PROJECT

SUPPORT TO ELIMINATION OF HUMAN AFRICAN TRYPANOSOMIASIS (SLEEPING SICKNESS) IN DRC

"HAT + PROJECT"

PHASE II

FINANCED BY:

GENERAL DIRECTION OF DEVELOPMENT COOPERATION AND HUMANITARIAN AID

Summary sheet

Total operating costs:		EUR (including overhead)		
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Summary:

The HAT+ project supports the elimination of Human African Trypanosomiasis (HAT) in DRC. The specific objective of the *HAT+ project* is to eliminate HAT transmission in 90% of the endemic *Zones de Santé* (health districts) of DRC by 2025. It is complementary to other HAT projectss supported by Belgium and the Bill & Melinada Gates Foundation. During the second phase of of 3 years, the focus will shift to interruption of transmission and build upon the lessons learned of the first phase.

Expected results are:

1. The HAT elimination strategy is effectively implemented and reviewed
2. The elimination strategy is supported by targeted research and innovation
3. HAT control activities are integrated in the primary health care system of HAT endemic health districts
4. The progress of HAT elimination is monitored and evaluated

ITM coordinates the program and assures the research, scientific support, monitoring and evaluation. For the 3rd result, it intends to build an international coalition and delegate activities to other partners who want to join the HAT elimination agenda.

Partner			
Full name and abbreviation:	Enabel (Belgian Agency for Development Cooperation)		
Contact information:	Address:	Phone:	E-mail :
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Contact person:	Jean Van Wetter		
Budget:	*to be defined*		
Description of the partner's role:	Enabel will contribute to the implementation of Result 3: HAT control activities are integrated in the primary health care system of HAT endemic health districts		
Start date of the partnership relationship:	The current contract is valid until 30 June 2022		

TABLE OF CONTENTS

List of Abbreviations and Acronyms

BMGF	Bill and Melinda Gates Foundation
CHARHAT	Cryptic Human and Animal Reservoir of HAT
DBS	Dried Blood Spot
DEP	*Direction d'Etudes et Planification*
DGD	General Direction of Development Cooperation and Humanitarian Aid
DHIS2	District Health Information System 2
DGLM	*Direction Générale de Lutte contre les Maladies*
DNDi	Drugs for Neglected Disease Initiative
DPS	*Division Provinciale de la Santé*
DRC	Democratic Republic of the Congo
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
ENABEL	The Belgian Agency for Development Cooperation
FIND	Foundation for Innovative Diagnostics
GIBS	*Groupe Inter-Bailleurs en Santé*
HAT	Human African Trypanosomiasis
INRB	*Institut de National de Recherche Biomédicale*
IRD	*Institut de Recherche pour le Développement*
ITM	Institute of Tropical Medicine
LSTM	Liverpool School of Tropical Medicine
mAECT	mini Anion Exchange Centrifugation Technique
MEMISA	*Medische Missie Samenwerking*
MSF	*Médecins Sans Frontières*
MOH	Ministry of Health
MoU	Memorandum of Understanding
NECT	Nifurtimox Eflornithin Combination Therapy
NGO	Non-Governmental Organization
NTD	Neglected Tropical Diseases
OECD/DAC	Organization for Economic Coopeartion and Development / Development Assistance Committee
PATH	Program for Appropriate Technology in Health
PNLTHA	*Programme National de Lutte contre la Trypanosomiase Humaine Africaine*
STPH	Swiss Tropical and Public Health Institute
TrypElim	Support to HAT elimination in the former province of Bandundu
VSAT	Very Small Aperture Terminal
WHO	World Health Organization

INTRODUCTION

Sleeping sickness, or Human African Trypanosomiasis (HAT), is an infectious disease that leads to death if the patient is not treated. The cause is a parasite that is transmitted by the bite of tsetse flies (Glossina genus). Sleeping sickness affects rural communities in Sub-Saharan Africa, where suitable tsetse habitats abound: riverine savannahs, forests, and mangroves. It is assumed that in the absence of appropriate treatment, HAT infection inevitably leads to death. HAT has two stages, the hemolymphatic stage with no or few specific symptoms, followed by the meningo-encephalitic stage when the causative parasite has crossed the blood/brain barrier. The second stage is characterized by neurological signs and personality changes. Damage to the hypothalamus may lead to disturbance of the normal sleep pattern, which has led to the disease being called 'sleeping sickness'. Today, the Democratic Republic of the Congo (DRC) is home to over 70 percent of the world's cases of sleeping sickness. In DRC, HAT is caused by *Trypanosoma brucei gambiense*. This West African HAT, also referred to as gambiense HAT or gHAT, is essentially a disease of humans. In contrast, East African HAT, caused by *Trypanosoma brucei rhodesiense*, has cattle and wild animals as a reservoir,

In 1960 the disease was prevalent in 24 African countries, but currently only 13 of them continue to report HAT cases. For decennia, HAT control was based on a "vertical" approach whereby specialized mobile teams tracked down HAT cases, which were treated in the villages or referred to reference centers. The diagnosis is complex while until recently the available drugs were difficult to administer and toxic. HAT management, therefore, required staff with specific knowledge and skills, an extended logistic organization and considerable operational resources. When control efforts were interrupted this often led to a recrudescence of the disease.

Over the last decade, major progress has been achieved in terms of diagnosis, treatment and vector control, changing the prospects for sustainable control. HAT was therefore considered by WHO as one of the Neglected Tropical Diseases (NTD) eligible for elimination as a public health problem by 2020 (defined as less than one case per 10,000 inhabitants per year in > 90% of endemic foci and less than 2,000 cases globally).

Belgium has a long tradition of supporting HAT control in the Democratic Republic of Congo (DRC), going back to the start of the 20th century. By the time of independance of DRC in 1960, hardly any cases were reported. After a sharp rise of the number of HAT cases by the end of the 1990s, the Belgian development cooperation supported HAT control through respectively Belgian NGOs, the Belgian Technical Cooperation[1] and specific scientific programs implemented by the Institute of Tropical Medicine Antwerp (ITM) and other academic partners. This support again resulted in rapid decline (Fig. 1). Since 2013, ITM has been implementing a HAT program that directly supports the national HAT control program (PNLTHA) in DRC, sponsored not only by the Belgian Government but also by the Bill & Melinda Gates Foundation (BMGF).

[1] In 2018, the Belgian Technical Cooperation (BTC) has been transformed into Enabel

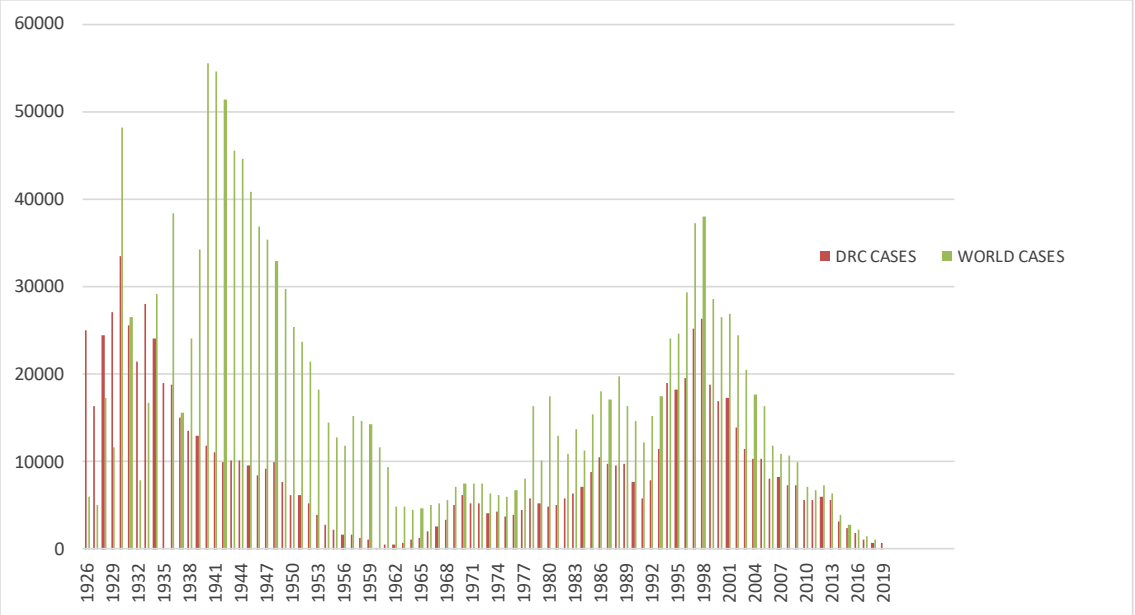

Fig. 1: Number of HAT cases reported in DRC and globally between 1926 and 2019 (Data source: PNLTHA and WHO).

In 2017, the Belgian Government and the Bill & Melinda Gates Foundation (BMGF) decided to join efforts and take the lead in the elimination of HAT. BMGF also supports HAT control interventions in other endemic African countries (i.e. Chad, Guinea-Conakry, Uganda & Ivory Coast). This joint donor commitment was formalized in a Memorandum of Understanding (MoU) between Belgium and BMGF, aiming at the provision of complementary and matched funding. The MoU endorses the following principles for the HAT elimination strategy in DRC:

- ITM is entrusted with the coordinating role for implementing this support program
- Data-driven decision making
- Decentralized funding approach
- Rational but pro-active integration of medical and entomological interventions in local health services
- Links with other disease programs to improve HAT program efficiency and impact

Within this framework, ITM was mandated by Royal Decree (July, 2017) to implement an additional 3-year intervention "Support to HAT elimination in DRC" which we call the *HAT+ project*. This project is financed by the Belgian Government, with 2 possible extensions up to 9 years and a phasing out until 2030. A first phase was implemented from September 2017 until September 2021, including a no cost extension of 1 year following a slow start. Considering the epidemiological evolution over the last years, the initiative of the Belgian Government and BMGF, to jointly take the lead in the elimination of HAT that should lead to the interruption of transmission by 2030, is on track.

The present document presents the second phase of 3 years of the HAT + project, building upon the results of Phase 1 of the HAT+ project. The specific objective of the *HAT+ project* is to eliminate HAT transmission in 90% of the endemic *Zones de Santé* (health districts) of DRC by 2025 (from a baseline of 219 endemic health zones in 2015).

1. CONTEXT

1.1. PNLTHA

In 1968, a "Bureau Central de Lutte Contre la Trypanosomiasis" was created, transformed in the *Programme National de Lutte contre la Trypanosomiase Humaine Africaine (PNLTHA)* in 2001. Its mission is to coordinate and organize sleeping sickness control in the DRC.

The Ministry of Health used to have 54 special disease control programs. In recent years, this number was reduced to 10, but PNLTHA was withheld. PNLTHA depends on the *Direction Générale de Lutte contre les Maladies* (DGLM). PNLTHA is organized into 11 provincial HAT coordination offices (Fig. 2), which do not corespond to the administrative organisation of the country (the population at risk is thought to be spread over 20 provinces).

The policy of HAT control applied by PNLTHA, is aligned with WHO guidelines and is based on a holistic approach including principles such as decentralization, integration, equity, community participation and sustainability. The emphasis is on early detection and treatment by mobile teams (Active Screening) and health services (Passive Screening) in endemic areas and includes also vector control. Currently, about half of the reported cases are detected by mobile teams, the other half by fixed health centers.

In recent years, the number of mobile teams has been reduced from 100 to 30, and further reductions are planned. In the region of the former Bandundu province, the PNLTHA also had 18 mini-mobile teams in 2020. According to a new decree signed in 2019, the provincial health divisions (DPS) should be involved in the management of the provincial mobile teams for sleeping sickness. However, at the national level, this reform has not yet been implemented. Therefore, the PNLTHA continues to manage the operations of the mobile teams. PNLTHA also manages directly part of the passive screening, through specialized fixed health facilities, that only focus on diagnosis and treatment of HAT. According to the overall policy, such centres should also become part of the integrated primary health care system.

The integration of sleeping sickness activities into the health system or the decentralization of mandates to the provincial level (DPS) also has its limits. The health system in DRC is extremely weak, with low attendance rates. Hence the chances of HAT cases being picked up by the system in a timely manner are low. As humans are the reservoir, passive case finding alone will not suffice to reach HAT elimination.

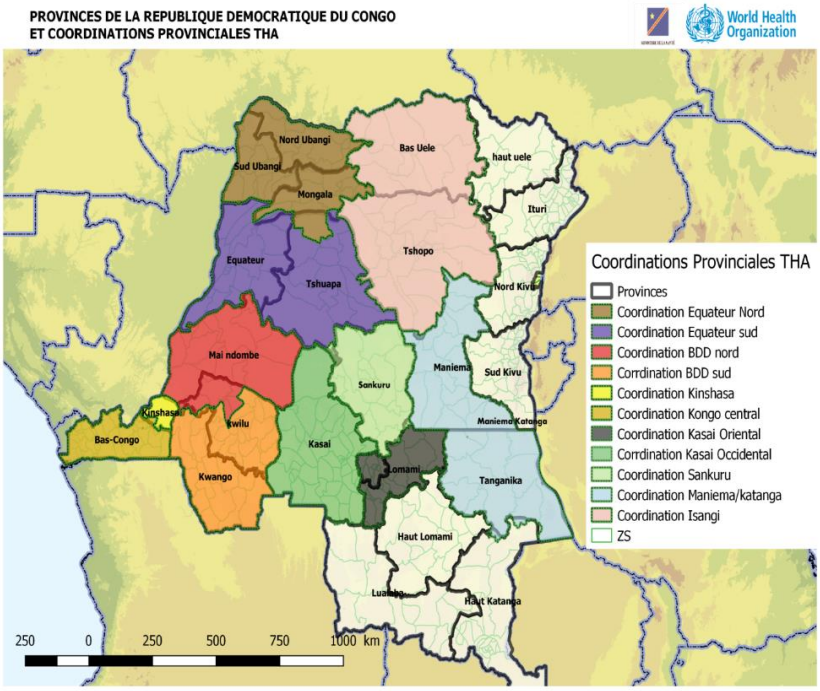

Fig. 2: Organization of the PNLTHA into 11 provincial HAT coordination offices

1.2. HAT Epidemiology

Despite an increase in numbers of people screened in recent years, the number of reported cases has continued to decrease, with 613 cases reported on about 3 million screened in 2019 (Fig. 3). As a consequence of the COVID-19 pandemic, activities were reduced in 2020, with about 400 cases detected on 2 million people screened (Table 2). The declining trend in recent years has been observed in all endemic zones of DRC (Fig. 4).

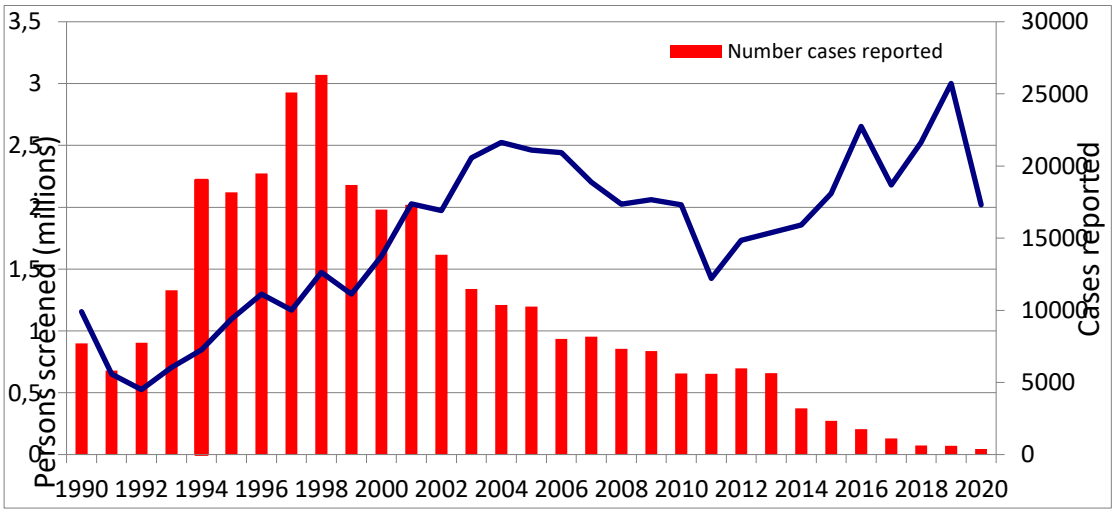

Fig. 3: Overview of the number of population screened compared to the number of reported HAT cases in DRC.

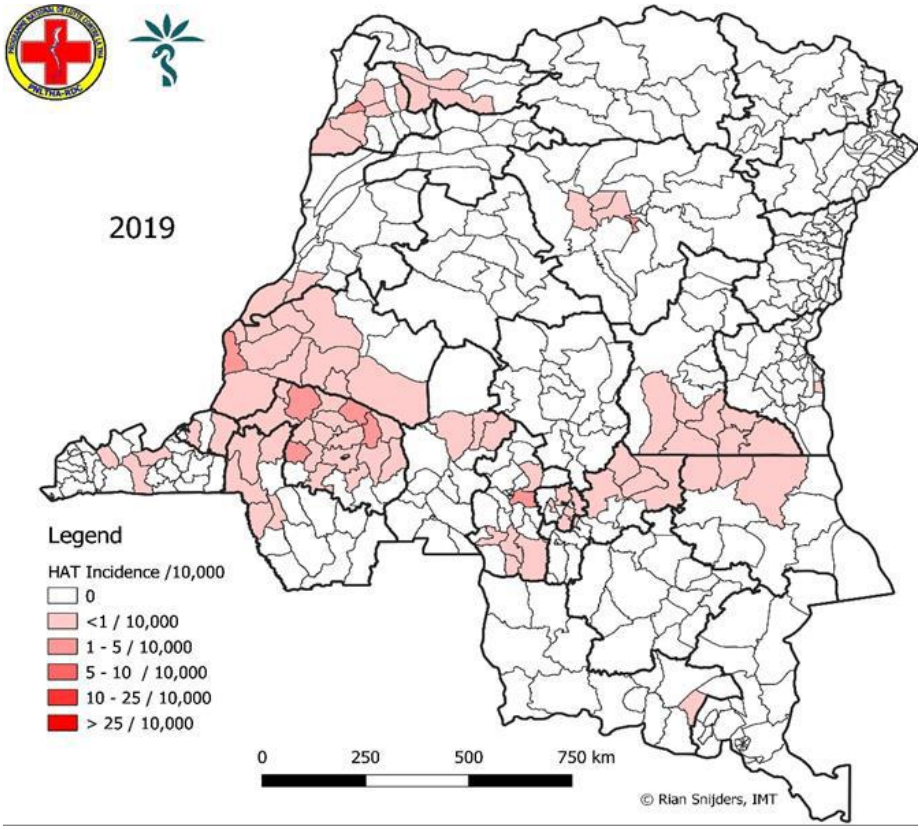

Fig. 4: HAT incidence per health zone in 2019

1.3. TOOLBOX

1.3.1. DIAGNOSTIC[2]

Three consecutive steps are used to diagnose a HAT case, i.e.: screening, confirmation and staging. Screening is done on the basis of a serological test. Since about 20 years, the card agglutination test for trypanosomiasis (CATT) has been used, based on the LiTat1.3 antigen produced at ITM. The CATT test uses capillary blood and can be performed under field conditions but does require a battery-operated rotator. For storage a cold chain is required. It has a specificity of around 95% and a sensitivity ranging from 87-98%. Since about 5 years, two rapid diagnostic tests (RDT) have become available, both based on native antigens produced at ITM (LiTat1.3 and LiTat1.5)[3]. They have the advantage of being individually packed, whereas the CATT is produced in vials of 50 doses that need to be used the same day. Another advantage of RDTs is that they are thermo-stable and do not require any equipment or source of electricity. RDTs based on recombinant antigen are still under development.

Confirmation of a HAT infection is based on microscopic observation of trypanosomes in blood, lymph node aspirate or cerebrospinal fluid and requires at least basic laboratory settings. Low parasitemia typically associated with gHAT, explains why it is difficult to detect trypanosomes in giemsa stained blood smears and

[2] Buscher Ph, Cecchi g, Jamonneau V & Priotto G (2017) The Human African trypanosomiasis The Lancet; 390(10110):2397-40

[3] Buscher, P., et al., *Sensitivity and specificity of HAT Sero-K-SeT, a rapid diagnostic test for serodiagnosis of sleeping sickness caused by Trypanosoma brucei gambiense: a case-control study.* Lancet Glob Health, 2014. **2**(6): p. e359-63

thick films. Concentration techniques can considerably increase sensitivity. PNLTHA promotes the use of mini-Anion Exchange Centrifugation Technique (mAECT) a concentration technique enabling to examine over 350 µl of blood and increasing the chance of visualizing moving trypanosomes. mAECT is locally produced in Kinshasa and can be performed in laboratories of health facilities and by mobile teams in the field. But it requires some basic equipment such as a centrifuge and a microscope, a source of electricity, and a trained laboratory technician. Sensitivity of this confirmation technique is estimated at 80%[4].

The final step in diagnosis of HAT is staging of the disease for all patients in whom parasites have been visualized. This requires a lumbar puncture to examine cerebrospinal fluid for the presence of trypanosomes or a raised white blood cell count. If either of the two is present, the patient is assumed to be in the meningo-encephalitic stage. Staging is necessary because the treatment for the meningo-encephalitic stage is different from the treatment of the hemolymphatic stage and until recently was highly toxic.

A range of other HAT diagnostics can be performed in DRC, albeit not as part of the current diagnostic algorithm of PNLTHA. The immune trypanolysis combines high sensitivity and specificity and is recognized by WHO as serological reference test to confirm exposure to *T.b. gambiense*. It is however an extremely complex test, not suited for use outside research laboratories. The ELISA/*T.b.gambiense* is an antibody detection test that uses the same antigens as CATT and RDTs. In 2020, encouraging results of a newly developed inhibition(i)ELISA test were presented. iELISA has the same characteristics as the ELISA/*T.b.gambiense* but with similar sensitivity and specificity as the Immune trypanolysis and offering new perspectives at a reasonable price[5]. Theoretically it can be considered for large scale screening on Dried Blood Spot (DBS) samples but hospitals of health districts in DRC do not have the capacity to conduct an ELISA technique. This implies that samples must be sent to reference laboratories whereby positive results equal suspicion of infection. In new strategies now under discussion, ELISA and iELISA conducted at regional intermediate level laboratories are thought to have potential in particular for surveillance of historic foci and exploration of blind spots (see further)[6].

In the hands of skilled laboratory technicians, tests based on visualizing parasites such as mAECT are highly specific but they do lack sensitivity. The development of molecular tests as an alternative to microscopic parasite detection has therefore been a research priority for many years. So far they have not yet been able to replace parasitology but new tests based on DNA or on RNA detection are currently being assessed in phase-3 studies in the field in DRC. Over time it is expected that one of these tests will become the new gold standard for HAT diagnosis. Molecular tests could be conducted on blood, lymph, skin or CSF, which is an advantage over antibody detection that can only be done on blood and CSF. However, complex storage requirements and high cost might still be a major disadvantage. Investments in molecular tests were part of the first phase of the HAT+ project.

Compared to other neglected tropical diseases, a reasonable number of new diagnostic tools have been developed for HAT, but the tests are not always available. The risk of high production costs for a market that nearly entirely depends on the willingness of two donors to invest, has been a major setback for producers. Affected countries lack resources to buy the tests or face competing priorities and there is no private market

[4] Mumba Ngoyi D, Ali Ekangu R, Mumvemba Kodi MF, Pyana PP, Balharbi F, et al. Performance of parasitological and molecular techniques for the diagnosis and surveillance of gambiense sleeping sickness. PLoS Negl Trop Dis. 2014 Jun 12;8(6):e2954.

[5] Geerts M, Van Reet N, Leyten S, Berghmans R, Rock KS, Coetzer T &Büsher Ph (2020) Trypanosoma brucei gambiense – iELISA: a promising New Test for the Post Elimination Monitoring of Human African Trypanosomiasis. Clinical Infectious Diseases, ciaa1264, https://doi.org/10.1093/cid/ciaa1264.

[6] Inocencio de Luz, Phanzu D, Kiabanzawoko O, Miaka E, Verle P, De Weggeleire A, Buscher Ph, Hasker E, & Boelaert M (2021) Appropriate serlogical screening and surveillance to eliminate Human frican trpanosomiasis in the Democratice Republic of the Congo. PLoS Neglected Tropical Diseases (in press)

mechanism. Within the framework of the HAT+ project, ITM tried to play the role of honest broker to look for solutions for HAT diagnostics. It committed to guarantee CATT production for as long as needed, to provide native antigens to private companies for the production of serological tests and to facilitate RDT purchase for other organizations to avoid stock-outs and to guarantee lower prices (see also 1.5). For the mAECT WHO serves as intermediary to provide gels essential for the production through a public private partnership, substantially reducing production costs.

1.3.2. TREATMENT

For decades HAT treatment depended on the stage of the disease, i.e. on whether or not trypanosomes have passed the blood brain barrier. For Stage 1, pentamidine administered intramuscularly has been the first choice treatment for many decades. For Stage 2, since the 1950s, the treatment of choice was the toxic Melarsoprol, responsible for the death of about 5% of the HAT patients treated. Since 2009, Melarsoprol has been replaced by a combination therapy called NECT, less toxic but with the major disadvantage that it needs 7 days of intravenous therapy, difficult to implement at health center level.

Since 2020 an oral drug, fexinidazole, has become available, which is effective for both stages of the disease. Following clinical trials conducted by DNDi, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use issued a positive scientific opinion but also had some remarks to be followed-up. WHO included the drug into its Essential Drugs List and defined new Interim Guidelines for the treatment of gambiense HAT in 2019. Fexinidazole is now the treatment of choice for individuals ≥6years with a body weight of ≥20 kg, who are either in the first or in second stage but with <100 leucocytes per µl. For serious HAT cases in stage II, NECT is still the preferred treatment because of a slightly higher effectiveness observed in such patients. In practice this means that lumbar puncture is no longer recommended for patients that present no signs of severe disease. However continued pharmacovigilance is requested by EMA and a new opinion can be expected in the following years.

It is hoped that another breakthrough will come by 2024, with the availability of another new oral treatment, acoziborole. The phase 3 evaluation of acoziborole, is currently in its final stages. Acoziborole is a single dose treatment, apparently of low toxicity, and could therefore be considered even without parasitological confirmation in case of a positive CATT or RDT.

The World Health Organization (WHO) is playing a key role in the provision of treatment of HAT. Since 2000, WHO has had a public private partnership with Sanofi (previously Aventis) and Bayer Health Care for HAT control support. Through this mechanism all HAT medicines are provided to endemic countries free of charge. This partnership has been renewed in 2020 and also includes the new oral treatments. Only the logistics still need to be financed, which for NECT is still a challenge because of the weight and volume of IV infusions. The arrival of oral drugs will very much simplify logistics.

1.3.3. VECTOR CONTROL

HAT vector control has been available for many decades (e.g. traps, sterilization of male flies, ..), has been widely applied in Eastern Africa but not as much in DRC. Though such approaches yielded good results in research settings, feasibility and sustainability were major challenges in the field. It is expensive and requires active cooperation from the local population. A more feasible approach to vector control has been developed by the Liverpool School of Tropical Medicine (LSTM) and the *Institut de Recherche et de Développement* (IRD), who started using 'Tiny Targets' [7]. These are insecticide treated screens that measure 25 x 50 cm and can be

[7] Tirados I., Hope A, Selby R. *et al.* (2020) Impact of tiny targets on Glossina fuscipes quanzensis, the primary vector of human African trypanosomiasis in the Democratic Republic of the Congo PLoS Neglected Tropical Diseases. 14(10):e0008270

mass-produced for less than 1 USD a piece. They are particularly effective against riverine tsetse species and have been shown to reduce vector density by as much as 90%.

Within the framework of the BMGF project coordinated by ITM, LSTM introduced Tiny Targets in DRC and piloted an intervention in the former province of Bandundu from 2015 onwards. By 2019, ~5,000 km^2 had been covered in Yasa Bonga and Masi Manimba health districts with an objective to cover 12,000 km^2 by 2021. The approach also includes awareness raising & community engagement and capacity dvelopment at central and provincial level[8]. Vector control activities have been integrated in the digital platform used to report HAT control activities in DRC.

The Vestergaard company committed to a donation agreement for tiny targets in 2017. The Liverpool School of Tropical Medicine (LSTM), facilitates the purchase of Tiny Targets in a way comparable to the role ITM plays for the purchase of diagnostic tests.

1.3.4. DIGITALIZATION

Digitalization has been gradually introduced in PNLTHA over the last five years. An important innovation was the introduction of electronic data capturing using a tablet.

Within the framework of the BMGF projects, the company Bluesquare developed a digital platform (trypelim.org) to support micro-planning, epidemiological surveillance and M&E, with the following characteristics:

- Android Mobile application to collect epidemiological, demographic and geospatial information of the population screened.
- Data is uploaded to a server and a data management center has been established at PNLTHA.
- A web based information and decision support system has been put in place to monitor activities in the field, compute statistics, facilitate reporting and allow rational planning.
- A quality assurance module making use of a camera attached to the Android tablet, inserted in the ocular tube of the microscope, allowing to capture short videos of live parasites seen.
- Synergy with population census conducted by UCLA

By the end of 2019, all mobile teams in former Bandundu province had been trained and equipped with these electronic data collection tools, by the end of 2021 all mobile teams active in DRC should be using them. Because this tool makes it possible to accurately determine the locations where screening activities take place, such activities can be supervised more closely and planned more rationally. They also overcome the issue of false positive diagnostic confirmation tests that had become more common in recent years. Diagnostic confirmation depends on visualizing live parasites but slides cannot be kept for post-hoc confirmation. Recording videos in the field solves this problem.

In recent years, major investments in the digitization of data management have been launched in DRC, including in the health sector. The National Health Information System (SNIS) of the DRC uses the District Health Information System 2 (DHIS2). This tool, developed in Norway and supported by WHO, is recognized as state-of-the-art in the field of health information systems. It is not only suitable for data collection, validation and analysis at the local level, but also for aggregating data at the central level with relatively easy access. The health districts have been equipped with Very Small Aperture Terminals (VSAT) satellite internet connections

[8] Vander Kelen C., Mpanya, A., Boelaert M., Miaka E., Chacon D., Pulford J., Selby R. & Torr S.J. (2020) Feasibility of community-based control of tsetse: A pilot project using Tiny Targets in the Democratic Republic of Congo PLoS Neglected Tropical Diseases. 14(9):e0008696

but in practice this system does not yet work as expected. It is obvious that in the coming years the digitalization of the HAT program should be linked to the general data collection system of MOH, but there is still some way to go.

1.4. HAT Control Strategy

The strategy of HAT control proposed by WHO is expected to change in the following years, in line with the changing context and the ambitions of interruption of transmission. The debate is no longer only focused on active vs. passive case finding. Under the lead of WHO, a combination of strategies is being developed that could be suitable in relation to local context. ITM and the Congolese partners are actively contributing to this process.

Key components are:

1. Passive case finding
2. Active case finding
    a. Active screening according to WHO strategy
    b. Reactive screening
    c. Probing of blind spots
    d. Surveillance of historic foci
3. Vector control

Figure 5 below shows the different components and how their relative importance is expected to change in the years to come. Components 1 and 2 should lead to proper treatment.

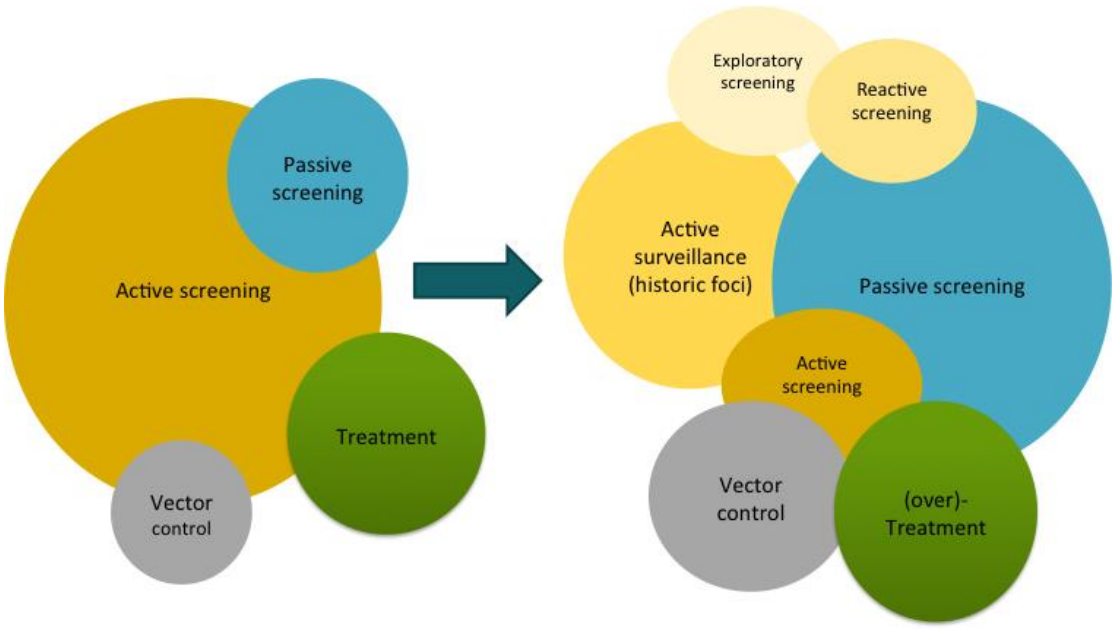

Fig. 5: Evolution of HAT control strategy in order to reach interruption of transmission.

The development and implementation of these strategies will be a dynamic process whereby regular review of epidemiological data will guide which geographical areas to target. Better targeting of adapted approaches should allow further rationalization over the coming years. As the health problems are vast in DRC, the

justification of using limited resources for a disease that is nearly eliminated is a permanent challenge, even more so when it is realized that the cost per new case detected will continue to rise.

1.4.1. Passive Case Finding

There is consensus that passive case finding should receive increased attention in the years to come, despite the shortcomings in the health system in DRC. However, there are also questions about which diagnostics to integrate at what level and who to target for testing. With HAT prevalence further decreasing, screening with an RDT at health center level will not automatically lead to more confirmed cases. The positive predictive value has become so low that the vast majority of referrals would be false positives. Recent studies revealed that most referred patients never make it to the hospital where diagnosis could be confirmed. Hence, at the moment, it may make more sense to concentrate passive screening and diagnostic confirmation in hospitals or larger well-frequented health centers. Once acoziborole becomes available (or if criteria for the use of fexinidazole would be broadened), one could consider treating on the basis of symptoms plus a positive RDT, without parasitological confirmation. This would mean that introducting RDTs at peripheral centers could then be reviewed. However, it will then also be necessary to have a mechanism in place to assure collection of a blood samples prior to treatment for post-hoc analysis in a reference laboratory and assess whether cases or just false positives were treated and to decide when to stop such approach. Results of the post-hoc laboratory analyses will also be crucial to guide on which/where active surveillance activities should be launched.

1.4.2. Active Case Finding

Taking into account the poor functionality and low utilization rate of the health system, it is considered that maintenance of a minimum number of mobile teams is essential to reach interruption of transmission in DRC. However this does not mean a continuation of business as usual. The set-up of the teams (mini vs large), and where they are stationed should be revised regularly and adapted to the changing epidemiological context. A first review, in February 2021, led to a revised set-up, with less large mobile teams (30 -> 27), but creation of some additional two-person mini-mobile teams to boost reactive screening and for better accessibility of remote areas.

We foresee 4 different active surveillance modalities:

a) Routine active screening:

This is a continuation of the current WHO strategy requiring any village that reported a case to be screened until no more cases are found for three years in a row, with one additional round of screening five years after the last case was found. However, in line with the declining prevalence, the number of village eligible for screening is expected to rapidly drop in the following years as well. This trend has already been observed.

b) Reactive screening:

Reactive screening should be conducted in the villages of origin of HAT cases detected during passive screening in health facilities, it these villages were not already included in the list of villages selected for routine active screening. Such reactive screening cannot be planned in advance, but resources should be reserved to enable rapid reaction. Such mobile teams will be directly attached to a provincial PNLTHA coordination, and will have a flexible action radius.

Reactive screening could be more effective if carried out by a (motorcycle-based) mini-team that can easily be transferred from one area to another and is capable of reaching even remote and hard to access areas. These teams should also be tasked with obtaining insight in possible sites of transmission. Therefore, the composition and the required skills will have to be reviewed. In 2021, the reactive screening approach has been initiated in the framework of the first phase of HAT+. The results of these pilots can influence the further development of this approach.

c) Probing of blind spots:

Probing of blind spots is a form of active screening in areas with suspected transmission which have not been under regular surveillance but are suspected to be potentially HAT endemic. Such activities can be planned in advance and should also be conducted by mini-teams. These teams could apply classical screen and confirm techniques but could also collect DBS samples on filter paper as an alternative. DBS samples could then be tested at a reference level laboratory, in case any infections are found these subjects will need to be revisited for treatment.

d) Surveillance of historic foci

Historic foci are areas that have been endemic for HAT in the past but where no cases have been reported for at least five years. Surveillance of such spots is important because in the past, recrudescence has always been first reported in such historic foci. It needs to be kept in mind that HAT has a patchy, very focal distribution; not finding any cases in one health area does not mean that the entire health zone is free of HAT. As symptoms of HAT can be aspecific for a long period, infection prevalence can be building up for quite some time before any cases are detected by the regular health care services.

Such surveillance can be based on a similar approach as used for probing of blind spots. They do not need to be screened every year but perhaps once in five years. The best rhythm (spacing and phasing out of surveillance) of such surveillance rounds needs to be further studied. To exclude with 95% certainty a prevalence of 1 per 1,000 would require a sample size of 3,000, which is still manageable. If resurgence can be detected at that stage it can still be controlled relatively fast. Aiming to detect prevalence in the order of magnitude of 1 per 10,000 is not feasible.

1.4.3. VECTOR CONTROL

Vector control based on the tiny targets proved to be effective in the former province of Bandundu, the area with highest endemicity for HAT in DRC for many years. Unsurprsingly, diminishing tsetse density can be an important asset to rapidly reach interruption of transmission. However, it is not feasible to cover the entire surface at risk for HAT in DRC and a targeted vector control approach is required to take full advantage of this tool. Based on sound epidemiological data and modeling, further areas can be identified where tiny targets can be deployed. Xeno monitoring can be considered but should be piloted first since numbers of tsetse flies are generally very low and only a very small fraction carries *T.b. gambiense*. The yield and cost would need to be compared to that of surveillance of the human population.

1.5. ITM IN DRC

ITM has long-standing partnerships and experience with collaborative research and support to disease control programs and the health system in DRC and in to HAT in particular.

ITM staff has been involved in HAT research from the beginning of the 20th century. Today ITM is renowned in the HAT community as leading scientific institution with proficiency in public health, epidemiology, biomedical and clinical sciences. ITM is represented in the different relevant expert committees organized by WHO and is one of 4 collaborating centers of HAT diagnosis for WHO worldwide. Over the last decades, ITM has been involved in the development of all newly developed diagnostic and screening tests for HAT. The CATT test, in use since the mid 1990s, and all native antigens essential for all serological tests currently in use are produced only at ITM.

In recognition of these assets, ITM has implemented and coordinated a number of HAT projects. The combination of these projects form the backbone of HAT control in DRC. In 2021, ITM was in charge of the following projects, combining research and support to HAT control:

- HAT+ (first phase) financed by the Belgian Government;
- Support to HAT control in DRC within the framework agreement between the Belgian Government and ITM (FA4 2017-2021);
- Tryp-Elim Bandundu (OPP1155293) financed by BMGF;
- iELISA research project to develop new diagnostic tests at ITM, financed by BMGF;
- CHARHAT research project to assess the Cryptic Human and Animal Reservoir of HAT; financed by the Flemish Community (Department of Economy, Science and Innovation).

In DRC, ITM mainly collaborates with four Congolese institutions or networks, that all play a role in the framework of HAT control.

PNLTHA

The *Programme National de Lutte contre la Trypanosomiasis Humaine Africaine* (PNLTHA) is in charge of HAT control in DRC (see higher);

INRB

The *Institut National de Recherche Médical* (INRB) has been an important partner for ITM for more than 20 years. INRB is the national reference laboratory in DRC for many diseases and is most famous for its role in the Ebola outbreaks. The new vision of INRB is to decentralize with reference laboratories at a regional level.

Also for HAT, INRB is the national reference center. With decreasing prevalence, INRB has an increasing role in training, confirmatory testing, and quality control of HAT diagnosis. Supported by ITM, it is also the only producer of the mini Anion Exchange Centrifugation Technique (mAECT), i.e. the best confirmation technique for HAT currently available. In 2019, INRB was recognized as one of 4 collaborating centers for HAT diagnosis by WHO (the only one in DRC). WHO collaborating centers can be asked to provide services also beyond DRC (e.g. training, quality assurance, ...).

CRSK

The *Centre de Recherche en Santé de Kimpese* (CRSK) has been created in 2017 by a consortium of four Congolese institutions: *Institut Médical Evangélique* (IME), *Université Protestante du Congo* (UPC), *Santé Rurale* (SANRU) & *Université de Kinshasa* (UNIKIN). CRSK is involved in research activities for HAT and the laboratory of CRSK based in Kimpese proved to be an asset for the implementation of new diagnostics (e.g. ELISA).

ITM also collaborates with individual members of CRSK. There exists a tradition of collaboration with IME for decades, in particular for mycobacteria. Unikin is strongly involved in pharmacovigilance for the new oral drugs of HAT. Until sofar the collaboration with SANRU has been limited, but as they implement health programs in over 500 health zones (e.g. as principal recipient of the Global Fund malaria grant, and “Appui aux soins de santé primaires” financed by DFID), this network could be an alternative to accelerate the integration of HAT control in the primary health care system. The chair of CRSK is a national reference for psychiatric disorders, which are typical symptoms for HAT patients in stage II.

Ecole de Santé Publique de Lubumbashi (ESP)

The Public Health School of Lubumbashi has been involved in research for the integration of HAT in the primary health care system.

Through the HAT program, ITM tries to stimulate collaboration between these four institutions. Investment through HAT should also create an appropriate environment to effectively manage other diseases for which no special funding is available. In 2020, the Belgian Government allocated an additional grant to ITM to strengthen the capacity of DRC to cope with Covid-19 and other emerging infectious diseases. This will increase the capacity of INRB, CRSK and ESP, and enable them to further develop as national and regional reference centers.

ITM has a tradition of collaborating with Belgian NGOs active in the health sector of DRC (e.g. MEMISA, Artsen zonder Vakantie, Damiaanfonds, Louvain Développement de l'UCL, ...) and recently started a closer relation with Enabel. Also on an international level, ITM has an extended network, including the major multilateral and governmental actors active in DRC (e.g. Global Fund, Tuberculosis, ..).

1.6. Other Stakeholders for HAT control

WHO has an important role in the elimination process of HAT in Africa. Through public private partnerships it has resources to strengthen control and surveillance at national level and fill the gaps, in particular in so called HAT orphan countries, countries that are affected by HAT but do not have specific donors to support HAT control. Since 2014, WHO has invested in a HAT elimination network comprising of a Scientific and Technical Consultative Group, Country Coordination Meetings and Implementation Coordination Meetings. The collaboration between WHO, ITM and PNLTHA is excellent. They alternatively organize HAT partner meetings involving all interested partners involved in HAT control in DRC and interactions are frequent. The WHO support in DRC is limited to the support of seven mobile screening teams, two sentinel site networks for passive case-finding and post-elimination surveillance, the provision of some diagnostic tests and some training. However its role is essential in making treatment available (as explained above).

The number of partners involved in support of HAT control in DRC is rather limited, explained by the fact that there are only two major donors apart from some public private partnerships. In the projects supported by Belgium, Enabel has been subcontracted since 2019 by ITM. Previously, the NGOs Memisa and MSF were also active in HAT control but this is no longer the case. In 2021 the Belgian Embassy will put HAT on the agenda of the *Groupe Inter-Bailleurs en Santé* (GIBS) to relaunch this dynamic. In the framework of the support by the Bill & Melinda Gates Foundation, ITM collaborates with LSTM (vector Control), the *Program for Appropriate Technology in Health* (PATH) for logistics and Bluesquare. PATH also implements an advocacy project for BMGF

Several research groups are active in the DRC on HAT related research. Until 2020, the French Institute for Research and Development (IRD) has been conducting diagnostic and epidemiological research, partly funded by the European Union through the European Developing Countries Clinical Trials Partnership (EDCTP). The Drugs for Neglected Diseases Initiative (DNDi), a non-profit research and development (R&D) organisation, conducts studies for the new HAT treatments. The Foundation for Innovative New Diagnostics (FIND) has been working for several years on the development and evaluation of diagnostics in the DRC. There are also several US and UK academic groups such as the University of California Los Angeles (UCLA), Institute of Disease Modeling (IDM), Warwick University, Yale University and Swiss TPH, which are primarily interested in mathematical modeling of sleeping sickness elimination in DRC. All of these research groups collaborate with PNLTHA.

1.7. Results and lessons learned from the first phase of HAT+

During the first phase of the HAT+ project, a number of important results were obtained towards the elimination of HAT in DRC, despite a difficult context. The monitoring and evaluation revealed the continuing declining trend of reported HAT cases. The overall trend of declining HAT cases reported should be attributed

to the combined impact of different projects that support HAT control in DRC. It is clear that HAT+ project also played a major role to obtain these results.

More in particular, the HAT+ project facilitated coordination of the HAT community and a dynamic of collaboration between all Congolese and international HAT partners involved in DRC. The HAT+ project actively supported PNLTHA in its policy assessment and development. The digitalization process launched in the framework of the BMGF project, was applied in provinces supported by the Belgian financing and a central data management and surveillance centre is operational in Kinshasa. Better data management should lead to improved planning/targeting of activities, quality control and insight in the gaps. HAT+ contributed to capacity development of Congolese partner institutions of ITM, involved in the HAT agenda. Also for surrounding countries affected by HAT, it had an impact by facilitating exchange (e.g. several HAT affected country programs participated in a quality assurance seminar).

The first phase enabled to make important progress in the development of new tools, in particular serological and molecular diagnostic tools, although it took more time than anticipated to get there. Hence, most field research (in particular phase 3 testing of newly developed tools) had to be delayed until 2021 and therefore the results of these studies can only be expected at the very end of the first phase of HAT+. All available and expected tools have their shortcomings but by combining them, we can go a long way to further improve the HAT situation in the coming years. Research in the second phase of HAT+ should therefore focus on the development and testing of new surveillance strategies, making use of the new tools, rather than focus on new tools only.

Flexible management structures enabled to resolve unexpected challenges, including changing context in DRC, unavailability of appropriate diagnostics, delayed availability of new treatment, delayed involvement of Enabel in the implementation and the Covid-19 pandemic. In particular in 2021, the HAT+ project enabled to fill gaps that other projects could not solve (e.g. deal with high increased of costs of tests).

Mainstreaming HAT in the primary health care system was an important expected result of the first phase of the HAT+ project, but the results obtained to date have been below expectations. In the first phase of HAT+, achieving this result was entrusted to Enabel. Due to difficult relations between Belgium and DRC in the period 2017-2018, the subcontract was signed late, but since then the start-up of activities has also been very slow. Consequently, ITM had to look for alternatives to ensure that screening of the population at risk remained at an acceptable level. This revealed the vulnerability of focusing on one approach only, partly explaining why in the new HAT control strategy a combination of approaches is proposed (e.g. multistakeholders approach, diversification of active case detection approaches, introduction of centralized testin, combinations with vector control, ...)

The delay in the meanstreaming of HAT in the primary health care system had other reasons than administrative red tape only. The initial approach was to fully integrate HAT control in a limited number of health districts, involving a maximal number of health facilities and to gradually spread throughout the country. This strategy would start in the health districts where Enabel was present. In other regions it was expected that Enabel would contract partners that implemented primary health care projects, but not one contract was concluded. Instead Enabel subcontracted PNLTHA to implement training activities, though it was known that PNLTHA has its limitations and vested interests likely to affect provision and contents of training. This raises questions of effectiveness. On the other hand, insights related to the integration process also changed. At the start of the HAT+ project, the idea was to ensure that in each health district a maximum of health facilities could provide HAT diagnostics in health districts where Enabel was active, and to gradually extend this coverage to other health districts over the years. Experience in a pilot zone has since shown that with the tools currently available, it is not realistic to extend diagnostic services beyond larger centers. The current consensus is that as quickly as possible all district reference hospitals of HAT endemic regions should be able to perform both RDTs and confirmation techniques in their laboratories, with a quality assurance

mechanism in place. Any positive case identified should then result in reactive screening of the village of origin. Provision to health facilities of RDTs only (without posibility for on the spot diagnostic confirmation), should be limited until acoziborole will be available and treatment based on a positive screening test can be considered. We have evidence that patients with a positive RDT, rarely travel to a reference hospital for a HAT confirmation test, meaning that most RDT testing at first line does not lead to consequent action and therefore a waste of resources.

2. STRATEGIC ORIENTATIONS

2.1. GUIDING PRINCIPLES

In the first phase of the HAT+ project, the short-term objective of PNLTHA was the "elimination of HAT as a public health problem by 2020" in line with the WHO roadmap for Neglected Tropical Diseases (NTD). This has been achieved. The second phase will coincide with the start of the endgame, i.e. "interruption of HAT transmission by 2030".

A key characteristic of the first phase was "flexibility" which enabled to tackle emerging challenges, even of other HAT projects. Flexibility will continue to be a basic guiding principle because the new objective of "interruption of transmission" implies that the agenda progresses into unknown territory requiring a new mind set.

Also the other basic guiding principles of Phase I will remain valid, adapted to the new context:

- QUALITY: Quality assurance (QA) will be further developed for all processes of the elimination agenda, including diagnosis, treatment, vector control, data management and surveillance. The QA system developed for HAT diagnosis in 2021 can serve as example.
- TAILOR MADE TARGETED APPROACHES: The elimination initiative requires a pragmatic and flexible approach that takes into account the rapidly changing epidemiological context, allowing for the rapid integration of new and innovative techniques and strategies. Experience with elimination of other diseases has shown that a holistic approach is most opportune, i.e. a strategy that uses all available tools for improvements in diagnosis, treatment, vector control and surveillance, although the precise impact of these strategies is not (yet) known. However, how to combine should be adapted to the local context taking into account the many parameters that play a role (e.g. geographical accessibility, degree of endemicity, quality and accessibility of health structures, security, etc.).
- INNOVATION:

  Innovation was a key element to argue that HAT elimination is feasible and this principle remains valid. Until now all hypotheses of expected innovations have been realized and further innovations are expected to materialize following investments during the first phase. With these achievements we can go further than anytime before in history but this should not be an excuse to stop looking for better ways. This explains why not only new research activities will be conducted but also why action research (pursuing control activities and research activities to understand the dynamics of HAT at the same time) will be integrated into all activities.
- COHERENCE AND COMPLEMENTARITY:

  ITM will continue to look for synergy, coherence and complementarity of HAT interventions it coordinates. The financial resources available to HAT control in the DRC via Belgium and the BMGF are significant, but may still be insufficient to ensure interruption of transmission. It is therefore important to constantly seek opportunities for synergy and complementarity. Duplication should be avoided.

  Adequate coordination mechanisms at national and international level are essential to avoid wasting available resources. All relevant stakeholders (i.e. central and provincial authorities, health districts, donors and implementing partners) should be involved. This should lead to a

broad coalition of partners in the health sector and beyond, who want to achieve these goals, based on a common vision, aiming at synergy and relying on some fundamental principles.

2.2. Implementation of the HAT Strategy

As for all HAT projects coordinated by ITM, the HAT+ project will continue to adhere to the holistic HAT strategy developed by WHO and adopted by PNLTHA for DRC. The HAT+ project will focus on increased implementation of passive HAT screening, integrated in the health system. As the implementation of integrated passive case detection during phase I did not live up to expectations, alternative approaches will be considered

In addition to increased passive screening support, the HAT+ project will also focus on post-elimination active screening in liaison with monitoring and evaluation. The results of these new approaches will be used to provide feedback to the strategic vision and potentially lead to fine-tuning of the strategy in DRC and beyond.

Improved data collection and data management will also be essential elements to provide feedback to the HAT policy, which can potentially lead to policy adaptations.

2.3. Capacity Development

The HAT+ project will boost capacity development of the partner institutions of ITM at institutional, organizational and individual level. With the declining HAT prevalence and availability of new diagnostic tests, the roles of PNLTHA and INRB will have to be reviewed and revised, but new strategies (with confirmatory testing done central/regional level) will only work when the different institutions have the required capacity.

A particular challenge is how to maintain expertise in HAT diagnosis. With declining prevalence the chance of regularly seeing parasites becomes rare and the chance that a lab technician will miss a positive case increases. For lab technicians of fixed health facilities, it can be questioned whether staff should learn a variety of tests, some of which they will rarely perform. Ultimately, it will become difficult to maintain widespread expertise for HAT diagnostics despite training and supervision. Already today, the available expertise to conduct immune trypanolysis is limited to two centers, worldwide. Even if overall, there is still ample HAT diagnostic expertise available in DRC, measures should be taken to ensure that for all available tests a minimal level of proficiency is maintained in the years ahead. This is not only a challenge for DRC but also in other HAT affected countries that report much smaller numbers of cases. The HAT+ project will facilitate investments in training to maintain diagnostic expertise and in tools facilitating the communication of test results between different levels involved. ITM is well placed to play a leading role.

2.4. Diagnostics

At the official launch of the new WHO 2030 road map for NTDs, Belgium announced its commitment to guarantee production and availability of HAT diagnostic tests. ITM will try to make this commitment come true, via the HAT+ project. ITM will continue to play the role of honest broker and facilitator to ensure that HAT diagnostics are produced and available in the field. With new approaches and larger diversity of tests available, the management and planning will become more complex but it is important to avoid wasting scarce resources. Assets of ITM are the specialised departments and its network with other institutes and with the private sector. ITM will continue to support the production of mAECT at INRB .

Feasibility of interruption of HAT transmission will depend on whether the diagnostic results are reliable. To successfully complete the endgame of HAT elimination, both under-diagnosis and over-diagnosis will be a continuous concern throughout the implementation of the project. Until recently, trying to avoid treatment of false positives was the main target, mainly because of the toxicity and complexity of available treatment

regimens. With the focus on interruption of transmission and the fact that a non-toxic oral regimen (fexinidazole) is now available this could drastically change, but the real game changer is expected to be acoziborole, the single dose oral treatment. Treatment approaches based on serological tests only, without confirmation, could become the new stratgey. But for epidemiological reasons, it will be important to know whether any real cases remain. This stresses the need for a well-functioning quality assurance (QA) system of diagnosis, including a system of post-hoc diagnostic confirmation. The quality assurance system set-up in collaboration with WHO, PNLTHA and INRB, will be further developed and will be made available for other HAT affected countries.

2.5. TREATMENT

Elimination is only possible if the entire population at risk has relatively easy access to health facilities that can adequately diagnose and treat sleeping sickness. During phase II of the HAT+ project, the availability of fexinidazole wiil be the major asset for further progess in comparison with Phase I. WHO and PNLTHA have both a role to play to ensure accessibility of HAT treatments. The HAT+ project will facilitate mitigation measures (e.g. avoid stock-outs) and pharmacovigilance activities of fexinidazole. By 2023, EMA will assess the results of the use of fexinidazole in DRC and potentially adapt its opinion.

It is expected that DNDi will submit the results of clinical trials with acoziborole to EMA by 2023. So in the best case scenario, the new drug will be available from 2024 onwards. This means that in the following years the current treatment guidelines will remain the basis for routine treatment and strategy.

2.6. VECTOR CONTROL

Vector control is integral part of the HAT strategy. It could be applied in the framework of the HAT+ project, but is not considered a priority in this framework. This could change, once results of field studies on HAT transmission and on impact of different strategies with and without vector control become available.

2.7. PROJECT MANAGEMENT

The design, approval and implementation of all conducted activities in the framework of the HAT+ project will rely on a continuous interaction between ITM and all relevant Congolese partner institutions involved.

Considering the complexity of the overall HAT program, the management will be based on the principles of lean management. This means that looking for the most efficient way of implementation will be a continuous concern. This is possible because, compared to the first phase, ITM is much better organized in Kinshasa and better equiped to manage administrative, logistic and financial issues in DRC and hence to better support Congolese partner institutions. This opens new perspectives to deal with logistic and administrative challenges. This increased capacity is a guarantee to assure that project activities can be conducted within a time frame of 3 years.

In the framework of the MoU between Belgium and BMGF, all reporting of HAT interventions coordinated by ITM, will be made available for both donors in order to increase transparancy and impact. As a consequence, the annual reporting of HAT+ will be in English. One step further could be a joint reporting as applied in a mechanism of common funds.

2.8. POLITICAL INVOLVEMENT

For both DRC and Belgium, the support to the elimination of HAT in DRC is a priority. Hence the HAT+ project should ensure that both political authorities are well informed, at all times. Therefore exchanges will be further developed with the directions of MOH that are indirectly involved (e.g. DEP, DGLM, Provincial authorities, ...).

In Kinshasa, ITM will provide timely relevant information and updates to the Belgian Embassy. In Belgium regular meetings will be organized to inform DGD and to facilitate exchange with representatives of BMGF in case they visit ITM Antwerp in the framework of the follow-up of other HAT projects. Also the Belgian Embassy in Geneva will be kept informed.

2.9. OPPORTUNITIES AND FILLING THE GAPS

The rapid progress of declining HAT prevalence, also reveals new problems and the need to fill remaining knowledge gaps. It is not the intention of the HAT+ project to solve them all and other funding is already available to solve some knowledge gaps (e.g. role of the cryptic human and animal reservoir in the transmission of HAT). However the HAT+ project can provide some support when such initiatives encounter challenges.

The HAT+ project will focus on specific domains of the implementation of the overall HAT strategy and operational research. However, within this support, opportunities will be looked for to support other control and research activities. As the parasites in the human population become rare, newly detected infection foci will be used as input for research on diagnostics, treatment and different strategies. Also the HAT specimen bank from WHO, based in Paris, containing samples of blood, serum, CSF, saliva and urine from infected patients will be exhausted in the medium term, unless samples are replenished.

Opportunities wil be seized to tackle relevant (essential) questions through other financing opportunities. This principle was already applied during phase 1, when ITM and PNLTHA were invited to join an EDCTP funded initiative for pharmacovigilance of fexinidazole (project still ongoing). Released budget will then be used for other activities, in agreement with DGD rules and regulations.

Capacity developed through HAT support will be made available to facilitate epidemiological insight and adequate response or other (emerging) diseases, whenever relevant.

3. INTERVENTION FRAMEWORK

3.1. GENERAL OBJECTIVE

The interruption of HAT transmission in DRC is reached by 2030

3.2. SPECIFIC OBJECTIVE

The elimination of HAT transmission is reached in 90% of the endemic *Zones de Santé* (health districts) of DRC by 2025.

3.3. RESULTS

Phase II of the HAT+ project will build upon the achievements of Phase I and further expand. This explains why the expected results are similar, but with higher expectations. The list of activities proposed below is not exhaustive and can be adapted during the course of implementation, in view of obtaining better results and impact.

Result 1. The HAT elimination strategy is effectively implemented and reviewed

Sub-Result 1.1. PNLTHA is strengthened *in its role of organizing and coordinating the HAT elimination program*

The following activities can be taken into account:

- Organization of assessments and revisions of the HAT strategy in line with the procedures of DRC;
  The strategic plan for HAT elimination should allow for the most efficient use of available resources and respond quickly to a changing context and unexpected challenges;
- Organization of Scientific Consultative Committee meetings, as foreseen in the national procedures of DRC. This should enable exchange and interaction between Congolese and international experts on technical and policy issues related to HAT;
- Organization of HAT partner meetings, uniting all organizations involved in HAT activities in DRC. This will enable to continue a joint initiative launched by PNLTHA, WHO and ITM;
- Organization of technical seminars
- Assistance to prepare PNLTHA for international happenings;
- Development and implementation of appropriate systems to respond to challenges (e.g. Quality Assurance systems as started in 2021), vision of appropriate passive detection strategy, ...) ;
- Capacity development in administrative, logistic and financial domains
  The development of appropriate implementation arrangements, including the management of available means, will have consequences such as human resource management.
- Defining training needs and support to develop and conduct training;

Sub-Result 1.2. *The HAT elimination program in DRC is supported by a* ***well functioning data management system***

- Phase II should enable to fully use in all HAT endemic provinces the digital information system initiated through BMGF support and extended by Belgian funding in Phase I. By the start of phase II,

the surveillance center at PNLTHA will be operational. This new facility will enable to better manage the digital field data (collection, quality assessment), provide feedback and timely react to emerging challenges. All mobile teams operational in DRC will use the tablets with the tool installed by the end of 2021.

Some resources will be required to maintain the system via an external company, Bluesquare;

Follow-up and refresher trainings will be needed throughout Phase II, also in data management and analysis skills at PNLTHA central level;

- Mapping efforts are required beyond the former Bandundu province, where all villages have been mapped in an effort coordinated by UCLA and financed by the BMGF. Some health zones have also been mapped by BTC but most remain uncovered. The intention is to look for a simpler approach, generating the minimally required data in a quick and efficient way.
- Data collection and management in/by passive screening sites will be further standardized. The integration of the information in the DHIS2 system is the ultimate goal,

Sub-Result 1.3. *The HAT elimination program in DRC is supported by capacity development*

- Capacity development activiteis for all Congolese partner institutions involved can be organized;
- INRB is supported to provide diagnostic training programs in line to identified needs for PNLTHA and potential other partners (see Result 3);
- The quality assurance system of diagnosis is implemented;
- The HAT+ project can support INRB and ITM in its role of Collaborating Centre for WHO, to provide training and quality assurance services, for other countries beyond DRC.

Result 2. The elimination strategy is supported by targeted research and innovation

Sub-result 2.1. *Improved diagnostic tools are developed and validated*

- This subresult was a major focus during phase I, but investments will be scaled down during the second phase and limited to finetuning of existing tools. This approach could be revisited if tools with major advantages in comparison to what already exists would emerge or if available tools run into problems;
- A priority research topic, is the need to improve sampling methods to enable testing in reference laboratories, because the currently used DBS on filter paper has considerable disadvantages;
- Options with industrial partners will be further explored, to ensure production of tests and to support them to find solutions for challenges such as the new registration rules in the EU context.

Sub-result 2.2. *Appropriate strategies are developed*

- The research in phase II will primarily focus on developing/testing appropriate HAT control strategies, adapted to different local contexts. Different combination of tools will be looked for;
- The choice will be influenced by research activities financed through other projects.

Sub-result 2.3. *Emerging epidemiological questions relevant to HAT elimination will be tackled*

- The research to have better insight of HAT transmission launched in phase I, will be continued. This will include research on vector control, e.g. to understand which population is most affected by tsetse flies;
- Attention will be paid to social-science topics relevant to the HAT elimination agenda.

Result 3. HAT control activities are integrated in the primary health care system of HAT endemic health districts

Sub-result 3.1. *The coverage of all HAT endemic health districts is assured*

The aim is to cover as quickly as possible all 189 remaining gHAT affected health districts in DRC with passive screening complemented with the above mentioned active screening approaches. However different approaches will be applied according to prevalence levels. Confirmation techniques will only be introduced if it can be expected that several cases per year are detected in the health facility. If not screening will be followed by sampling of DBS that will be examined at a regional laboratory. HAT+ will be the main financing sources for this approach (see Table 1 in annex).

The implementation of activities to reach this result will strongly depend on the way forward with Enabel. As the contract with Enabel comes to an end by June 2022, an external evaluation of the performance of Enabel will be conducted in Q1 of 2022, to assess obtained results, including value for money and effectiveness. This should lead to determine the role of Enabel in phase II and the resources that are necessary. The close relations of Enabel with DEP and DGLM remain an asset.

The extension of an international HAT coalition, involved in passive detection will be a priority for phase II of the HAT+ project, implying more partners than ITM and Enabel. Several implementation organizations already expressed interest to be involved, and challenges such as availability of tests, that impeded progress during Phase I have been resolved. The question “how” to reach a broad integration in the primary health care system will be assessed and also depends on the future mandate of Enabel. Initiatives launched to this effect in 2021 by ITM, will be further developed (e.g. initiatives via CRSK).

Alternative approaches do exist to develop the intended international coalition. Through the Belgian embassy and the GIBS, the integration of HAT can be put on the agenda. The HAT+ project could at least provide diagnostics, clear guidelines and training opportunities for lab technicians and clinicians and provide follow-up. In return, punctual reporting to PNLTHA should be ensured.

Applying Quality Assurance (QA) for fixed health facilities is a priority, because QA is currently lacking for passive case finding. Remote quality assurance through electronic storage of images, as applied for mobile teams, is relatively labor intensive and currently considered NOT suitable for passive case finding applied at a large scale. Site visits and corrective actions by experts can be useful to improve the basic skills of lab technicians but will not be sufficient, even if such expertise is available. The chances of having true positive samples at the time of a supervision visit will be minimal and more external quality assurance activities will be needed.

A confirmed HAT infection should trigger reactive screening of the village of origin. Reactive screening activities will not be financed through the HAT+ project, but it would be a pitty to waste resources for false positives implying the necessity for external quality control and post-hoc confirmation of caseson stored samples in a quality-assured laboratory. This means the need for sampling Dried Blood Spot samples (DBS) or venous blood samples (or lymph or CSF) for confirmation. Samples should be sent to a reference laboratory, either for immune trypanolysis, for iELISA or for molecular testing. Decisions to launch reative screening activities could wait for this post-hoc confirmation within certain limits.

A training, follow-up and refresher training of laboratory technicians is essential to ensure adequate coverage as soon as possible. The challenges concerning training identified during phase I, will be tackled and we will ensure that the right partners are involved.

Sub-result 3.2. *Provision of RDTs and mAECT tests is assured*

Considering the difficulties with RDT production and the price increase, ITM will ensure the purchase of RDTs to be used in health facilities. Centralizing purchase of RDTs for the different projects will help to obtain lower prices but also to enable better stock-management: i.e. to prevent stock-outs and to prevent that RDTs are unused before reaching the expiry date. The use of CATT is not an option as this is not suitable for individual diagnosis.

The production and purchase of mAECT is ensured

Result 4. The progress of HAT elimination is monitored and evaluated

Sub-result 4.1. *Monitoring is assured*

- PNLTHA is assisted with overall monitoring;
- The HAT+ project will contribute to the implementation of the new approaches of the active screening in relation to monitoring are implemented i.e.;

  i) Probing blind spots in areas with suspected transmission, which have not been under regular surveillance but are suspected to be potentially HAT endemic;

  ii) Surveillance of historic foci previously endemic for HAT.

  These activities can be conducted either by applying the classical screen and confirm techniques, or by collecting DBS samples on filter paper, or alternatively doing RDTs on the spot and collection of DBS samples only for those RDT positive. Such DBS samples could then be tested at a reference laboratory.

  Per provincial coordination, a yearly program will be elaborated in collaboration between national and provincial level.

Sub-result 4.2. *The progress of the elimination program is evaluated and results are disseminated*

- The project is evaluated by an external expert, at least once during the phase II
- Results of the HAT+ project will be disseminated both in DRC and at international level and serve as input for coordination or scientific invents.

3.4. INDICATORS

Results	Indicators	Source	Baseline value	Target value year 2
The HAT elimination strategy is effectively implemented and reviewed	Number of workshops, seminars and international meetings	Activity reports PNLTHA	0	15
	Digital tool is applied by all mobile teams	Activity reports PNLTHA	0% (June 2021)	100%
The HAT elimination strategy is supported by targeted research	Improved sample methods are applied	Study reports ITM	-	1
	Number of operational research studies	Study reports ITM	0	5
	Results of operational research studies are applied	Study reports ITM	0	2
HAT Control is integrated in the primary health care system	At least 1 health facility in high endemic health districts can detect gHAT.	Passive screening activity reports	30%	100%
The progress of elimination is monitored and evaluated	Number of people screened (disaggregated by province, area of residence, screening strategy)	PNLTHA Report / electronic data	2 million (data of 2020)	2.5 million
	Number and % of positive (serological, confirmation) tests by province and area of residence	PNLTHA Report / electronic data	0.5% CATT positive	<0,5% CATT +, of which <5% confirmed
	Numner of historic foci of HAT are screened	PNLTHA Report / electronic data	0	20
	Number of blind spots screened	PNLTHA Report / electronic data	0	10
	External evaluation of program	Evaluation report	0	1

4. RISK ANALYSIS

Risk description	Probability	Impact	Risk mitigation plan
Instable context of DRC leads to difficult working conditions and unsafety in certain areas	Medium to High	Medium	New tools should enable to limit extended stays in areas at risk. Priorization of expansion of passive case finding in primary health care in such type of areas (example Maniema/Katanga).
The lockdown measures for COVID-19 are prolonged (e.g. persistence of travel ban, limitation of human interactions,…) impacting the implementation of the project	Medium to High	Low to Medium	Technology and practice of interaction via social media developed during the lockdown in Belgium and DRC have dramatically improved
Administrative and logistical problems hamper the progress of the implementation	Medium	Medium	ITM invested in administrative, logistics and fiancial capacity of its representation, which can be used to strengthen capacity in these domains of the different Congolese institutions involved in HAT; ITM initiated an official registration process, not only deemed essential for increased effectiveness and efficiency of its work; but also to increase its impact at policy level.
The capacity of ITM is too low to deliver results within the planned timeframe of 3 years	Low	Medium	The ITM representation of ITM in Kinshasa has been strengthened in 2020-2021, covering all aspects needed for effective project management; A variety of ITM expertise can be called upon, covering all relevant HAT expertise domains. Via the different projects that ITM coordinates in DRC, budgets reserved for human expertise are used to finance a wide range of complemantary expertise.
The capacity of PNLTHA is too low compared to the ambitions of the program	Medium	High	In all activities, capacity development is taken into account; During the previous years, ITM has provided additional funding for PNLTHA staff to follow MSc and PhD programs; A new facilty has been created to enable young scientists to benefit from a “Marleen Boelaert fellowship”.
The capacity of INRB is too low to answer to increased demand for support	Medium	High	Within the current phase of the HAT+ project, a budget line has been ensured to cover extra capacity development activities to INRB
The capacity and utilization of the primary health care system is too low to assure good coverage of the populations at risk.	High	High	Complementary active population-based surveillance methods will be maintained.
The integration of HAT diagnostics and treatment services through Enabel continues to be low	Medium	High	New strategies are developed A thorough assessment will be conducted of Enabel performance in 2022;

			ITM looks for alternatives (e.g. SANRU via CSRSK,, a partner institute of ITM, covers nearly all endemic health zones in DRC).
Unexpected new foci are reported reversing the declining trend of HAT reporting	Medium	Low	The HAT+ strategy has been based on preparing for such emerging foci.
The promisiing new expected diagnostic tools ultimately do not live up to expectations	Low	Medium	Increased efforts on quality assurance have been set-up The available tools already developed in recent years do already allow to progress further than ever before. The impact would mainly mean that more time is needed.
Companies that produce diagnostic tests decide to stop production	Medium	Medium	The main reason to stop would be low return on investment, implying that a higher price would probably solve most issues
The final testing of the new drug acoziborole reveal unacceptable side effects	Low	High	Fexinidazole can serve as a replacement. The main impact will be that more time at a higher cost will be required to reach the same results
DRC becomes reinfected through HAT infected cases from surrounding countries crossing the border	High	Medium	HAT authorities of surrounding countries are invited to participate in capacity development events; The surrounding countries can all upon expertise of ITM; Organizations (e.g. MSF) are approached to ensure monitoring of HAT in these border areas.
Problems of corruption and fraud emerge as reported in a recent study by DFID	Medium	High	ITM has invested in a new accountancy tool that provides more insight in bookkeeping; Several measures are taken to reinforce financial control mechanisms in DRC and at ITM.

5. BUDGET

In line with the Royal Decree of 2017, the activities have been developed for a period of 3 years. However as the budget will be obligated for a period of 2 years only, the budget structure has been adapted accordingly. The total budget for 2 years is 5,600,000 Eur.

Table 1. Overview of the Budget in EUR

	Year 1	Year 2	Total Y1 & Y2	Year 3
Result 1: The HAT elimination strategy is effectively implemented and reviewed	**300,000.00**	**300,000.00**	**600,000.00**	**300,000.00**
1.1 PNLTHA is strengthened	100,000.00	100,000.00	200,000.00	100,000.00
1.2 Well functioning data management system	130,000.00	130,000.00	260,000.00	130,000.00
1.3 Capacity development	70,000.00	70,000.00	140,000.00	70,000.00
Result 2: The elimination strategy is supported by targeted research	**300,000.00**	**300,000.00**	**600,000.00**	**300,000.00**
2.1 Improved diagnostic tools are developed	100,000.00	100,000.00	200,000.00	100,000.00
2.2 Appropriated strategies are developed	170,000.00	150,000.00	320,000.00	150,000.00
2.3 Epidemiological questions	30,000.00	50,000.00	80,000.00	50,000.00
Result 3: HAT integrated in the primary health care system	**1,508,872.67**	**1,500,000.00**	**3,008,872.67**	**1,504,436.33**
3.1. Coverage of all HAT endemic health districts	1,000,000.00	500,000.00	1,500,000.00	500,000.00
3.2 Provision of RDTs and confirmation tests is assured	508,872.67	1,000,000.00	1,508,872.67	1,004,436.33
Result 4: The progress of HAT elimination is monitored and evaluated	**300,000.00**	**300,000.00**	**600,000.00**	**300,000.00**
4.1 Monitoring is assured	200,000.00	200,000.00	400,000.00	200,000.00
4.2 Progress is evaluated and results disseminated	100,000.00	100,000.00	200,000.00	100,000.00
TOTAL DIRECT COSTS	**2,408,872.67**	**2,400,000.00**	**4,808,872.67**	**2,404,436.33**
TOTAL INDIRECT COSTS	**396,293.51**	**394,833.83**	**791,127.33**	**395,563.67**
GRAND TOTAL	**2,805,166.18**	**2,794,833.83**	**5,600,000.00**	**2,800,000.00**

The budget is in the same order as during phase 1, but the division between the 4 results has been modified aligned to the focus on integrating HAT in the primary health care system.

As in the first phase, the indirect costs will be composed of management costs (10%) and structural costs (5%). Subawards will follow the same criteria as defined in the first phase (12% for Enabel). Subawards will never lead to higher transaction costs overall. A copy of all agreements with implementation partners will be transmitted to the administration. Derogations of this budget can be proposed to DGD during the implementation of the project

During the implementation of the project, the relevant legal framework will be respected, such as the Law of 19 March 2013 with respect to the Belgian Development Cooperationg, the law of 22 May 2003 regulating the budget organization and accountancy of the Federal State of Belgium, and the Royal Decree of 11 September 2016 regulating the Non Governmental Development Cooperation (in particular annex 4 determining non reinbursable costs). For each derogation, a request will have to be introduced to DGD and a permission at issue obtained, prior to the disbursement.

The Budget will be made available through 3 yearly installments, on conditon that a claims is introduced for the relevant year from January 15 onwards and on condition that the cumulative conditions have been respected , stipulated in article 32 of the Royal Decree of 11 September of 2016.

6. MANAGEMENT

6.1. GENERAL

The HAT+ project is the result of the political decision for Belgium to, jointly with BMGF, take the lead in the elimination of HAT. The implications of this initiative fall within the mandate of DGD, both in DRC and in Belgium. The Belgian embassies in DRC and Geneva have a crucial role to enable a suitable environment required to reach the objectives, respectively with the Congolese authorities and with WHO.

ITM is in charge of the daily management of the project and to ensure that the expected results are reached. As it coordinates several other HAT projects it assures that the guiding principles as defined in chapter 2 are respected. ITM will provide guidance for Enabel and other partners involved in the implementation of the project.

6.2. STEERING COMMITTEES

6.2.1. STEERING COMMITTEE IN BRUSSELS

The Brussels Steering Committee will ensure follow-up and guidance of the overall project and review the progress of the 4 expected results. It can also be used to facilitate meetings between Belgium and BMGF.

The composition of the Brussels Steering Committee is as follows

- Representative of DGD (chair of D2)
- Representative of ITM
- Representative of Enabel

The composition can be adapted to a changing context, observers can be invited at any time.

The committee will unite at least once per year, but can also be organized on an *ad hoc* basis for particular occasions. ITM will provide the secretariat, propose the agenda and ensure the minutes and follow-up.

6.2.1. STEERING COMMITTEE IN KINSHASA

The Kinshasa Steering Committee will focus on the follow-up and guidance of result 3 of the project, i.e. the integration of HAT diagnostics and treatment in the primary health care system.

The composition of the Kinshasa Steering Committee is as follows

- Representative of PNLTHA (chair)
- Representative of ITM (Co-chair)
- Representative of DEP
- Representative of DGLM
- Representative of Enabel
- Respresentative of other organisations involved in the implementation of HAT into the primary health care system.

The composition can be adapted to a changing context, observers can be invited at any time.

The committee will meet at least once per year, but can also be organized on an *ad hoc* basis for particular occasions. ITM will provide the secretariat, propose the agenda and ensure the minutes and follow-up.

6.3. EXTERNAL EVALUATION

At the end of phase II of the HAT+ project, an external evaluation will be conducted. It will focus on the impact, the intervention's achievements as well as on its lessons learned. It will also take into account the overall progress of the HAT elimination agenda and the complementarity with other HAT projects.

6.4. AUDIT

The HAT+ project will be audited following the rules and regulations conducted for other ITM projects financed by DGD, i.e. a yearly audit.

7. MOTIVATION TOWARDS OECD/DAC CRITERIA

7.1. RELEVANCE

Support to the elimination of HAT, is in line with the Sustainable Development Goals (SDG) to end poverty and ending inequality. It supports SDG 3"Ensure healthy lives and promote well-being for all at all ages" and focuses on target 3.3 "Infectious diseases"[9]. The latter stipulates to end by 2030, the epidemics of AIDS, tuberculosis, malaria and neglected diseases, and to combat hepatitits, waterborne diseases and other communicable diseases (HAT is one of the NTDs). As the HAT control activities directly affect the rural poor, the HAT+ project also adheres to Goal 1. "End Poverty in all its forms everywhere". Also Goal 17 "Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development" is certainly relevant.

Support to the elimination of HAT in DRC and the strategic orientation of phase II of the HAT+ project is in line with the policy of Development Cooperation of the current Government, expressed by Minister Kitir In her policy statement to the Belgian parliament at the beginning of her tenure.[10] , whereby accessibility to health care and support to health systems are key. At the official launch of the new WHO 2030 road map for NTDs, Belgium announced its commitment to guarantee production and availability of HAT diagnostic tests. This Belgian commitment can be reached through the proposed activities of the HAT+ project[11]. The HAT+ project will support the international visibility of Belgium by realizing its commitments.

The funding for HAT control acitivities in DRC (and other affected countries in Africa) mainly comes from Belgium and BMGF; the contribution of DRC is limited to payment of salaries and existing office and health facility infrastructures. Considering the huge challenges in the health sector of DRC, it is logic that DRC should focus on health priorities with a larger disease burden and not on the few hundred of new cases of HAT reported annually. On the other hand, if support to HAT would abruptly stop, it might be expected that the disease would return to the level of a full scale epidemic in a number of years and much higher costs would be required to control it, as was the case at the end of the 1990s. Considering the investments in innovation and new tools over the last decade, it would be a pity not to apply them and try to progress as far as possible in the elimination process.

The approach of the HAT+ project is in line with other interventions of ITM in DRC. It contributes to the achievement of the strategic target "*Promote equitable access to health care, towards universal health coverage*" by strengthening the capacities of the institutions involved, as explained in the Theory of Change that ITM applies towards DRC in FA4 and FA5[12]. In the partner institutions, ITM invests in human resources, technical platforms, collaborations, and management so that they are better armed to conduct program monitoring and research autonomously and propose evidence-based solutions to health priorities in DRC. These enhanced capacities of the partner institutions will impact health policies in the DRC. The research supported by ITM focuses on relevant and current health problems in order to propose efficient solutions for the control of communicable diseases and other priority health problems.

The strategic orientations and activities are expected to contribute to all strategic goals defined in the joint strategic framework for "Higher Education and Science for Sustainable Development", which will be part of the next framework agreement between ITM and DGD, i.e.:

1. Increased individual capacity
2. Enabling individuals to act as change agents
3. Increased capacity of Higher Education and Science Institutions
4. Enabling Higher Education and Science Institutions to operate as drivers of change

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[9] Indicator 3.3.5. of target 3.3 is the number of people requiring interventions against neglected tropical diseases

[10] doc 55 1610/018, beleidsverklaring internationale solidariteit, p.10

[11] Address of Belgian Prime Minister at the launching event of 2030 WHO Road Map for NTDs http://bit.ly/Launch-NTDRoadmap2030. (around 2:26)

[12] The preparation of the FA5 strategy is in progress

5. Co-creation, transfer and application of relevant knowledge
6. Science-society interface strengthened

Stakeholders from the public sector, from the private sector and from the civil society are involved in the HAT+ project. Thanks to the combination of research and support to control, considerable impact is expected. The HAT control strategy has already thoroughly changed over the last decade, whereby the experiences in DRC played a leading role for innovations. The results of the operational research and impact of new strategies will also impact other African countries that are still affected by HAT.

7.2. EFFECTIVENESS

The objectives are very ambitious because very few infectious diseases have been eliminated in the past. The monitoring activities during phase I, indicated that the HAT elimination process is on track, but effectiveness remains a major concern. This explains why the operational research included in phase II, focuses on appropriated strategies. A holistic approach, combining all available tools, should lead to increased effectiveness of HAT control, and increase impact not only of the HAT+ project but also of the HAT elimination process overall. Ultimately, tools will be ncessary to prove that interruption of transmission has been reached.

The continued focus on improved data management is an essential part of the elimination strategy which should enable to make evidence based decisions, to quickly adapt strategies and take into account the local context.

The results obtained in the framework of HAT also have an effect on other diseases. A strengthened presence of ITM in DRC will accelerate the establishment of joint research projects, as well as the strengthening of the partners' capacities. The in-country presence will allow us to exchange more efficiently and flexibly with partners who have profound expertise in emerging diseases (e.g. Ebola) and as a result to act more effectively in a time when rapid action counts more than ever.

7.4. EFFICIENCY

In an elimination context, the concept of “efficiency” is somewhate tricky. Experiences in other diseases have shown that in order to be effective, some overlap of approaches is required to ensure that no cases are missed, that treatment is effective and that affected vectors do not get the chance to infect new individuals. However this reflection should not impede the implementation of a “rationalization process”, already started during the first phase but which could be improved. Rationalization will not only be key at organizational level but also at institutional level because following the rapid decline of HAT prevalence, the context has changed. Therefore ITM will play the role as honest broker between all Congolese organisations and directions of MOH involved.

Efficiency and making better use of available resources was an important incentive to sign the MoU between Belgium and BMGF. During phase II of the HAT+ project, ITM will continue to facilitate complementarity between different projects and initiatives it coordinates. Coordination with other relevant partners and HAT interventions (both support to control and research) will be high on the agenda: ITM will continue to organize HAT partner meetings jointly with PNLTHA and WHO.

7.5. SUSTAINABILITY

Sustainability of results is a major concern for any HAT project, as in the past it was observed several times that HAT cases started to rise, as soon as the support stopped. With the current available tools, the context has considerably changed to provide better chances for sustainability. First of all, as explained above, previously it was near impossible to integrate an effective HAT control program into the primary health care system because of the combination of complex diagnosis and toxic treatments requiring hospital settings. With RDTs and (single dose) oral treatment this is no longer the case. Also, as explained above, a minimum number of small mobile teams at provincial level will remain, but such mobile teams could also be an asset for a province to tackle health problems beyond HAT. The laboratory skills required by mobile teams could be reduced and replaced by a small teams of specialized teams. Finally, with available means, the opportunity is there to decrease prevalence much further than ever before, meaning that the Ro could be below 1, for the entire country.

The second question is whether the financial sustainability can be guaranteed. Considering the enormous health challenges of DRC, it cannot be expected that DRC invests more than it actually does (mainly salaries of staff). Hence HAT should become further integrated in health systems and be part of the entire challenge.

However, some questions remain unanswered, such as the role of cryptic human and animal reservoirs, awaiting for clarification. Another major treat is the uncontrolled situation of HAT in unsafe surrounding countries (e.g. CAR, South Sudan).

7.6. GENDER AND ENVIRONMENT

The HAT+ project takes into account the aspects " genre " and " environment" according to the Theory of Change applied in the framework agreements between ITM and DGD. The actions are supported by a number of values and principles that we share, including respect for the environment and attention to the gender dimension. Gender balance will be taken into account in this project at all levels: staff involved in the project, beneficiaries of services, etc. At no time will discrimination be made on the basis of gender. Positive discrimination in favor of the female gender will be encouraged in the recruitment procedures in case of equal competencies.

The focus of the HAT+ project focusing on HAT integrating in the primary health care system will have an impact on women and children as these tend to use more the fixed health infrastructure than the male. Also the introduction of oral treatments are expected to have an impact, as this will remove some barriers of accessibility to treatment closer to home. On the other hand, there are indications that young adult males are at higher risk for infection, which should be clarified through ongoin research.

8. ANNEXES

8.1. EPIDEMIOLOGICAL OVERVIEW

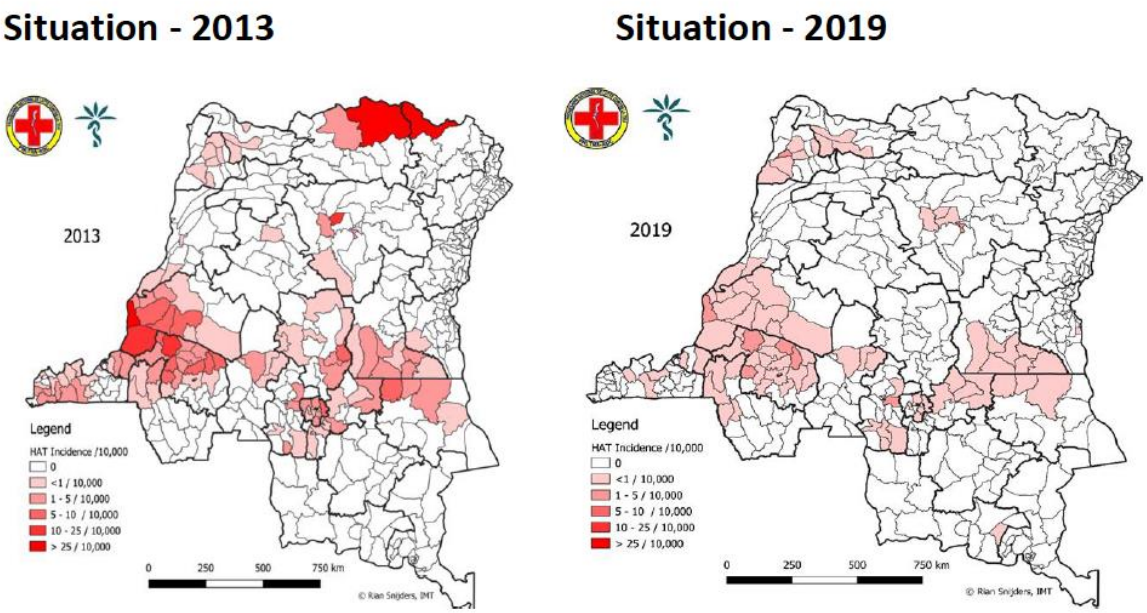

Fig. 6: Comparison of HAT incidence per health district in DRC between 2013 and 2019 (Source PNLTHA)

Table 2: Epidemiological Data per province in 2020* (Source PNLTHA)

	Mobile Team	Mini Team	Total Population Examined	Total Pop Active Screened	New Cases Active Screened	Total New Cases
Bandundu N	7	9	630,473	478,515	28	82
Bandundu S	6	9	614,684	590,769	37	92
Kasaï Oriental	4	0	133,624	127,639	29	43
Kasaï Occidental	3	0	136,914	112,624	37	66
Maniema-Katanga	2	0	62,622	45,952	15	40
Sankuru	1	0	34,195	23,556	5	25
Isangi	1	0	22,852	15,054	9	13
Kinshasa	1	0	18,854	15,826	4	11
Equateur N	3	0	297,793	107,289	8	14
Equateur S	1	0	27,328	21,497	0	3
Kongo Central	1	0	41,398	14,319	0	0
TOTAL	**30**	**18**	**2,020,737**	**1,553,040**	**172**	**389**

* Due to Covi19 activities have been decreased

8.2. Division of Labor

Besides the operational synergies, we will also look for organizational and logistical synergies between all actors involved in gHAT control and research. The indicative division of labor is shown in Table 1. For the different forms of active screening, the BMGF support will focus on the former provinces of Bandundu and Kasai Occidental; the Belgian support will focus on the other provinces (Fig. 7)

Table 1: Division of Labor between the projects in support of gHAT control in DRC

Project Activities	TrypElim Phase II BMGF	HAT+ Phase II Belgium	FA5 Belgium	WHO	Others
Passive Screening	±	+++	±	+	DNDi
Active Screening					
• Traditional (WHO guidelines)	++	-	++	+	
• Reactive screening	++	-	+		
• Screening of blind spots	+	++	+		
• Screening of historic foci	+	++	+		
Vector Control (LSTM)	+++	-	-		
Treatment	+	+	+	+++	DNDi
INRB & Regional laboratories (QA, screening and confirmation)	++	+	++	+	
Data management - Digital tools - Data centre - Mapping	 +++ +	 ++ ++ +	 + - -		
Support to Biobank	+	+	+		

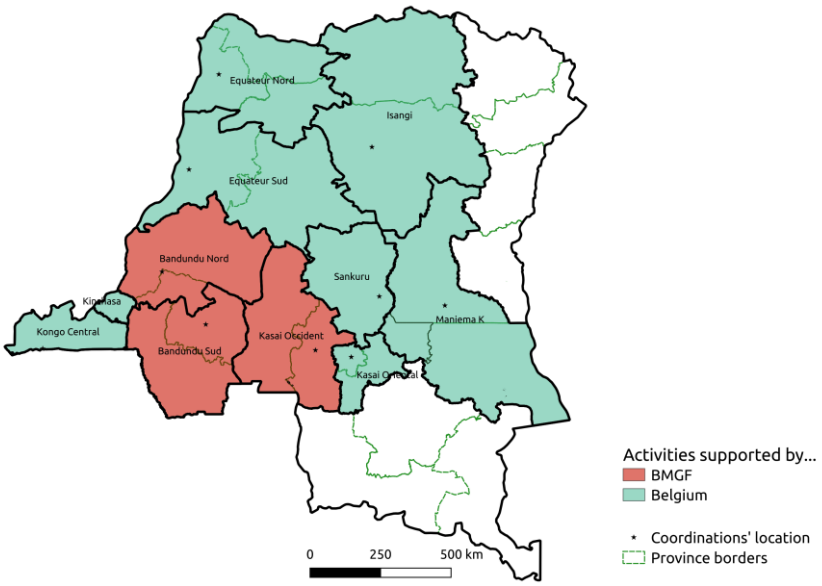

Fig 7: Geographical division of labor for active HAT screening in DRC from 2022 onwards

8.3. DETAILED BUDGET FOR 3 YEARS

Indicative budget per year, to be adapted according to the number of years obligated

	Year 1	Year 2	Year 3	Total
Result 1: The HAT elimination strategy is effectively implemented and reviewed	**300,000.00**	**300,000.00**	**300,000.00**	**900,000.00**
1.1 PNLTHA is strengthened	***100,000.00***	***100,000.00***	***100,000.00***	***300,000.00***
Organization of assessments of the HAT strategy in line with the procedures of DRC	10,000.00	10,000.00	10,000.00	30,000.00
Coordination activities, seminars and workshops	25,000.00	25,000.00	25,000.00	75,000.00
Administratitve, logistic and financial capacity support	10,000.00	10,000.00	10,000.00	30,000.00
Scientific support by ITM	55,000.00	55,000.00	55,000.00	165,000.00
1.2 Well functioning data management system	***130,000.00***	***130,000.00***	***130,000.00***	***390,000.00***
Support the national surveillance center	30,000.00	30,000.00	30,000.00	90,000.00
Follow-up and refresher trainings in data management and analysis skills at PNLTHA	20,000.00	20,000.00	20,000.00	60,000.00
Development of the digital information system (TrypElim App)	80,000.00	80,000.00	80,000.00	240,000.00
1.3 Capacity development	***70,000.00***	***70,000.00***	***70,000.00***	***210,000.00***
Organization of Capacity development activities for all DRC partners involved	40,000.00	40,000.00	40,000.00	120,000.00
Support INRB to provide diagnostic training programs	10,000.00	10,000.00	10,000.00	30,000.00
Implement the quality assurance system of diagnosis	10,000.00	10,000.00	10,000.00	30,000.00
Support INRB and ITM in their role as Collaborating Centres for WHO	10,000.00	10,000.00	10,000.00	30,000.00
Result 2: The elimination strategy is supported by targeted research	**300,000.00**	**300,000.00**	**300,000.00**	**900,000.00**
2.1 Improved diagnostic tools are developed	***100,000.00***	***100,000.00***	***100,000.00***	***300,000.00***
Improve sampling methods to enable testing in reference laboratories	35,000.00	35,000.00	35,000.00	105,000.00
Conduct phase 3 studies in the field	65,000.00	65,000.00	65,000.00	195,000.00
2.2 Appropriated strategies are developed	***170,000.00***	***150,000.00***	***150,000.00***	***470,000.00***
Conduct HAT transmission studies	100,000.00	100,000.00	100,000.00	300,000.00
Conduct impact studies of different strategies	70,000.00	50,000.00	50,000.00	170,000.00

2.3 Epidemiological questions	***30,000.00***	***50,000.00***	***50,000.00***	***130,000.00***
Research on vector control	20,000.00	25,000.00	25,000.00	70,000.00
Conduct social-science studies to improve insight in transmission and impact of strategies	10,000.00	25,000.00	25,000.00	60,000.00
Result 3: HAT integrated in the primary health care system	**1,508,872.67**	**1,500,000.00**	**1,504,436.33**	**4,513,309.00**
3.1. Coverage of all HAT endemic health districts	***1,000,000.00***	***500,000.00***	***500,000.00***	***2,000,000.00***
Application of appropriate strategies in health zones affected by gHAT, adapted to context	450,000.00	250,000.00	250,000.00	950,000.00
Organization of training sessions for for lab technicians and clinicians	400,000.00	100,000.00	100,000.00	600,000.00
Application of Quality Assurance (QA) for fixed health facilities	150,000.00	150,000.00	150,000.00	450,000.00
3.2 Provision of RDTs and confirmation tests is assured	***508,872.67***	***1,000,000.00***	***1,004,436.33***	***2,513,309.00***
Purchase of screening tests	428,872.67	900,000.00	904,436.33	2,233,309.00
Production and purchase of confirmation tests (INRB)	80,000.00	100,000.00	100,000.00	280,000.00
Result 4: The progress of HAT elimination is monitored and evaluated	**300,000.00**	**300,000.00**	**300,000.00**	**900,000.00**
4.1 Monitoring is assured	***200,000.00***	***200,000.00***	***200,000.00***	***600,000.00***
Surveillance of blind spots	100,000.00	100,000.00	100,000.00	300,000.00
Surveillance of historic foci	100,000.00	100,000.00	100,000.00	300,000.00
4.2 Progress is evaluated and results disseminated	***100,000.00***	***100,000.00***	***100,000.00***	***300,000.00***
Continuous M&E follow-up	60,000.00	50,000.00	60,000.00	170,000.00
External evaluation of HAT strategy	0.00	30,000.00	0.00	30,000.00
Disemination of results both in DRC and at international level and serve as input for coordination or scientific invents	40,000.00	20,000.00	40,000.00	100,000.00
TOTAL DIRECT COSTS	**2,408,872.67**	**2,400,000.00**	**2,404,436.33**	**7,213,309.00**
TOTAL INDIRECT COSTS	**396,293.51**	**394,833.83**	**395,563.67**	**1,186,691.00**
GRAND TOTAL	**2,805,166.18**	**2,794,833.83**	**2,800,000.00**	**8,400,000.00**

8.4. REFERENCES

The references below provide an overview of gHAT scientific output (not exhaustive), produced over the last years in the framework of support to gHAT control in DRC, whereby PNLTHA, INRB and ITM were involved. This output has influenced the gHAT control strategy currently proposed by WHO and was used as basis for the strategic orientations of the present project, including the new strategies for active screening.

- Inocencio de Luz R, Phanzu D, Kiabanzawoko O, Miaka E, Verle P, De Weggeleire A, Buscher Ph, Hasker E, & Boelaert Appropriate serlogical screening and surveillance to eliminate Human frican trpanosomiasis in the Democratice Republic of the Congo PLoS Neglected Tropical Diseases 2021; 15, 6, e0009407.
- Geerts M, Van Reet N, Leyten S, Berghmans R, Rock KS, Coetzer T & Büsher Ph. Trypanosoma brucei gambiense – iELISA: a promising New Test for the Post Elimination Monitoring of Human African Trypanosomiasis. Clinical Infectious Diseases, 2020; ciaa1264, https://doi.org/10.1093/cid/ciaa1264.
- Snijders R, Fukinsia A, Claeys Y, Mpanya A, Hasker E, Meheus F, Miaka E & Boelaert M. Cost of a new method of active screening for human African trypanosomiasis in the Democratice Republic of the Congo PLoS Neglected Tropical Diseases 2020; 14, 12, 13 p., e0008832.
- Snijders R, Fukinsia A, Mulanga P, Claeys Y, Mpanya A, Hasker E, Mpanya A, Miaka E, Meheus F, Lutumba P & Boelaert M. Costing of an integrated approach for human African trypanosomiasis case finding in the Democratice Republic of the Congo Transactions of the Royal Society of Tropical Medicine and Hygiene 2020; 14, 12, 13 p., e0008832.
- Snijders R, Fukinsia A, Claeys Y, Hasker E, Mpanya A, Miaka E, et al. Costs and Outcomes of Integrated Human African Trypanosomiasis Surveillance System Using Rapid Diagnostic Tests, DRC. Emerging Infectious Disease journal. 2021; 27(8), https://wwwnc.cdc.gov/eid/article/27/8/20-2399_article.
- Vander Kelen C, Mpanya A, Boelaert M, Miaka E, Chacon DP, Pulford J, et al. Feasibility of community-based control of tsetse: A pilot project using Tiny Targets in the Democratic Republic of Congo. Plos Neglected Tropical Diseases. 2020;14(9). doi: 10.1371/journal.pntd.0008696. PubMed PMID: WOS:000576169300001.
- Tirados I, Hope A, Selby R, Mpembele F, Miaka EM, Boelaert M, et al. Impact of tiny targets on Glossina fuscipes quanzensis, the primary vector of human African trypanosomiasis in the Democratic Republic of the Congo. Plos Neglected Tropical Diseases. 2020;14(10). doi: 10.1371/journal.pntd.0008270. PubMed PMID: WOS:000581741700003.
- Miaka E, Hasker E, Verle P, Torr S & Boelaert M. Trypanosomiasis in the Democratic Republic of Congo. The Lancet Neurology 2019;18(11):988-989.
- Hasker E, Kwete J, Inocencio da Luz R, Mpanya A, Bebronne N, Makabuza J, Claeys Y, Ilunga J, Lejon V, Ngoyi DM, Buscher Ph, Boelaert M & Miaka E. (2018) Innovative digital technologies for quality assurance of diagnosis of human African trypanosomiasis PLoS Neglected Tropical Diseases 2018;12(9): https://doi.org/10.1371/journal.pntd.0006664.
- Van Reet et al. Single nucleotide polymorphisms and copy-number variations in the Trypanosoma brucei repeat (TBR) sequence can be used to enhance amplification and genotyping of Trypanozoon strains, PLOS One in press.