

Plateforme THA



REGIONAL PLATFORM FOR CLINICAL RESEARCH

NEWSLETTER N°11 / AOUT 2012



©Photo W. MUTOMBO

HAT PLATFORM STEERING COMMITTEE MEMBERS

Ndjamena, May 2012

Contents

Editorial

NEWSLETTER
N° 11, August,
2011



EDITORIAL P.2



p3

EPIDEMIOLOGICAL
SITUATION OF HAT
IN THE PLATFORM
COUNTRIES
IN END 2011



p5

LATEST SCIENTIFIC
EVENTS AND
MISCELLANEOUS
INFORMATION

UPDATE ON ON-GOING RESEARCH..... P.16



p17

LISTENING TO HAT
PATIENTS AND
HEALTH WORKERS
(YEI, SOUTH SUDAN)

SCIENTIFIC MEETINGS, PROGRAMS FOR THE
SECOND QUARTER P.19

RECENT PUBLICATIONS ON HAT P. 20

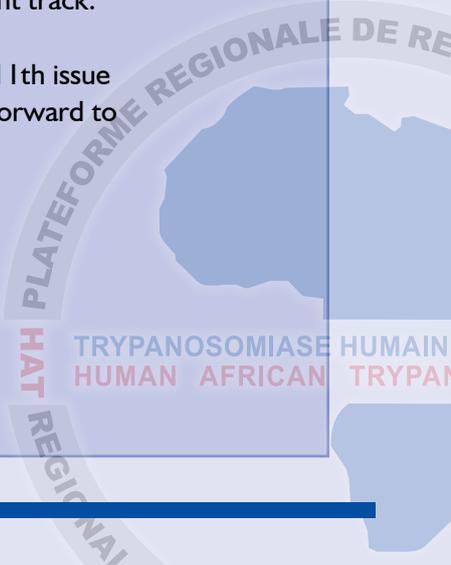


Dr Kadima Ebeja
HATplatform
Coordinator

Any research filed away in a drawer is a waste of time, energy and money. This is why our HAT Platform is committed to circulating the results of research conducted by its members to the general public (readers) via its Newsletter.

In this 11th issue, we review the epidemiological situation in the HAT Platform member countries in 2011. We also present our achievements so far towards the set objectives, such as strengthening clinical trial capacities through training of the personnel involved in the various sites. We continue our raising awareness campaign on the problem of funding the control of sleeping sickness. Happily, our update on current research shows that we are on the right track.

We hope you will enjoy this 11th issue of our Newsletter and look forward to presenting you the next one.



EPIDEMIOLOGICAL SITUATION OF HAT IN THE PLATFORM COUNTRIES IN END 2011

We present here a brief overview of the situation of HAT in the 7 member countries of the Platform between 2009 and 2011.

The number of cases reported in each country and year-on-year variations are presented in the table below. Results with a negative sign represent a reduction in the number of cases.

By the end of 2009, NECT was added to the list of HAT drug treatments, with the hope to achieve a significant disease control. This was verified in 2010 with a 25% reduction over 2009. Less toxic than melarsoprol and easier to administer than eflornithine alone, NECT has rapidly become the treatment of choice for late-stage *T.b. gambiense* infections.

Country	Number of cases			Variation in %	
	2009	2010	2011	2009-10	2010-11
DRC	7183	5629	5595	-21.6	-0.6
CAR	1054	425	122	-59.7	-71.3
South Sudan	353	247	297	-30.0	20.2
Uganda	221	225	123	1.8	-45.3
Chad	215	212	247	-1.4	16.5
Angola	295	210	154	-28.8	-26.7
Republic of Congo	87	87	61	0.0	-29.9
Total HAT Platform countries	9408	7035	6599	-25.2	-6.2

In 2011, this optimistic outlook was somewhat revised, as the reduction in the number of cases slowed down to only 6% over 2010. However, these results came within a general reduction in screening activities and a disengagement of donors supporting control activities, with the exception of the WHO and MSF.

Democratic Republic of Congo (DRC)

As specified in the current HAT control agreement, the pluriannual support program of the Belgian Technical Cooperation Agency CTB is nearing to its end, expected in 2013. No formal plan to extend this support in DRC has been agreed, in spite of the fact that in 2011, this country accounted for 85% of all cases reported in the HAT Platform member countries, i.e. over $\frac{3}{4}$ of all worldwide cases. The stagnation of the detection rate is associated with a strong reduction in screened populations, from 2,019,175 in 2010 down to 1,424,235 in 2011, i.e. a 29.5% drop. However, MSF increased its activities in 2011 in the Orientale Province (Bas Uel ), targeting high prevalence zones and thereby increasing the detection rate in this province (986 cases in 2010 and 1351 in 2011, i.e. a 37% rise). The number of reported cases also increased in the provinces of Kasai Occidental and Equateur in 2011.

Central African Republic (CAR)

Due to worsening safety conditions in the Batangafo/Ouham foci, MSF has been forced to reduce its active screening activi-

ties, resulting in a substantial reduction in the number of reported cases in 2011. In the Maitikoulou foci, the involvement of MSF was terminated as the number of cases dropped markedly over two consecutive years.

South Sudan

The rise in the number of cases in this new country has been associated with a strong increase in cases detected passively in Yei Hospital. Active screening activities have been sporadic since the departure of most NGOs involved in HAT control. A very detailed article was published recently by Ruiz-Postigo JA, Franco JR, Lado M, Simarro PP (2012), Human African Trypanosomiasis in South Sudan: How Can We Prevent a New Epidemic? PLoS Negl Trop Dis 6(5): e1541.

Uganda

A major reduction in the number of cases was observed in 2011 in the north west region where *T.b. gambiense* is prevalent. However, the *T.b. rhodesiense* foci remains active, most cases being treated in Lwala Hospital (53 cases, i.e. 43% of total).

Chad

The higher number of cases has been associated with the increased support for active screening in 2010 and 2011, as well as higher passive detection rates, particularly in the Mandoul foci (Bodo treatment centre) responsible for 90% of all national reported cases.

Angola

The drop in number of cases in 2011 (27%) follows to a lesser degree the reduction in screened population (down by 15%). The cases remain mostly located in the 5 north-western provinces: Kwanza Norte (45), Zaire (34), Bengo (30), Luanda (21) and Uige (23). Almost 80% of cases were diagnosed as late-stage HAT.

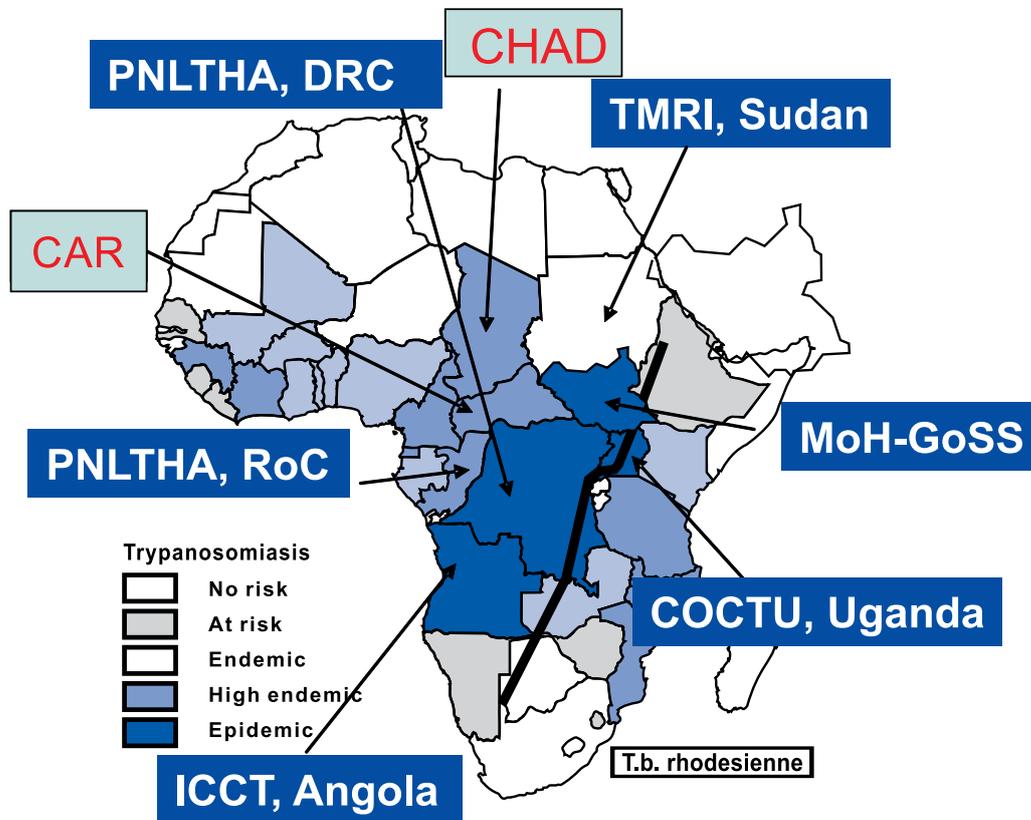
Republic of Congo (RoC)

Although figures dropped markedly in 2011 following a stagnation in 2010 over 2009, this information must be taken with

precaution, as the means available for active screening are too limited for the same populations to be visited each year.

In conclusion, we must remain vigilant and with our current means, the eradication of HAT by 2010 will clearly not be possible. Greater involvement from the international donors is required to support the activities of national programs in the field.

HAT PLATFORM COUNTRIES



Active screening in Congo Brazza

©Photo S. NGAMPO



Active screening in CRA by the MSF team

©Photo J. POTET

EPIDEMIOLOGICAL SITUATION OF HAT IN THE PLATFORM COUNTRIES IN END 2011



©Photo W. MUTOMBO

Opening ceremony of Fexinidazole training by the PI (Dr KANDE), Kinshasa, Centre Caritas June 2012

a) Training of investigators, nurses and laboratory technicians involved in the fexinidazole study (January 2012 in Kinshasa) by Dr Kadima Ebeja Augustin, HAT Platform Coordinator

In 2012, the HAT Platform organised a training session in Kinshasa (DRC) from 18 to 21 January then 23 to 25 January, targeting the three main actors involved in the

implementation of clinical trials: investigating physicians, laboratory technicians, and nurses. A total of 65 people from various sites selected for the pivotal phase II/III study on fexinidazole (see below) participated in the training sessions held at the CARITAS centre, CNPP, Clinique Ngaliema and INRB laboratory.

This training was funded and coordinated by DNDi, with the help of the national HAT control program of DRC (PNLTHA), Swiss TPH, IMT-Antwerp and INRB Kinshasa.

Table 1: Origin of the participants

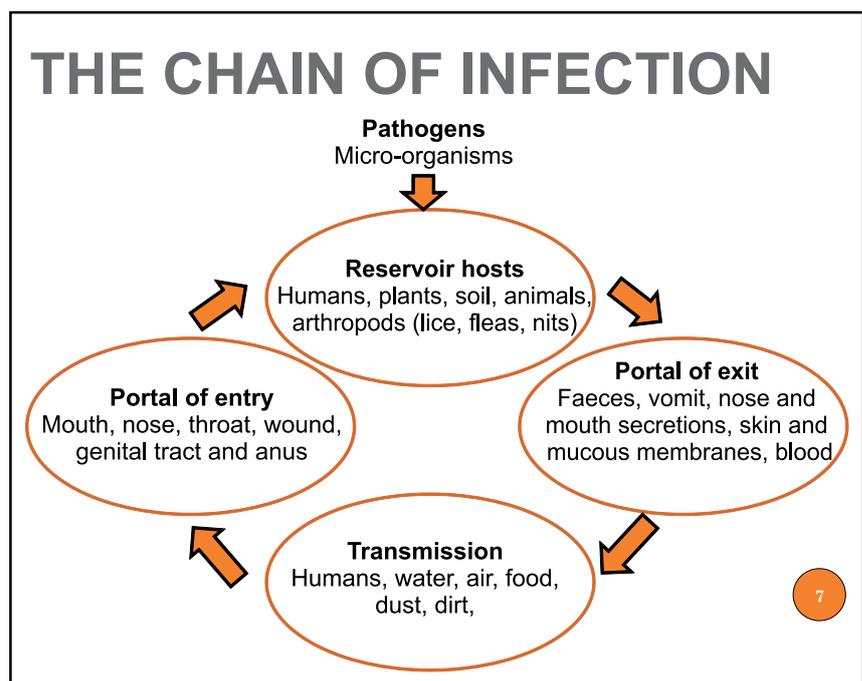
Location of origin	Investigators	Laboratory technicians	Nurses	TOTAL
Bandundu ville	3	3	6	12
Masimanimba	3	3	6	12
Vanga	3	3	6	12
Bonga Yasa	1	1	1	3
Cdt Dipumba Mbuji Mayi	2	1	1	4
Batangafo (Bangui/ CAR)	1	2	5	8
Orientale Province (MSF-CH)	2	3	5	10
Kinshasa (PNLTHA/INRB)	1	1		2
Mobile team (MSF-B)	1	1		2
TOTAL	17	18	30	65
Facilitators	6	4	4	14

Following one day of joint theoretical training for all at the CARITAS centre, the three groups were separated for the practical training (with patients or in the laboratory). In line with our capacity building objective, the participants

were given another high quality lecture with pragmatic interventions from the facilitators, who were all highly experienced in the field aspects of HAT control.

DAY 1	DAYS 2 AND 3			DAY 4
JOINT TRAINING FOR ALL	INVESTIGATING PHYSICIANS	NURSES	LABORATORY TECHNICIANS	ALL PARTICIPANTS
Epidemiological update on HAT	Review of the internal medicine aspects of HAT - Heart and cardiovascular examination - ECG and trypanosomiasis - Endocrinology Neurology, clinical examination, frontal syndrome	Hygiene and waste management	Review of HAT diagnosis - CATT; - mAECT Buffy Coat - Cerebrospinal fluid (CSF)	Practical exercise with a draft e-CRF - Evaluation of the procedures with a patient
Introduction on standard precautions and HAT clinic		Nursing procedures - Peripheral venous access - Lumbar puncture - Drug preparation and administration	Hematology - Blood test with dipstick - WBC count and differential, platelet count	Open discussion
Diagnosis and differential diagnosis		Pharmacy management	Specific devices - Piccolo Xpress - HemoCue 201 - Combur 9	
Current treatment and adverse effects			Standard laboratory precautions	Closing address and certificates
Presentation of fexinidazole				

The brief presentation on standard precautions included the definition of the chain of infection, represented in the diagram below:



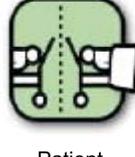
To avoid the transmission de micro-organisms, **all healthcare professionals must apply the standard precautions at all times and everywhere**. Standard precautions are defined as follows:

A series of simple measures to be applied during all healthcare procedures, including in situations of emergency and with all patients, to reduce as much as possible the risk of micro-organism transmission.

Standard precautions must be applied by all healthcare professionals for all patients, each and every time there is a risk of contact with body fluids, whether they contain blood or not, with the exception of sweat: **blood, urine, faeces, vomit, sputum, saliva, nasal secretions, sperm, vaginal secretions**.

In practice, there are 10 essential recommendations:

STANDARDS PRECAUTIONS: 10 RECOMMANDATIONS

				
Hand hygiene	Protective gloves	Respiratory and eye protection gear	Protective clothing	Decontamination of reusable medical devices and equipment
				
Treatment of laundry	Waste management	Decontamination of the environment	Staff protection	Patient protection



FEXINIDAZOLE training, Kinshasa, Centre Caritas january 2012

©Photo W. MUTOMBO



Practical demonstration
Dr Richards Mvuala, Anesthésiste Réanimateur

©Photo W. MUTOMBO

For the group of investigators, the aim was not to repeat information on HAT they knew already, but to provide demonstrations and practical exercises on specific and common issues in neurology, cardiology and endocrinology, focusing on clinical examinations.

The nurses' group being the largest, it was split into two small groups of 15 participants for practical purposes. The training was provided in two sessions. The demonstrations focused on the strict application of hygiene recommendations in all procedures to protect patients and personnel.

Laboratory technicians were shown all the equipment required for the most recent diagnostic tests, as well as for hematology and biochemistry tests. Practical demonstrations were given by the facilitators at the INRB laboratory.

All these sessions provided the necessary information to ensure that the fexinidazole study is carried out in strict compliance with the Good Clinical practice (GCP) and Good Laboratory Practice (GLP).

b) Funding prospects of HAT control in the Democratic Republic of Congo: an analysis by MSF

In February 2012, MSF (*Médecins Sans Frontières* - Campaign for Access to Essential Medicines) conducted a mission in the Democratic Republic of Congo (DRC) to evaluate the funding prospects of HAT control.

The vast majority of HAT cases in DRC are diagnosed and treated by Health Ministry agents, mostly as part of the national HAT control program (PNLTHA). International NGOs (MSF-Switzerland, MSF-Belgium, MEMISA) are also involved, in partnership with PNLTHA. Some thirty mobile units are operational in DRC.

HAT control is still faced with many obstacles in DRC. There are numerous very active foci in terms of transmission in Bandundu, Kasai Oriental and Province Orientale. Mobile screening units are the main control instruments, in addition to the accredited treatment centres. However, as less than 20% of the population at risk is screened on a yearly basis, there are probably many other undetected active foci.

It is essential to detect such foci as quickly as possible, e.g. through passive screening, and send mobile units on site rapidly to avoid the disease reaching epidemic proportions.

Unfortunately, HAT control is under threat in DRC. The continued funding granted since 1997 by the Belgian Technical Cooperation Agency CTB to PNLTHA, of around €2.5 million per annum, is being reduced gradually, and will be stopped by mid 2013. The consequences are already visible as the number of screening tests performed in DRC dropped by 30% between 2010 and 2011.

The other main financial partner involved in HAT control is the World Health Organisation (WHO), which supplies treatments free of charge as part of a donation agreement from Sanofi-Aventis, and provided additional funding in 2011 and 2012 to purchase CATT tests in DRC. However, this aid is not sufficient to compensate for the reduced funding from other donors.

Finally, the Ministry of Health of DRC provides a small financial support to HAT control, mainly through the payment of a basic allowance to the personnel affiliated to the PNLTHA.

Intense discussions are also under way in DRC on HAT control strategies. The Ministry of Health would like to include HAT control in the services provided by cross-functional teams in the health zones. MSF considers that the HAT control capacities must be reinforced within primary healthcare services, but without hindering the action of specialist mobile teams.

Given the current challenges of the disease's diagnosis and late-stage treatment, it is unreasonable to expect the health zone teams to perform all the screening and treatment activities required to control the endemic disease, even if a few specialists are called in to help here and there. Integration should instead be considered as a gradual process. The first step is to reinforce passive screening capacities:

over the past few years, the percentage of cases detected through passive screening in DRC remained stable, at approximately 50%. A full integration of the activities is subject to the development of new tools to control the disease, particularly a rapid diagnostic test, and an oral treatment active on both stages of the disease.

In the meantime, specialist and experienced teams must be maintained in place. In the short term, the main actors of HAT control, including the Belgian Technical Cooperation Agency and the government of DRC, must provide guarantees for a funding of HAT control beyond 2013. If funding was to be suspended, the mobile units may be disbanded and the expertise accumulated over the years may disappear. Other partners must be approached now to secure funding over the medium term.

HAT control in DRC is on the right track. Suspending funding now, when we are half-way there, will undoubtedly cause an epidemic rebound in a few years, as seen several times in the past few decades.

Epidemiological survey

in Lui and Yei, South Sudan

In the preparatory stage of the multicentre study on fexinidazole, DNDi initiated with the HAT Platform a two-stage epidemiological survey in selected sites in South Sudan (Lui and Yei).

The objective was to determine the geographical origin of the patients, and whether the mobile teams would be able to match the expected inclusion rate of 5 patients per month.



HUMAN AFRICAN TRYPANOSOMIASIS HAT

REGIONAL PLATFORM FOR CLINICAL RESEARCH

A rapid survey technique was used, different from the standard mobile screening, targeting only a sample of the inhabitants in each location to cover a greater geographical area in a short time.

Logistics

This mission was conducted in Lui from 20 to 26 February 2012 in 13 villages of both counties (Mundri East and Mundri West), and in Yei from 23 to 26 April 2012 in 10 villages.

A team from Kinshasa, including two laboratory technicians from PNLTHA of DRC (Lui: André Luslatomi Kabwemi and Jean Roger Kalo Lilo ; Yei: Dieudonné Tshimanga and Charles Shamba), and the HAT Platform coordinating physician (Dr Augustin Kadima Ebeja) were received by the Director for Endemic Tropical Diseases Control (Dr Mounir Lado) and the Director for Scientific Research (Dr Richard Laku) of the Ministry of Health of the Republic of South Sudan.

In Lui, the local CUAMM (*Collegio Universitario Aspiranti Medici Missionari*) team from the hospital provided three laboratory technicians and three nurses (Stephen Zabi, Repent Buba, Simon Bring, Rachael James, Nelson Odrande and Jackson Lobojo). The administrator and depot manager provided logistical support.

In Yei, the hospital director lent us staff from his local team: Rose Ititu, Grace Nyoka, Charles Kwaje, Moses Amule, Augustin Towongo, Steven Duku, Edward Lasu, Mary Opani, Nelson

Alli, Rejoice Ajonye and Joice Sadia.

Most of the equipment (CATT, mAECT and ancillaries) was brought from Kinshasa, but the hospital contributed consumables, such as alcohol, swabs and additional diagnostic material. Transport vehicles and generators were provided in Juba.

Technique

Each team included one of the technicians from DRC, those from Lui and Yei hospitals, and the nurses. The CATT test was the first step of examination just after registration by the secretary.

A lymph node palpation was performed in all patients with a positive CATT test, and if enlarged lymph nodes were found, an aspiration was performed to analyse the aspirate.

CATT dilution was performed on blood (see results).

Mini-anion exchange column technique (mAECT) and Giemsa-stained thick blood smear were used for the case confirmation. An anamnesis was collected from suspect's cases and from former cases with a positive CATT.

Cases positive at dilutions of 1/8 and over 1/32 (definition of positive trypanosome infection according to the country policy) were referred to the hospital for a lumbar puncture (identification of the parasite and disease staging).

Results

Back in Juba, we presented the results to the Ministry of Health and to the CUAMM country representative (Lui).

Epidemiological survey in Lui (Mundri East & Mundri West)

VILLAGE	PTE	CATT +			mAECT		PG		G E		NC
		Nég	posit	dil	Neg	Posit	Neg	posit	neg	Posit	
BUAGYI	101	101		0	0	0					
KOROBA	102	100	2	1	2	0			2		
KEDIBA	114	114		0	0	0					
AMADI	103	103		0	0	0	1				
MINGA	152	145	7	4	7		1		7		
AGYI	154	152	2	2			1		2		
JAMBO	145	138	7	7	7		0	0	6	1	4
MARIBA	205	201	4	4	2	0			4		
MUNDRI WEST	115	110	5	5	5		1		5		1
BARI	160	158	2	2			1		2		
LOZOH	102	98	4	1	4		2		4		
SINGIRIWA	113	110	3	3					3		2
WITOH	90	87	3	3	3		1		3		
TOTAL	1656	1617	39	32	30		8		38	1	7



©Photo A. EBEJA



©Photo A. EBEJA



©Photo A. EBEJA



©Photo A. EBEJA

Active screening in villages in South Sudan, february 2012

In Lui, the presence of microfilariae in mAECT and thick blood smears, as well as positive CATT dilutions were considered as HAT cases.

Village	mAECT		TBS		CATT dilution	
	Total	microf	Total	microf	dil 1/16	> 1/32
MINGA	7	4	7	3	0	0
JAMBO	7	5	7	4	1	2
MUNDRI WEST	5	5	5	2	0	1
LOZOH	4	4	4	3	0	0
WITOH	3	1	3	1	0	0
SINGIRIWA					0	2
TOTAL	26	19	26	13	1	5

In Lui, out of the 1,656 people given a CATT test in the 13 villages visited, only 7 patients were positive, and only one of those was confirmed parasitologically.

In Lui, the presence of microfilariae in mAECT and thick blood smears, as well as positive CATT dilutions were considered as HAT cases.

Result of the epidemiological survey in the region of Yei:

Village	PTE	CATT +			Woo		mAECT		NC
		(-)	(+)	Dil	(-)	(+)	(-)	(+)	
RONRONYO	212	204	8	0	7	0	3	0	0
AGONYA KIRI	156	149	7	6	0	0	2	0	1
YORONDU /DIMU I	200	200	0	0	0	0	0	0	0
MITIKA	257	253	4	4			4		1
DIMU II	281	277	4	0	4	0	0	0	0
PISAK	169	165	4	4	4	0	2	0	2
MUNDO	258	258	0	0	0	0	0	0	0
LOGO	232	224	8	8	6	0	8	0	0
NYORO EAST KOYOKI	63	63	0	0	0	0	0	0	0
LASU PHC	177	174	3	3	0	0	3	0	0
TOTAL	2005	1967	38	25	21	0	22	0	4



Active screening in villages in South Sudan, february 2012

© Photo A. EBBA

Microfilariae identified by mAECT and Woo tests, as well as CATT dilutions (only highest dilution is represented here):

Village	mAECT		Woo		CATT DILUTION				Comments
	Total	Mf	Total	Mf	dil 1/4	dil 1/8	dil 1/16	dil 1/32	
RONRONYO	3	3	7	6	0	0	0	0	
AGONYA KIRI	2	1	0	0	1	0	1	0	4 CATT (-) dilution 1/2
MITIKA	2	0	0	0	0	1	1	0	2 CATT (+) dilution 1/2
DIMO II	0	0	4	4	0	0	0	0	
PISAK	4	0	4	0	1	0	1	1	1 CATT (-) dilution 1/2
LOGO	8	1	6	1	3	5	0	0	
LASU PHC	3	1	0	0	2	1	0	0	
TOTAL	22	6	21	11	7	7	3	1	2 dilutions at 1/8 were former cases
NYORO EAST /KOYOKI	0	0	0	0	0	0	0	0	
LASU PHC	3	1	0	0	2	1	0	0	
TOTAL	22	6	21	11	7	7	3	1	2 dilutions à 1/8 sont des anciens cas

Conclusions/recommendations

Sleeping sickness is present in this region and the population is well informed on the endemic disease. The healthcare facilities we visited do not take part in the control of the disease and do not have the means to do so (with the exception of Lui and Yei hospitals).

The population answered massively to active screening, and we were forced to limit the number of applicants once 100 had been examined, or once the daily allowance of reagent had been used up.

In terms of the fexinidazole study, and subject to all possible biases due to our sample being limited to first comers, the fact that only one case was parasitologically confirmed raises doubts about the ability to recruit enough patients.

Following exchanges with the Ministry of Health in Juba and the MSF-H team, several recommendations were made:

A head of the HAT program with the means to implement the HAT control measures must be designated and operational.

Refresher practical courses on trypanosomiasis diagnostic techniques must be provided for the personnel.

Close supervision of the teams involved in HAT control program must be provided to help them remain focused on their work and promote quality.

Hospital physicians should be more involved in the diagnosis and care of patients with trypanosomiasis.

A specific study on HAT diagnosis based on molecular biology is required to understand why the rate of CATT serology confirmation with the Woo test and mAECT was so low.

Dr Augustin **Kadima Ebeja**
HATplatform Coordinator

d) Meeting of the steering committee in Ndjamena

For almost six years, the HAT Platform steering committee has been meeting twice a year in different countries.

After Bamako in Mali (September 2011), this time it was Ndjamena in Chad which hosted this meeting crucial for the life of our Platform. The event took place in the Novotel La Tachadienne from 30 to 31 May 2012.

The General Secretary of the Ministry of Health took part in the opening ceremony, addressing a message of hope and encouragement to all participants.

All the member countries were present, with the exception of Angola. The countries presented the situation of sleeping sickness in their own country in 2011, the HAT Platform achievements and the difficulties met. Our regular partners, DNDi, Swiss TPH and MSF presented on-going research's.

The meeting provided a great opportunity for all sorts of exchanges between members of the steering committee. We also wish to insist on the following general guidelines to ensure that our platform operates smoothly:

1) All members of the HAT Platform must use the website (Global Access to Health HAT Platform: <http://globalaccess-tohealth.net>). The website moderator (Dr. Olaf Valverde, DNDi) must send invitations to the new members so they can access the website.

2) Each country must boost the activities of the local platform.

3) The countries must provide training sessions on strengthening the capacities of the ethics committees in their country.



HAT Platform steering committee work shop Ndjamen, May 2012

©Photo: W. MUTOMBO

- 4) The fexinidazole study will be submitted to the ethics committees in DRC and to the scientific committee in the CAR. Following its approval, the study is expected to be launched during the second quarter 2012.
- 5) Approved Standard Operating Procedures (SOPs) must be defined for the ethics committees by the relevant national authorities.
- 6) The 2012-2014 action plan must include all the recommendations from the countries, particularly where the budget is concerned.
- 7) The possibility of providing our Platform with a legal personality must be examined, based on the approach used by MSF and EANETT, and the example of the Chagas Platform.
- 8) To improve communication within the HAT Platform, the coordinator must be informed of any new data or activity taking place in each country.
- 9) The members of the steering committee must promote the wide distribution of the Platform's Newsletter (within their country and abroad).
- 10) The joint scientific meeting with EANETT expected to take place in September 2012 in Juba has been postponed until the first quarter 2013 and transferred to Nairobi (Kenya).
- 11) A training session on the Good Clinical Practice (GCP) will be given in South Sudan in Juba from 11 to 13 September 2012.
- 12) The next steering committee meeting will be held in Juba, South Sudan, from 14 to 15 September 2012.
- 13) A link must be created to post documents on the website including neglected tropical diseases.

Dr **Augustin Kadima Ebeja**
HATplatform Coordinator



Dr Pyana PATI, INRB, Kinshasa

© Photo: I.N.R.B.

e) Treatment failure in HAT

The causes of the high relapse rate among patients treated with melarsoprol in the Mbuji-Mayi HAT foci in DRC remain unknown. To explore the hypothesis of drug resistance, *T.b. gambiense* parasites were isolated via inoculation to the thicket rat *Grammomys surdaster* and adaptation to *Mus musculus*.

A unique collection of 85 strains of *T.b. gambiense* was isolated from HAT patients, among which 24 originated from 12 patients before treatment (BT) and after treatment (AT) pairs and 13 from cured patients (BT). These strains were provided by patients participating in a study on shortening the post-treatment follow-up in HAT (THARSAT). A total of 41 strains were adapted to *Mus musculus* and 15 among them were tested *ex-vivo* for their sensitivity to melarsoprol, pentamidine, nifurtimox and DB75, but no evidence of resistance was found. An *in vivo* investigation using the murine model of acute HAT is on going.

So far, 40 strains, of which 11 from cured patients and 10 strain pairs, have been tested with 0 and 10 mg of melarsoprol per kg bodyweight, with a 90 day post-treatment follow-up. The preliminary results show no resistance at 10 mg from the 4 BT strains, or from the 10 strain pairs provided by the relapse patients.

The molecular study focuses on several genes, including that encoding for the P2 adenosine receptor, required for melarsoprol to enter the parasite's cytoplasm. Another gene encoding for the multi-drug resistant protein A (MRPA) and

fully expressed in *Trypanosoma brucei gambiense* will also be investigated to determine which of these strains expresses this gene fully.

It is very important to understand the reasons behind this treatment failure, not to say melarsoprol resistance, and thereby extrapolate future research on the AAT6 receptor required for the entry of eflornithine into the parasite's cytoplasm when mutated. In the NECT study, although negligible, a number of treatment failures were nevertheless reported in Mbuji-Mayi, the site where patients were treated with melarsoprol. Half a century ago, the melarsoprol relapse rate was so small that no one expected this 37% parasitologically confirmed relapses in the THARSAT study.

Finding an alternative new drug is a good thing, but understanding why this drug is no longer able to cure more than 70% of patients is even better. Indeed, if drug

resistance is the cause of the high relapse rate in the Mbuji-Mayi HAT foci, evidence of this resistance must be found in the parasite's phenotype and/or genotype.

by Dr. **Pyana Pati**, LNRHAT (*Laboratoire National de Référence pour la Trypanosomiase Humaine Africaine*) and INRB (*Institut National de Recherche Biomédicale*)

f) Early prediction of the efficacy of the treatment of late-stage *T.b. gambiense* human African trypanosomiasis

Curing a patient is morally satisfying to the physician. This may happen quickly with certain diseases, but it may take a long time for others, as is the case for human African trypanosomiasis (HAT) or sleeping sickness.

Given that no drug is 100% effective, HAT patients undergoing treatment should be monitored for 2 years, with control visits at 3, 6, 12, 18 and 24 months. In addition to the clinical examination, these visits also include the collection and examination of blood and cerebrospinal fluid samples. A patient will be considered as cured if after 24 months of follow-up, no trypanosome is detected in any of the body fluids and if the parameters have returned to or have remained normal.

Unfortunately, the long follow-up is rarely implemented. For various reasons, the patients fail to comply with the control visit schedule, their attendance decreasing with time.

If a relapse is diagnosed late, the patient may keep disabling

sequelae for life.

Shortening the post-treatment follow-up period therefore seemed an essential target, especially for the patient's well being and comfort.

Mumba *et al.* developed a new algorithm, based on the detection of trypanosomes and the WBC count in the cerebrospinal fluid (CSF), to shorten the post-treatment follow-up to 12 months, with one interim visit at 6 months.

With this approach, a large proportion of patients are classed as relapses (50 WBCs/ μ l or presence of trypanosomes) or cures (\leq 5 WBCs/ μ l). The former are then given another treatment and the latter are declared as cured. In the remaining patients (6-49 WBCs/ μ l, absence of trypanosome), the follow-up must be maintained. At the test of cure visit scheduled at 12 months, these patients will be classed into one of the above categories, based on the presence of trypanosomes and WBC count in the CSF, the cut-off limit being 20 WBCs/ μ l (5-50-20 algorithm).

Before using this follow-up algorithm on a large scale, including in clinical trials and in patients infected with *T.b rhodesiense*, an evaluation of its performance in cohorts of patients treated with other drugs was recommended.

This has just been done by Priotto *et al.* who published their results in the article Early Prediction of Treatment Efficacy in Second-Stage Gambiense Human African Trypanosomiasis; *PLoS Neglected Tropical Disease* (2012). In this multicentre study, data was collected from 12 different programs directed by MSF in 6 countries, in a population of patients (2,190) 10 times greater than that examined by Mumba *et al.*

This study also explored several other algorithms, but the 5-50-20 algorithm proved to be the best, with the highest likelihood ratio and a proportion of false negatives not significantly different from that in the other algorithms.

False negatives are the main problem associated to this algorithm, even though their proportion is relatively low. Patients can sometimes be declared as cured when in fact the disease is still progressing silently. However, even if a follow-up is maintained for 24 months, this problem cannot be avoided altogether, as relapses can occur 24 months after treatment. Therefore, irrespective of the algorithm used, it is important to instruct patients to contact a healthcare professional immediately if they feel unwell.

This shortened follow-up algorithm is based mainly on the detection of trypanosomes and on the white blood cell count in the cerebrospinal fluid (CSF). It is therefore important to improve the performance of the techniques used to measure these two markers.

The modified single centrifugation (MSC) and mAECT are currently the most sensitive techniques to detect trypanosomes in the CSF and in the blood, respectively. Unfortunately, their routine use is still limited. These two tests are available at INRB (*Institut National de Recherche Biomédicale*). It would be preferable to measure the WBC count in single-use counting chambers rather than reusable chambers, because the strict rules applicable to the latter are not always implemented in the field.

Therefore, this algorithm for a shortened post-treatment follow-up, as well as all other successful algorithms are seen as a message of hope:

- A message of hope for HAT patients. There will be less control visits, and consequently the number of required lumbar punctures will be appreciably reduced.
- A message of hope also for clinical trials, which will be easier. A clinical trial on HAT currently lasts at least three years. With this follow-up algorithm, 6 months after treatment will be enough to determine clearly whether the tested drug is effective or not.
- A message of hope also for HAT control programs. A follow-up period shortened to 12 months will clearly provide considerable operational and financial advantages.

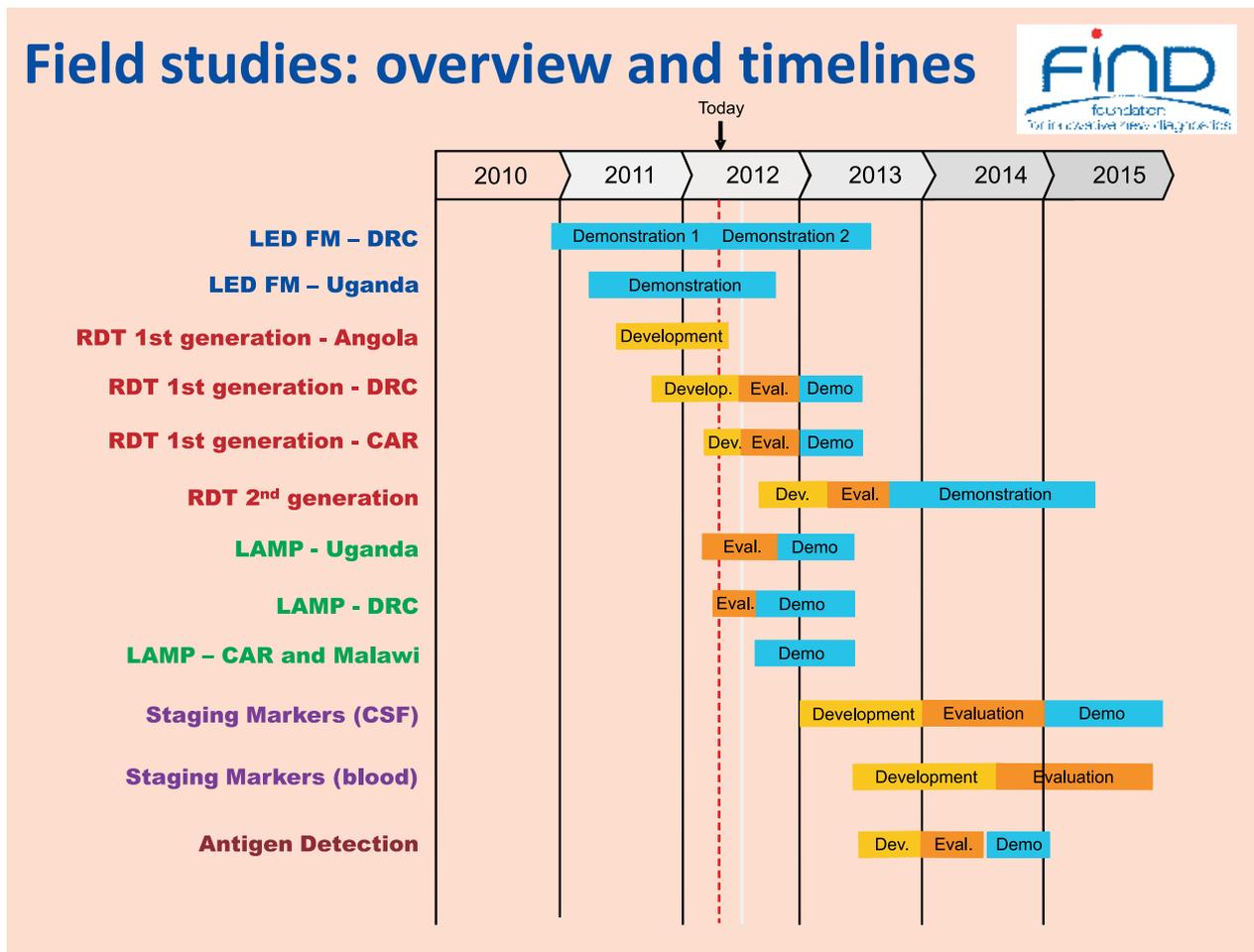
References

- World Health Organization (1998). Control and surveillance of African trypanosomiasis. *WHO Technical Report Series*, 881, 1-113.
- Küssel *et al.* Briefing Document for Informal Consultation on Clinical Trials for Registration of New Drugs for HAT, Geneva, 9-10 September 2004
- Mumba Ngoyi, D., Lejon, V., Pyana, P., Boelaert, M., Ilunga, M., Menten, J., Mulunda, J. P., Van Nieuwenhove, S., Muyembe Tamfum, J. J. & Büscher, P. (2010). How to shorten patient follow-up after treatment for *Trypanosoma brucei gambiense* sleeping sickness? *Journal of Infectious Diseases*, 201, 453-463.
- Priotto G, Chappuis F, Bastard M, Flevaud L, Etard J-F (2012) Early Prediction of Treatment Efficacy in Second-Stage Gambiense Human African Trypanosomiasis. *PLoS Negl Trop Dis* 6(6): e1662. doi:10.1371/journal.pntd.0001662

Prof **Dieudonné Mumba**
Laboratoire National de Référence pour la Trypanosomiase
Humaine Africaine (LNRTHA)
Institut National de Recherche Biomédicale (INRB)

UPDATE ON ON-GOING RESEARCH

a) Research conducted by FIND



b) Research conducted by DNDi jointly with Swiss TPH

NECT-Field

This study, which we talk about in almost all our Newsletters (see issues n° 8 and 10), is nearing to its end (expected around September 2012). On 4 May 2012, the post-treatment follow-up period in this study was as follows:

- Passive follow-up until 18 months (finished)
 - 6 months 79% (488/618)
 - 12 months 69% (415/604)
 - 18 months 61% (364/597)
 - 24 months 72% (398 seen, on-going)
- Active follow-up after 24 months: last patient due on 20 May 2012, to end September 2012.

To date, there has been 6 confirmed relapses and 2 probable relapses, all of them in East Kasai Province.

Once the sites have been closed, all the data will be analysed and final results will be published.

Fexinidazole

This new molecule has completed the clinical phase I of its development (in healthy volunteers) and is about to enter the phase II/III in five sites in DRC (Bandundu Ville, Masimanimba, Vanga, Dipumba and Dingila) and in one site in CAR (Batangafo). The protocol has been submitted for approval and authorisation to the local regulatory authorities (DRC ethics committee, CAR scientific committee, and the drugs regulatory authority of the Ministry of Health in both countries).

The study personnel have been trained and the sites are ready, so the study is expected to start shortly.

Listening to HAT patients and health workers (Yei, South Sudan)

LISTENING TO HAT PATIENTS AND HEALTH WORKERS (YEI, SOUTH SUDAN)



© Photo A. EBEJA

Active screening in villages in South Sudan, february 2012

We used the opportunity of being in Yei for the epidemiological survey for the fexinidazole study to ask patients and health workers the same questions we had put to the patients in DRC (see Newsletter n° 10).

The first person we interviewed was Jaine Sunday, a female patient aged 32 and living in Logo Boma.

When asked for how long she had had sleeping sickness, she replied that, long before, she had been suffering from headaches, fever and sometimes weakness, as well as drowsiness during the day. In 2009, she went to the Clinique de Malteser for a HAT screening, and that is when she was diagnosed with the disease.

When asked where she thought she might have caught the disease, she replied that she had lived all her life in Logo Boma, near the Konbgwo river. There was no known case of sleeping sickness in her family, and she was the only one to have it. Once

she had been diagnosed, the people in her village encouraged her to go the hospital to receive treatment.

We asked her how sleeping sickness used to be treated, but she said she did not know how it was done in the old days. She said that in her case, the treatment lasted a few days, with two infusions per day, and oral tablets for 10 days.

She added that during the treatment, she vomited, had generalised pain and feeding problems. She had been asked to come back for a check-up in three months. Today (April 2012), she felt well and had no particular complaint connected with sleeping sickness.

The second person we interviewed was a 62 year old man named Onesimo Lubari, also living in Logo Boma. When asked about the history of his disease, he said that in 2010, he had faint spells, with headaches, muscle ache, fever and sometimes drowsiness during the day and insomnia at night. He went

to the hospital several times and was treated for malaria and typhoid fever, but to no avail.

On 22 January 2012, he decided to go to the sleeping sickness department of Yei hospital for an examination, and the disease was confirmed and a treatment was initiated.

When asked where he thought he might have caught the disease, he said that he probably caught it near the Konbwo river, where there are many tsetse flies, and where he farmed some land.

He told us that all his family (older brothers, wife and children) had sleeping sickness except him. While he was suffering from all the signs mentioned above, his relatives told him to go to Yei hospital, and if the disease was confirmed, to get treated otherwise he would die.

We asked him how the disease was treated in the old days, and he said that when he was young, he remembers a group of white men going through the villages to examine people and feel their neck (looking for enlarged lymph nodes). Those who were found to be ill had to stay in hospital for three months to be treated. He did not know which drugs they were given, but it was injections.

His treatment however had been very short, only roughly two weeks: oral tablets and infusions.

The main problem during treatment was vomiting on the third day of treatment (once a day for three days). One month after leaving hospital, he had pains in his back and chest, and the nurse who examined him told him he had a stomach ulcer and gave him some drugs for that.

He did not want to take these drugs, and he went to see the sleeping sickness team passing through his village, to ask whether he should take the drugs or not.

We reassured him and recommended that he did take these drugs, as there was no contraindication to any drug after a treatment for sleeping sickness. His clinical condition was good and we found no parasite (trypanosome).

We also interviewed Grace Nyoka, the health worker in charge of the hospital's HAT patients unit. She had used melarsoprol for a long time, then DFMO as single agent therapy, and now NECT. She found that NECT had greatly reduced her workload and made the management of encephalopathies much easier. She rejoiced at the fact that current research is aimed at finding an oral treatment for late-stage sleeping sickness, which, in her words, would constitute a true revolution.



Active screening in villages in South Sudan, february 2012

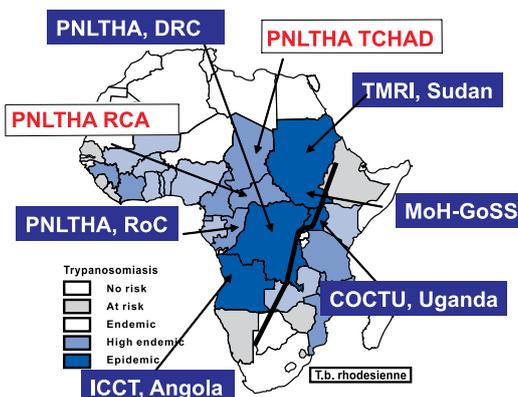
©Photo A. EBELJA

SCIENTIFIC MEETINGS, PROGRAMS FOR THE SECOND QUARTER AND WEBSITES OF INTEREST

Event date	Location	Event Name
16 or 17 August	Campinas, Brazil	Forum on Neglected Diseases at UNICAMP
14-15 September	JUBA / Sout Sudan	HAT PLATFORM Board Meeting
17-18 September	LSTMH, London, UK	RSC (BMCS) Medical Chemistry of Tropical Diseases: emerging paradigms in anti-infective drug design
17-21 September		28th Pan American Sanitary Conference, 64th Session of the Regional Committee of WHO for Americas
23-27 September	Rio, Brazil	XVIII International Congress for tropical Medicine and Malaria MSF symposium : «Fighting Neglect : Finding ways to manage and control visceral leishmaniasis, human African trypanosomiasis and Chagas disease»
12-14 December	Kinshasa DRC	Congrès International des Pathologies Infectieuses et Parasitaires

HATPLATFORM

National HAT control programs in the most affected endemic countries



DNDi
Swiss TPH

Other partners:
National and international research groups: ITMA, INRB, CDC, TRC-KARI, etc.

- NGOs operational in HAT control
- FIND
- WHO
- EANETT, PABIN, AMANET...

Extract of the mission of HATP latform :

The HAT Platform is a regional network, scientific and technical, dedicated to the Human African Trypanosomiasis (HAT), more commonly called "sleeping sickness". Its main objective is to set up a pool of highly qualified regional skills through relevant training in order to facilitate clinical trial and develop new diagnostics and treatment tools against the disease.



RECENT PUBLICATIONS ON HAT

1. Wyllie S, Patterson S, Stojanovski L, Simeons FR, Norval S, et al. (2012) The anti-trypanosome drug fexinidazole shows potential for treating visceral leishmaniasis. *Sci Transl Med* 4: 119re111.
2. WHO/TDR (2012) Global Report for Research on Infectious Diseases of Poverty (http://www.who.int/tdr/stewardship/global_report/en/)
3. Watson CP, Dogruel M, Mihoreanu L, Begley DJ, Weksler BB, et al. (2012) The transport of nifurtimox, an anti-trypanosomal drug, in an in vitro model of the human blood-brain barrier: evidence for involvement of breast cancer resistance protein. *Brain Res* 1436: 111-121.
4. Truc P, Lando A, Penchenier L, Vatunga G, Josenando T (2012) Human African trypanosomiasis in Angola: clinical observations, treatment, and use of PCR for stage determination of early stage of the disease. *Trans R Soc Trop Med Hyg* 106: 10-14.
5. Simarro PP, Franco JR, Cecchi G, Paone M, Diarra A, et al. (2012) Human African trypanosomiasis in non-endemic countries (2000-2010). *J Travel Med* 19: 44-53.
6. Simarro PP, Franco J, Diarra A, Postigo JA, Jannin J (2012) Update on field use of the available drugs for the chemotherapy of human African trypanosomiasis. *Parasitology*: 1-5.
7. Njamnshi AK, Seke Etet PF, Perrig S, Acho A, Funsah JY, et al. (2012) Actigraphy in human African trypanosomiasis as a tool for objective clinical evaluation and monitoring: a pilot study. *PLoS Negl Trop Dis* 6: e1525.
8. Mpanya A, Hendrickx D, Vuna M, Kanyinda A, Lumbala C, et al. (2012) Should I get screened for sleeping sickness? A qualitative study in Kasai province, Democratic Republic of Congo. *PLoS Negl Trop Dis* 6: e1467.
9. Matovu E, Kazibwe AJ, Mugasa CM, Ndungu JM, Njiru ZK (2012) Towards Point-of-Care Diagnostic and Staging Tools for Human African Trypanosomiasis. *J Trop Med* 2012: 340538.
10. Bisser S, Courtioux B (2012) [Sleeping sickness: End of the epidemic outbreak?]. *Rev Neurol (Paris)*.
11. Bieler S, Matovu E, Mitashi P, Ssewanyana E, Bi Shamamba SK, et al. (2012) Improved detection of *Trypanosoma brucei* by lysis of red blood cells, concentration and LED fluorescence microscopy. *Acta Trop* 121: 135-140.

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

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



Editorial committee:

Chairman: Augustin Kadima Ebeja

Members: Olaf Valverde ; Charles Wamboga ; Sylvestre Mbadingai ; Gédéon Vatunga ; Richard Laku ; Victor Kande and Nicolas Mbongo

Advisers: José Ramon, Cecilia Schmid and Laurence Flévaud.

HAT Platform coordination address

4 Avenue Révolution, quartier SOCIMAT
Kinshasa, Gombe
Democratic Republic of Congo
Email: aebeja@dndi.org
Tel: 00243 81 081 22 38