**VIEWPOINTS** 

# Human African trypanosomiasis control: Achievements and challenges

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#### **Abstract**

Sleeping sickness, also known as human African trypanosomiasis (HAT), is a neglected disease that impacts 70 million people living in 1.55 million km² in sub-Saharan Africa. Since the beginning of the 20th century, there have been multiple HAT epidemics in sub-Saharan Africa, with the most recent epidemic in the 1990s resulting in about half a million HAT cases reported between 1990 and 2015. Here we review the status of HAT disease at the current time and the toolbox available for its control. We also highlight future opportunities under development towards novel or improved interventions.



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Human African trypanosomiasis (HAT) is a neglected disease that impacts 70 million people living in 1.55 million km² of sub-Saharan Africa [1]. Since the beginning of the 20th century, there have been three major HAT epidemics, the most recent in the 1990s resulting in about 500,000 HAT cases reported between 1990 and present [2,3]. The disease is caused by two distinct subspecies of the African trypanosomes transmitted by tsetse flies (*Glossina* spp.: Diptera). In east and southern Africa, *Trypanosoma brucei rhodesiense* causes the acute Rhodesiense form of the disease, while in central and west Africa. *T. b. gambiense* causes the chronic Gambiense form of the disease (about 95% of all reported HAT cases). The disease normally affects remote rural communities where people get exposed to the bite of the tsetse during their daily outdoor activities. Unless treated, HAT disease is normally fatal. Besides HAT, related parasites, such as *T. b. brucei*, *T. congolense*, *T. vivax*, *T. evansi*, and *T. equiperdum*, cause wasting diseases in livestock, termed animal African trypanosomiasis (AAT), which result in major economic losses in the concerned countries [4].

An ambitious campaign led by WHO, many nongovernmental organizations (NGOs), and a public–private partnership with Sanofi-Aventis and Bayer that donated the necessary drugs for distribution in affected countries reduced the global incidence of Gambiense HAT to <3,000 cases in 2015. Based on the success of the control campaign, there are now plans to eliminate Gambiense HAT as a public health problem by 2020 [5]. Gambiense HAT is generally considered to be an anthroponosis, and hence control has relied heavily on active and/or passive case detection and treatment programs [6]. Control of Rhodesiense HAT has been

more complex, as disease transmission involves domestic animals, which serve as reservoirs for parasite transmission by the tsetse vector. Hence, for Rhodesiense HAT, control of the parasite in the domestic reservoirs, and/or reduction of tsetse vector populations, plays a key part, with medical interventions being used only for humanitarian purposes.

Despite extensive research into the biology of the trypanosome, the toolbox for diagnostics and treatment of sleeping sickness had remained extremely small and plagued with difficulties [7]. However, the recent epidemic has mobilized financial resources available for basic and applied research, which has led to new knowledge on both parasite and tsetse vector physiology, genetics, and genomics and expanded the prospects for translational science for sustainable HAT control. Below, we review some of the progress made in the last decade towards growing the toolbox for HAT elimination.

## Controlling disease in the mammalian host

Achieving disease control in the mammalian host has been difficult given the lack of mammalian vaccines due to a process of antigenic variation the parasite displays in its mammalian host. Hence, accurate diagnosis of the parasite and staging of the disease are important, particularly because of the toxicity of current drugs. Although powerful molecular diagnostics have been developed in research settings, few have yet reached the patient or national control programs [8]. For Gambiense HAT, a sensitive and specific test is available for active serological screening by mobile teams [9]. However, when prevalence becomes low, targeted door-todoor surveys may become an attractive alternative to mass screening [10]. It wil also become crucial to integrate passive case detection in fixed health centers [5]. The development of individual rapid sero-diagnostic tests (RDTs) will certainly facilitate the involvement of fixed health centers in passive case detection, yet their diagnostic accuracy remains uncertain [11]. Screening for *T. b. rhodesiense* infection still relies on clinical features in the absence of serological tests available for field use. Although recent improvements have been made to parasitological confirmatory tests, their sensitivity remains insufficient in Gambiense HAT [12]. Regarding treatment, the introduction of the effornithine-nifurtimox combination therapy (NECT) has made treatment of Gambiense HAT safer and more efficacious [13].

## Reducing vector populations

While vector control is essential for Rhodesiense HAT, it has not played a major role in Gambiense HAT, as it was considered too expensive and difficult to deploy in the resource-poor settings of HAT foci. However, modelling, historical investigations, and practical interventions demonstrate the significant role that vector control can play in the control of Gambiense HAT [14, 6, 15], especially given the possibility of long-term carriage of trypanosomes in both human and animal reservoirs [16,17]. Recent models suggest vector control will be essential if we are to reach the set target of elimination of the disease as a public health problem by 2020 [18]. Vector control can be particularly effective at times of low endemicity during which active surveillance campaigns may be too costly to operate, and it is, so far, the only prophylactic measure existing to protect people against the infectious bite of the tsetse vector. In addition, the use of commercially-available loop-mediated isothermal amplification (LAMP) kits as a highly sensitive tool for xenomonitoring has also been suggested to identify potential sleeping sickness transmission sites, especially during periods of low endemicity [19].

For vector reduction efforts, the use of Sterile Insect Technique continent-wide has been suggested by the African Union, following the success of the eradication program in Zanzibar [20]. However, the feasibility of the application of this method continent-wide has come into question given the diversity of species that can transmit the parasite, its high cost, and

dependence on major infrastructure such as large insectaries, irradiation facilities, and airplanes [21]. It has been possible to modify the existing insecticide-treated targets to produce a more cost-efficient and sustainable vector control method for use in HAT foci. Tiny targets consisting of a small square of blue cloth flanked by a similar-sized piece of black netting have been shown to be efficacious and more cost-effective than traps or large targets typically used in control campaigns for the Gambiense vector species [14, 22]. To monitor the efficacy and sustained impact of tsetse control interventions, sensitive serological tools are being developed using tsetse-saliva-based biomarkers [11, 23]. A major advancement that has fueled research into the fundamental aspects of tsetse and trypanosome transmission biology has been the completion of the genome sequence of G. morsitans morsitans [24] and five additional vector species [41]. This information has been mined to understand the olfactory [25, 26], symbiotic [27], and reproductive [28] physiologies of tsetse, with the goal of identifying targets suitable for population reduction efforts. Knowledge on olfactory physiology can be harnessed to enhance the efficacy of traps and targets by identifying novel attractants, while the obligate dependence of tsetse on their endosymbionts provides a weak link in this vector's ability to reproduce, both providing ideal targets for new vector control methods.

In addition, there has been growing knowledge on the population genetics of tsetse vectors in disease-endemic areas in Africa. This new information can help identify natural barriers to fly dispersal and routes and hence can provide important information for field control programs that aim to reduce vector densities through traditional tools, such as traps/targets, Sterile Insect Technique, or aerial sprays [29, 30].

One fundamental reason vector control methods are highly effective in tsetse is the already low reproductive capacity this insect has due to its viviparous reproductive physiology. The molecular and biochemical aspects of tsetse's viviparity and its dependence on the obligate symbiont *Wigglesworthia*-provided products are being unraveled. This fundamental knowledge provides many new targets for interference with tsetse fecundity to reduce tsetse populations [28].

## Controlling the parasite in the tsetse vector

The increased knowledge of tsetse and trypanosome genomics has also expanded knowledge on the molecular aspects of host-parasite interactions with several practical implications. It has been shown that an important bottleneck for parasite transmission occurs early in the infection process in the tsetse's midgut, characterized by a tug-of-war between trypanosome immune modulatory activities and the tsetse's antiparasitic immune responses [31, 32]. The molecular details of the complex host-parasite interactions that eventually enable the trypanosomes to colonize the flies [33, 34], followed by modulation of the fly saliva immunomodulatory components by parasites, and the impact of this modification on trypanosome transmission dynamics in the host bite site favoring parasite transmission are all being unraveled and provide novel points of interference for the parasite's transmission [35, 23]. One approach whereby the parasite infection can be eliminated from tsetse populations involves the ability to engineer refractoriness in tsetse [36, 37]. Towards that end, one commensal symbiont of tsetse present in the midgut, Sodalis, has been identified, and a genetic modification system has been developed [38]. Candidate antitrypanosomal molecules have also been identified and expressed in Sodalis to reduce trypanosome infections as a novel approach [39, 40]. Many of these early-stage fundamental discoveries have been achieved as a consequence of the applications of-omics technologies to the field of tsetse and trypanosomes and have opened up the feasibility of novel targets for new innovative approaches.

# **Highlights**

- 1. The Gambiense HAT epidemics that ravaged sub-Saharan Africa in the 1990s have been controlled, leading the way to an elimination phase. The elimination of Rhodesiense HAT poses challenges because of the vast animal reservoirs.
- Simplification, standardization, and proper test evaluation of diagnostic tools in the target setting should be an important focus for future development to maintain low endemicity and to monitor disease prevalence in the post elimination phase.
- 3. A safe and oral drug that cures both disease stages and both disease forms is needed.
- 4. Control strategies will progressively shift from active case detection by mobile teams towards passive case detection by fixed health centers.
- 5. The capacity built towards HAT diagnosis and treatment should be preserved at times of low endemicity and post elimination.
- 6. Application of vector control alongside medical interventions will be needed to achieve the targets within the set time frame.
- 7. The molecular targets discovered through parasite and tsetse genomics/genetics studies form the pipeline for new drugs, potential antitsetse-based vaccines, and fly inhibitory compounds, which should be explored as novel biological control methods.
- 8. The time has come for donors, private companies, and all stakeholders to commit to the elimination of HAT, in order to avoid resurgence as seen in the past.

#### References

- Simarro P.P., Cecchi G., Franco J.R., Paone M., Diarra A., Ruiz-Postigo J.A., Fevre E.M., Mattioli R.C., and Jannin J.G. (2012). Estimating and mapping the population at risk of sleeping sickness. PLoS Negl Trop Dis 6, e1859. https://doi.org/10.1371/journal.pntd.0001859 PMID: 23145192
- Barrett M.P. (1999). The fall and rise of sleeping sickness. Lancet 353, 1113–1114. https://doi.org/10. 1016/S0140-6736(98)00416-4 PMID: 10209970
- Headrick D.R. (2014). Sleeping sickness epidemics and colonial responses in East and Central Africa, 1900–1940. PLoS Negl Trop Dis 8, e2772. https://doi.org/10.1371/journal.pntd.0002772 PMID: 24763309
- Alsan M. (2015). The Effect of the TseTse Fly on African Development. American Economic Review 382–410.
- Franco J.R., Simarro P.P., Diarra A., Ruiz-Postigo J.A., and Jannin J.G. (2014). The journey towards elimination of gambiense human African trypanosomiasis: not far, nor easy. Parasitology 141, 748– 760. https://doi.org/10.1017/S0031182013002102 PMID: 24709291
- Lehane M., Alfaroukh I., Bucheton B., Camara M., Harris A., Kaba D., Lumbala C., Peka M., Rayaisse J.B., Waiswa C., et al. (2016). Tsetse Control and the Elimination of Gambian Sleeping Sickness. PLoS Negl Trop Dis 10, e0004437. https://doi.org/10.1371/journal.pntd.0004437 PMID: 27128795
- Molyneux D., Ndung'u J., and Maudlin I. (2010). Controlling Sleeping Sickness—"When Will They Ever Learn?". PLoS Negl Trop Dis 4(5), e609. https://doi.org/10.1371/journal.pntd.0000609 PMID: 20520799
- Buscher P., and Deborggraeve S. (2015). How can molecular diagnostics contribute to the elimination of human African trypanosomiasis? Expert review of molecular diagnostics 15, 607–615. <a href="https://doi.org/10.1586/14737159.2015.1027195">https://doi.org/10.1586/14737159.2015.1027195</a> PMID: 25786994
- Magnus E., Vervoort T., and Van Meirvenne N. (1978). A card-agglutination test with stained trypanosomes (C.A.T.T.) for the serological diagnosis of T. B. gambiense trypanosomiasis. Annales de la Societe belge de medecine tropicale 58, 169–176. PMID: 747425
- Koffi M., N'Djetchi M., Ilboudo H., Kaba D., Coulibaly B., N'Gouan E., Kouakou L., Bucheton B., Solano P., Courtin F., et al. (2016). A targeted door-to-door strategy for sleeping sickness detection in low-

- prevalence settings in Cote d'Ivoire. Parasite 23, 51. <a href="https://doi.org/10.1051/parasite/2016059">https://doi.org/10.1051/parasite/2016059</a> PMID: 27849517
- Jamonneau V., Camara O., Ilboudo H., Peylhard M., Koffi M., Sakande H., N'Dri L., Sanou D., Dama E., Camara M., et al. (2015). Accuracy of individual rapid tests for serodiagnosis of gambiense sleeping sickness in West Africa. PLoS Negl Trop Dis 9, e0003480. https://doi.org/10.1371/journal.pntd. 0003480 PMID: 25642701
- 12. Mumba Ngoyi D., Ali Ekangu R., Mumvemba Kodi M.F., Pyana P.P., Balharbi F., Decq M., Kande Betu V., Van der Veken W., Sese C., Menten J., et al. (2014). Performance of parasitological and molecular techniques for the diagnosis and surveillance of gambiense sleeping sickness. PLoS Negl Trop Dis 8, e2954. https://doi.org/10.1371/journal.pntd.0002954 PMID: 24921941
- Priotto G., Kasparian S., Mutombo W., Ngouama D., Ghorashian S., Arnold U., Ghabri S., Baudin E., Buard V., Kazadi-Kyanza S., et al. (2009). Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. Lancet 374, 56–64. https://doi.org/10.1016/S0140-6736(09)61117-X PMID: 19559476
- Courtin F., Camara M., Rayaisse J.B., Kagbadouno M., Dama E., Camara O., Traore I.S., Rouamba J., Peylhard M., Somda M.B., et al. (2015). Reducing Human-Tsetse Contact Significantly Enhances the Efficacy of Sleeping Sickness Active Screening Campaigns: A Promising Result in the Context of Elimination. PLoS Negl Trop Dis 9, e0003727. https://doi.org/10.1371/journal.pntd.0003727 PMID: 26267667
- Solano P., Torr S.J., and Lehane M.J. (2013). Is vector control needed to eliminate gambiense human African trypanosomiasis? Front Cell Infect Microbiol 3, 33. https://doi.org/10.3389/fcimb.2013.00033 PMID: 23914350
- Ilboudo H., Jamonneau V., Camara M., Camara O., Dama E., Leno M., Ouendeno F., Courtin F., Sakande H., Sanon R., et al. (2011). Diversity of response to *Trypanosoma brucei gambiense* infections in the Forecariah mangrove focus (Guinea): perspectives for a better control of sleeping sickness. Microbes Infect 13, 943–952. https://doi.org/10.1016/j.micinf.2011.05.007 PMID: 21658462
- Molyneux D.H. (1973). Animal reservoirs and Gambian trypanosomiasis. Annales de la Societe belge de medecine tropicale 53, 605–618. PMID: 4204667
- Rock K.S., Torr S.J., Lumbala C., and Keeling M.J. (2015). Quantitative evaluation of the strategy to eliminate human African trypanosomiasis in the Democratic Republic of Congo. Parasit Vectors 8, 532. https://doi.org/10.1186/s13071-015-1131-8 PMID: 26490248
- Cunningham L.J., Lingley J.K., Haines L.R., Ndung'u J.M., Torr S.J., and Adams E.R. (2016). Illuminating the Prevalence of *Trypanosoma brucei s.l.* in *Glossina* Using LAMP as a Tool for Xenomonitoring. PLoS Negl Trop Dis 10, e0004441. https://doi.org/10.1371/journal.pntd.0004441 PMID: 26890882
- Kabayo J.P. (2002). Aiming to eliminate tsetse from Africa. Trends Parasitol 18, 473–475. PMID: 12473355
- 21. Rogers D.J., and Randolph S.E. (2002). A response to the aim of eradicating tsetse from Africa. Trends Parasitol 18, 534–536. PMID: 12482537
- Shaw A.P., Tirados I., Mangwiro C.T., Esterhuizen J., Lehane M.J., Torr S.J., and Kovacic V. (2015). Costs of using "tiny targets" to control *Glossina fuscipes fuscipes*, a vector of gambiense sleeping sickness in Arua District of Uganda. PLoS Negl Trop Dis 9, e0003624. https://doi.org/10.1371/journal.pntd. 0003624 PMID: 25811956
- Van Den Abbeele J., Caljon G., De Ridder K., De Baetselier P., and Coosemans M. (2010). Trypanosoma brucei modifies the tsetse salivary composition, altering the fly feeding behavior that favors parasite transmission. PLoS Pathog 6, e1000926. https://doi.org/10.1371/journal.ppat.1000926 PMID: 20532213
- Aksoy S., Attardo G., Berriman M., Christoffels A., Lehane M., Masiga D., and Toure Y. (2014a).
  Human African trypanosomiasis research gets a boost: unraveling the tsetse genome. PLoS Negl Trop Dis 8, e2624.
- 25. Macharia R., Mireji P., Murungi E., Murilla G., Christoffels A., Aksoy S., and Masiga D. (2016). Genome-Wide Comparative Analysis of Chemosensory Gene Families in Five Tsetse Fly Species. PLoS Negl Trop Dis 10, e0004421. https://doi.org/10.1371/journal.pntd.0004421 PMID: 26886411
- Obiero G.F., Mireji P.O., Nyanjom S.R., Christoffels A., Robertson H.M., and Masiga D.K. (2014). Odorant and Gustatory Receptors in the Tsetse Fly Glossina morsitans morsitans. PLoS Negl Trop Dis 8, e2663. https://doi.org/10.1371/journal.pntd.0002663 PMID: 24763191
- Michalkova V., Benoit J.B., Weiss B.L., Attardo G.M., and Aksoy S. (2014). Vitamin B6 generated by obligate symbionts is critical for maintaining proline homeostasis and fecundity in tsetse flies. Appl Environ Microbiol 80, 5844–5853. https://doi.org/10.1128/AEM.01150-14 PMID: 25038091

- Benoit J.B., Attardo G.M., Baumann A.A., Michalkova V., and Aksoy S. (2015). Adenotrophic Viviparity in Tsetse Flies: Potential for Population Control and as an Insect Model for Lactation. Annu Rev Entomol. Vol. 60:351–371
- Aksoy S., Caccone A., Galvani A.P., and Okedi L.M. (2013). Glossina fuscipes populations provide insights for human African trypanosomiasis transmission in Uganda. Trends Parasitol 29, 394–406. https://doi.org/10.1016/j.pt.2013.06.005 PMID: 23845311
- Solano P., Ravel S., and de Meeus T. (2010). How can tsetse population genetics contribute to African trypanosomiasis control? Trends Parasitol 26, 255–263. https://doi.org/10.1016/j.pt.2010.02.006 PMID: 20202905
- Aksoy S., Gibson W.C., and Lehane M.J. (2003). Interactions between tsetse and trypanosomes with implications for the control of trypanosomiasis. Adv Parasitol 53, 1–83. PMID: 14587696
- Dyer N.A., Rose C., Ejeh N.O., and Acosta-Serrano A. (2013). Flying tryps: survival and maturation of trypanosomes in tsetse flies. Trends Parasitol 29, 188–196. <a href="https://doi.org/10.1016/j.pt.2013.02.003">https://doi.org/10.1016/j.pt.2013.02.003</a>
   PMID: 23507033
- Aksoy E., Vigneron A., Bing X., Zhao X., O'Neill M., Wu Y.N., Bangs J.D., Weiss B.L., and Aksoy S. (2016). Mammalian African trypanosome VSG coat enhances tsetse's vector competence. Proc Natl Acad Sci U S A 113, 6961–6966. https://doi.org/10.1073/pnas.1600304113 PMID: 27185908
- 34. Mantilla B.S., Marchese L., Casas-Sanchez A., Dyer N.A., Ejeh N., Biran M., Bringaud F., Lehane M.J., Acosta-Serrano A., and Silber A.M. (2017). Proline Metabolism is Essential for *Trypanosoma brucei brucei* Survival in the Tsetse Vector. PLoS Pathog 13, e1006158. <a href="https://doi.org/10.1371/journal.ppat.1006158">https://doi.org/10.1371/journal.ppat.1006158</a> PMID: 28114403
- Caljon G., Van Den Abbeele J., Sternberg J.M., Coosemans M., De Baetselier P., and Magez S. (2006). Tsetse fly saliva biases the immune response to Th2 and induces anti-vector antibodies that are a useful tool for exposure assessment. Int J Parasitol 36, 1025–1035. https://doi.org/10.1016/j.ijpara. 2006.05.002 PMID: 16777113
- Aksoy S., Weiss B.L., and Attardo G.M. (2014b). Trypanosome Transmission Dynamics in Tsetse. Curr Opin Insect Sci 3, 43–49.
- Weiss B., and Aksoy S. (2011). Microbiome influences on insect host vector competence. Trends Parasitol 27, 514–522. https://doi.org/10.1016/j.pt.2011.05.001 PMID: 21697014
- Aksoy S., Weiss B., and Attardo G. (2008). Paratransgenesis applied for control of tsetse transmitted sleeping sickness. Adv Exp Med Biol 627, 35–48. <a href="https://doi.org/10.1007/978-0-387-78225-6\_3">https://doi.org/10.1007/978-0-387-78225-6\_3</a> PMID: 18510012
- **39.** De Vooght L., Caljon G., De Ridder K., and Van Den Abbeele J. (2014). Delivery of a functional anti-try-panosome Nanobody in different tsetse fly tissues via a bacterial symbiont, *Sodalis glossinidius*. Microb Cell Fact 13, 156. https://doi.org/10.1186/s12934-014-0156-6 PMID: 25376234
- De Vooght L., Caljon G., Stijlemans B., De Baetselier P., Coosemans M., and Van den Abbeele J. (2012). Expression and extracellular release of a functional anti-trypanosome Nanobody(R) in *Sodalis glossinidius*, a bacterial symbiont of the tsetse fly. Microb Cell Fact 11, 23. <a href="https://doi.org/10.1186/1475-2859-11-23">https://doi.org/10.1186/1475-2859-11-23</a> PMID: 22335892
- International Glossina Genome Initiative, (2014). Genome sequence of the tsetse fly (Glossina morsitans): vector of African trypanosomiasis. Science 344, 380–386. https://doi.org/10.1126/science. 1249656 PMID: 24763584