presence of Africa WHO regional Director and Prof. Hopkins*

- Participation of the HAT Platform coordinator and the Head of the DNDi DRC office to Innovation & Access; DNDi partners meeting in Rio de Janeiro, 6-8 June 2016 Brazil



Speech of President of DNDi Administration council

HAT activities of MSF's Operational Centre in Amsterdam (OCA) in the DRC in 2016



Active screening organized by mobile team of MSF Holland in DRC

The 2016 MSF mobile HAT team includes 5 international staff: Project Coordinator (PC), Information Education and Communication (IEC) officer, laboratory scientist, technical logistician, and logistical administrator. This team travels within the DRC but also in other countries in search of hot spots to initiate passive and/or active screening. The international members are not able to do all the work on their own.

They depend very much on the national staff being present on the project's location, but also on technical and qualified staff which accompany the team within the country.

The total size of the national staff team for the DRC has varied from 24 to 48 national staff, with a core team of 7 technical and qualified staff on average.

After winding down on both passive and active HAT screening activities in the Ango health zone, the mobile HAT team started explorations to collect data on major hot spots in the Maniema province. These explorations and assessments resulted in the production of a road map for the Maniema, Kasai and Tanganyika provinces. It took the team some time to arrange and move from the Ango health zone to Kindu and Kasongo. The usual constraints included the logistics involved in project relocation and general supply and preparations for the program.

This took until March 2016 when the team started both passive and active HAT screening in Kasongo. Interestingly, Kasongo is among the many other health zones MSF OCA is planning to screen, including Kimbombo and Lusangi health zones in the Maniema province, the Lubau health zone in East

Kasai and the Kongolo health zone in Tanganyika. Due to the late start in the year, the team managed to screen 6,053 people with 19 HAT cases identified and treated.

As a neglected tropical disease (NTD), sleeping sickness is among the many other diseases competing for priority within the national health system. The mobile HAT team is aware of this challenge, and tried to identify the key cause of morbidity in the communities and incorporate this medical need into the HAT activities.

In the DRC and especially in Kindu and Kasongo, malaria is the main cause of sickness, with > 80% of the screened population being RDT-positive. The inclusion of malaria diagnosis and treatment in HAT screening and treatment activities boosted the communities' appreciation and acceptance of MSF.

Screening and treating sleeping sickness is also necessary in areas where health facilities are difficult to reach, mainly due to the large distances and sometimes to financial constraints. In its endeavour to improve the communities' understanding of these activities, as well as coordination and information

sharing, the team discovered that communities prefer the radio as a local means of communication. Radio stations were then used to increase community awareness about MSF OCA activities in Kasongo and in the villages scheduled for active screening. The positive outcome of the radio dramas and messages on sleeping sickness resulted into several patients showing up at the hospital for passive screening.

To identify, diagnose and treat people with HAT, we need a field team backed by specialised technical support at times. The use of a new technology with a camera attached to a microscope has proved very useful to share data with the technical support at headquarters and thereby improve microscopy interpretation/reading. We were also able to send all laboratory technicians for a three to four day-seminar in Antwerp, Belgium.

"Sleeping sickness is still a neglected tropical disease and MSF OCA will remain committed in 2017" to screen and treat people in very hard to reach remote areas.

Norman Sitali

To identify, diagnose and treat people with HAT, we need a field team backed by specialised technical support at times.



Filariasis in the DRC: a need for new treatments

Main facts on onchocerciasis

Predominantly found in West and Central Africa

An estimated 37 million people are infected with *Onchocerca volvulus* worms, which cause severe itching and may result in blindness or impaired vision

The disease is transmitted by the bite of black flies (Simulium).

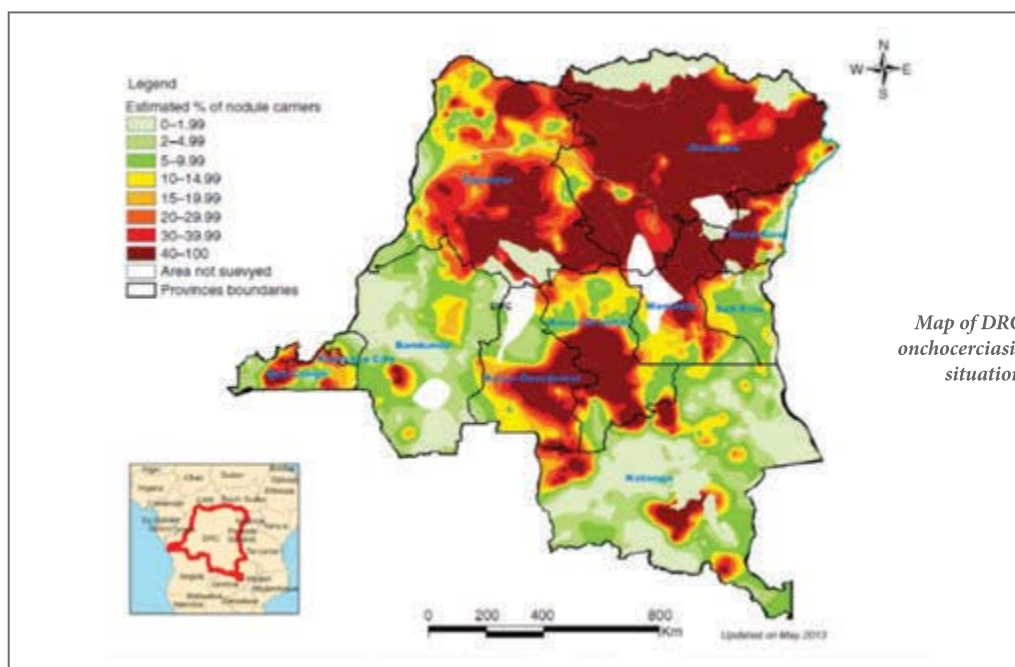
Situation of onchocerciasis in the DRC

504 health districts

394 endemic for onchocerciasis

21 community-directed treatment with ivermectin (CDTI) projects

42,779 endemic communities



Despite large-scale successes in controlling onchocerciasis (river blindness) in Africa, the DRC remains deeply affected by this debilitating parasitic disease. Up to 43 million people in the country – more than half the population – are at risk of developing onchocerciasis,¹ and estimates have pointed towards 15 million people infected in the country.²

1. African Programme for Onchocerciasis Control, The World Health Organization Year 2015 Progress Report (Burkina Faso, 2015)

2. Makenga Bof, J.-C., Maketa, V., Bakajika, D. K., Ntumba, F., Mpunga, D., Murdoch, M. E., Hopkins, A., Noma, M. M., Zouré, H., Tekle, A. H.,

Mass drug administration (MDA) programs led by the African Programme for Onchocerciasis (APOC) have been very effective in controlling the disease. MDA programmes are based on annual community-directed treatment with the antiparasitic drug ivermectin (CDTI). These programs have been instrumental in controlling onchocerciasis. In APOC countries, the prevalence of the infection has been reduced by about 73% compared with pre-APOC

Katabarwa, M. N. and Lutumba, P. (2015), Onchocerciasis control in the Democratic Republic of Congo (DRC): challenges in a post-war environment. Trop Med Int Health, 20: 48–62. doi:10.1111/tmi.12397

levels.³ Thanks to these successes, APOC - which officially closed in 2015 - is considered to be one of the most successful post-war public health programmes ever established. But why then has the DRC seemingly been left behind?

DRC faces some of the same challenges in controlling onchocerciasis as other African countries, but they are exacerbated by the country's weak public health infrastructure. A large population at risk spread over a massive geographic area presents a significant challenge. Limited resources have been available so far, and the end of APOC means even less funding and technical support. As described in a 2014 paper by Makenga Bof *and al.*⁴, CDTI projects face two main barriers in the DRC: the danger of severe adverse effects due to another filarial infection and armed conflict.

Another filarial worm infection called loiasis, that affects over 10 million people in Africa, is endemic in the DRC and present in many of the onchocerciasis-endemic regions. Patients with a large amount of *Loa loa* larvae (microfilariae) in the blood are at risk of life-threatening complications if they receive ivermectin. This co-infection has been a major barrier to MDA programmes in forested regions of West and Central Africa.

Up to 16 of the 21 CDTI projects in the DRC are directed at joint loiasis and onchocerciasis infections.

In 2004-2005, a number of deaths associated with ivermectin were recorded in the DRC. This required mapping of *Loa loa* endemicity in the country, which delayed MDA activities. Moreover, MDA activities were henceforth required to follow-up on adverse effects during MDA campaign. This slowed down MDA and as the news of adverse effects spread, fear of ivermectin increased in affected communities.

Conflict and instability are also considerable barriers to the control of onchocerciasis – a challenge that is

very familiar to those of us working in human African trypanosomiasis.

New tools to help control efforts in DRC

The development of new tools – diagnostics and treatments – could greatly help with control and elimination efforts in the DRC. Ivermectin is a very safe and effective drug – its creators received a Nobel Prize in Medicine in 2015 – but it only kills juvenile worms, leaving adult worms alive in the body. Therefore, MDA programmes need to be repeated for the entire lifespan of adult worms, i.e. more than 10 years.

DNDi's strategy is to develop a new compound with macrofilaricidal activity (that kills adult worms) to be used as a safe and field-adapted macrofilaricidal drug in individual patients and possibly later as MDA if needed.

As a medium-term strategy, DNDi is assessing emodepside, currently commercialized by Bayer under license from Astellas as an anthelmintic veterinary drug for cats and dogs, in combination with praziquantel (Profender®), and in combination with toltrazuril (Procox®). DNDi has a collaboration with Bayer to jointly develop emodepside for the treatment of onchocerciasis.

“Onchocerciasis is a major public health issue in the DRC, which keeps those affected in a cycle of poverty. Treatment with ivermectin

is organized every year – in my region of Kisangani, already 11 have been administered. When patients come to me for treatment in between these distributions, I can only give them antihistamines to calm their itching. However, these patients need a curative treatment, not just a symptomatic.” Dr Clarisse Molopakwa, Kisangani, RDC

As a long-term strategy, DNDi is assessing additional opportunities through an active screening programme of drug compounds emanating from animal health/pharmaceutical companies and academic institutions, with the goal of selecting one or two candidates for clinical development.

Another filarial worm infection called loiasis, that affects over 10 million people in Africa, is endemic in the DRC

3. *Achievements of Community-directed treatment with ivermectin (CDTI)* <http://www.who.int/apoc/cdti/achievements/en/> Accessed 4/11/16

4. *Makenga Bof, and al 2015*

Exploratory visit of the team of DNDi Geneva filariasis program in the DRC

Dr Belen Pedrique of the DNDi Geneva filariasis program conducted the first exploratory visit from 18-24 March 2016 in the DRC to determine the feasibility of clinical studies on new molecules for the treatment of filariasis in general, and in onchocerciasis in particular. During this visit, she participated in the meeting of partners involved in the control of neglected tropical diseases on preventive polychemotherapy, organised by the DRC

Ministry of Health. Contacts were also established with the Director of the DRC National Onchocerciasis Control Program, research institutions (INRB, the parasitology department of the School of Medicine and the clinical pharmacology department of the School of Pharmacy of the University of Kinshasa). Visits were organised in hospitals, such as the Hospital of Mont Amba, Hospital Mutombo Dikembe and Hospital du Cinquantenaire de Kisangani, as well as in endemic villages in the three health zones (HZ) (Masa HZ in Central Kongo, Wanie Rukula HZ in the Tshopo province and Moanza HZ in Kwilu province), with the support of the personnel of the Onchocerciasis Control Program and the HAT Platform coordination.

Belen Pedrique, Ilan Moss and Florent Mbo



Visit of DNDi team at Masa HZ accompanied by the Director of the DRC National Onchocerciasis Control Program (NOCP, DRC) with her team and the representatives of Masa HZ

Birth Notices

Births in DNDi Geneva families and investigators of clinical trial sites in DRC:



Mathianna Nkieri,
daughter of
Dr Matthieu Nkieri,
co-investigator, DRC



Alexandre Préveaux,
son of Sandra Rambry,
Clinical Manager DNDi
GENEVA



Holiness Mandula,
daughter of
Dr Guylain Mandula,
investigator, DRC



Jojo-Robert Kavunga,
son of Dr Papy Kavunga,
investigator, DRC



**Radieuse NGANZOBO
LEMVIE,** daughter of
Dr Pathou Nganzobo,
Provincial coordinator,
NSSCP, DRC

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