REVIEW

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Gambiense human African trypanosomiasis: the bumpy road to elimination

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Purpose of review
Gambiense human African trypanosomiasis (gHAT), a disease that has killed hundreds of thousands as recently as the 1990s, could be on the verge of elimination or even eradication. This review describes recent developments that give us reasons for optimism as well as some caveats.

Recent findings
New developments in diagnostic and vector control tools, and especially in treatment, make it possible to strive for elimination of transmission of gHAT by 2030, perhaps even eradication.

Summary
Gambiense human African trypanosomiasis is a deadly infectious disease affecting West and Central Africa, South Sudan and Uganda, and transmitted between humans by tsetse flies. The disease has caused several major epidemics, the latest one in the 1990s. Thanks to recent innovations such as rapid diagnostic tests for population screening, a single-dose oral treatment and a highly efficient vector control strategy, interruption of transmission of the causative parasite is now within reach. If indeed gHAT has an exclusively human reservoir, this could even result in eradication of the disease. Even if there were an animal reservoir, on the basis of epidemiological data, it plays a limited role. Maintaining adequate postelimination surveillance in known historic foci, using the newly developed tools, should be sufficient to prevent any future resurgence.

Keywords
African trypanosomiasis, elimination of transmission, epidemiology, treatment, vector control

INTRODUCTION

Human African trypanosomiasis (HAT) is a parasitic disease affecting rural areas of sub-Saharan Africa. There are two forms of the disease, the West-African form caused by the protozoan *Trypanosoma brucei gambiense* (Gambiense human African trypanosomiasis) and the East-African form caused by *T. brucei rhodesiense* (rhodesiense HAT or rHAT), both being transmitted by tsetse flies (*Glossina*) [1–3]. Whereas rHAT, is in principle, a zoonosis in which humans are accidental hosts, gHAT is an anthroponosis with transmission occurring in a human–fly–human cycle, exclusively in sub-Saharan Africa. Of the two forms, gHAT is by far the most common, accounting for over 95% of all cases reported since 2010 and is the focus of this review [4]. The fact that gHAT is an anthroponosis, dependent on a vector, makes it theoretically feasible to strive for elimination. WHO has set a target of interruption of transmission of *T. brucei gambiense* by 2030 [5].

THE HISTORY OF GAMBIENSE HUMAN AFRICAN TRYPANOSOMIASIS IN SUB-SAHARAN AFRICA

Since the 19th century, gHAT is known to have caused several devastating epidemics. It is estimated that at the turn of the 20th century, 300 000–500 000 people died of gHAT, with another epidemic occurring in the 1920s–1930s [6]. By 1960,

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KEY POINTS

- Gambiense human African trypanosomiasis may be on the verge of elimination or even eradication.
- New developments in diagnostics, vector control methods, and treatment in particular, allow for new approaches.
- Mass treatment of serological suspects is an option once safety of the new single-dose oral drug, acoziborole, has been confirmed.
- Existence of cryptic human or animal reservoirs cannot be fully excluded at present but they appear to play a limited role.

intensive efforts had brought the disease under control in most endemic countries but when measures were neglected, it reemerged. The most recent flare-up in the 1990s in all probability again killed hundreds of thousands [7]. Figure 1 shows case notification numbers in the Democratic Republic of the Congo (DRC) since 1926 based on data from the national HAT control program (PNLTHA) and overall figures for gHAT case notification across Sub-Saharan Africa since 1990 as reported to WHO. Also shown are the numbers screened each year in DRC since 1990.

Continent-wide trends are clearly driven by the DRC caseload. At the height of the most recent outbreak, in 1998, DRC reported 26 318 cases but only 12% of the population at risk was covered by active screening [8]. Given the weak health systems in the areas affected, WHO estimates that the true incidence may have been up to 10 times higher [9].

CLINICAL ASPECTS

The clinical course of HAT is classically divided into two stages, the hemolymphatic stage (first or early stage), corresponding to the dissemination of the trypanosomes in the blood and reticuloendothelial system, followed by the meningoencephalitic stage (second or late stage), when the causative parasite has crossed the blood–brain barrier. Second stage can only be diagnosed by lumbar puncture and examination of cerebrospinal fluid (CSF) [10]. The two forms of HAT have very different clinical presentations. rHAT mainly presents as an acute systemic febrile illness sometimes complicated by multiple organ failure and is mostly diagnosed during the first stage [10]. In contrast, gHAT more often presents as a chronic neurological disease. Neurological manifestations include disturbances of sleep pattern (daytime sleeping and/or insomnia), motor weakness, sensorimotor deficit, and behavior change [11]. In the absence of appropriate treatment, all HAT infections are assumed to eventually be fatal [1].

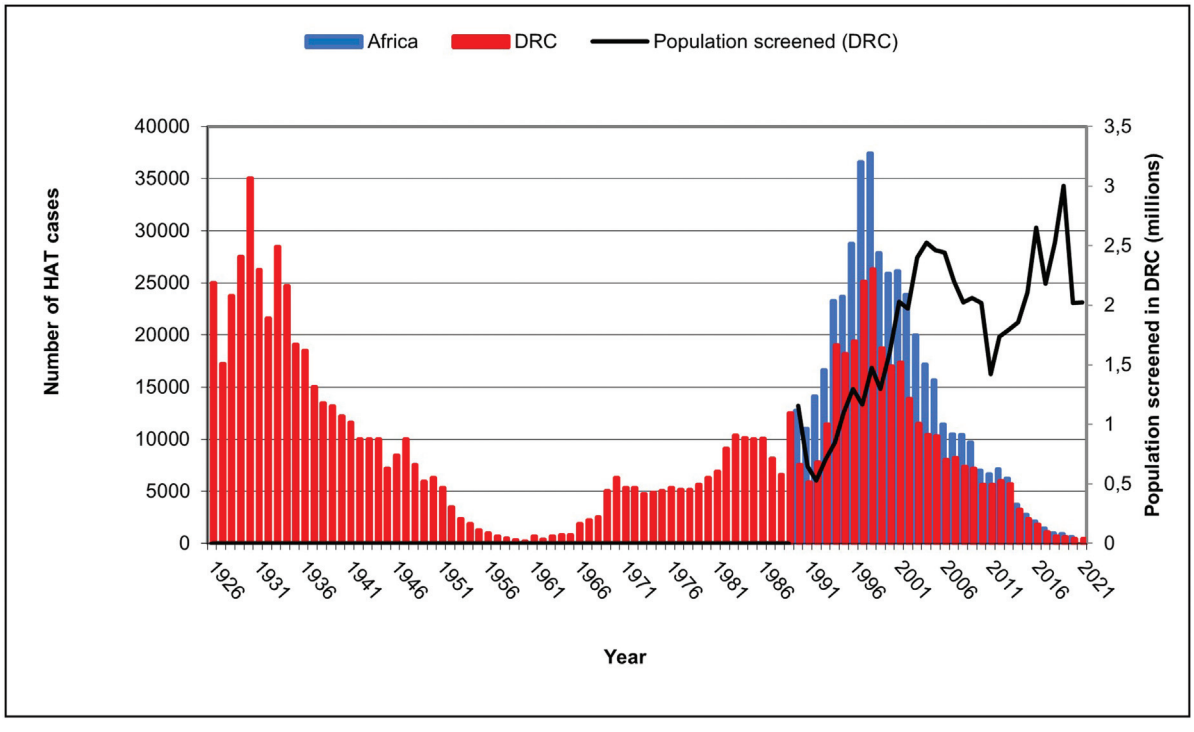

FIGURE 1. Gambiense human African trypanosomiasis case notification in the Democratic Republic of Congo (DRC) (1926–2021) and all of sub-Saharan Africa (1990–2020), as well as population screened in DRC (1990–2021).

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DIAGNOSIS AND TREATMENT

Although the treatment of first-stage gHAT has for a long time relied on fairly well tolerated 7-day intramuscular administration of pentamidine, therapy for second-stage gHAT was until recently limited to a very toxic drug, melarsoprol, an arsenical derivative combined with an antidote to world war I era battle gases [12,13]. An estimated 3–6% of patients treated with melarsoprol died from an encephalopathic syndrome, during or shortly after treatment, and many patients developed other toxicities [14]. To avoid overtreatment, complex diagnostic procedures were introduced. These include screening of HAT suspects with an antibody-detecting serological test, followed by the cumbersome search for parasites in those found seropositive, by microscopic examination of blood or lymph node aspirate. Whenever parasites are found in blood or lymph, CSF must be examined to determine the disease stage. (Supplementary Materials: Video 1, http://links.lww.com/COID/A38, Trypanosomes in blood, Video 2, http://links.lww.com/COID/A39, Trypanosomes in CSF).

Since 2010, eflornithine was introduced as an alternative drug, and it was effective and much less toxic [15]. However, its complex mode of administration, requiring intravenous infusions every 6 h for 2 weeks, was problematic in HAT-endemic areas. Two new treatments have since emerged that made a real difference for first-line health practitioners. First the nifurtimox–eflornithine combination therapy (NECT) reduced the need for intravenous infusions to twice daily for 1 week [16–19]. More recently, fexinidazole, an all-oral 10-day treatment, has been positively evaluated in clinical trials [20▪,21]. Fexinidazole is active against both stages of the disease, thus obviating the need for lumbar puncture and is now the first choice treatment for gHAT [22]. Only for cases with clinical symptoms suggestive of severe meningoencephalitic stage (>100 white blood cells/μl in CSF), is NECT still recommended.

STRATEGIES FOR CONTROL OF GAMBIENSE HUMAN AFRICAN TRYPANOSOMIASIS

The backbone of gHAT control has always been active case-finding, followed by treatment [23]. This is likely to remain the case for the foreseeable future. In the strategy defined by WHO, villages from which gHAT cases have been reported are to be screened annually until no further cases are found for 3 years in a row [24]. They are to be screened once more 5 years after the last case was reported and if no new cases are found, surveillance is shifted to passive mode. Finding a new case means the village returns to the list of villages to be screened annually.

Passive case-finding relies on symptomatic patients presenting at fixed health facilities for diagnosis and treatment of HAT. Simarro *et al.* [25] in 2014 identified 632 fixed health facilities that had been providing such services across all endemic countries from 2000 till 2012. At the time of writing, 41, 71 and 83%, respectively of the population at-risk for gHAT were assumed to be living within 1, 3 and 5 h travel of a facility that can provide diagnosis. Unfortunately, such facilities in gHAT-endemic areas are typically poorly equipped and poorly attended [26,27]. As was explained earlier, current diagnostic procedures are complex. They require visualization of *T. brucei gambiense* through microscopy, preferably making use of concentration methods that enhance sensitivity [28]. Apart from the fact that such methods require electricity and equipment, such as a centrifuge and a microscope, they also require skills that are hard to maintain whenever lab technicians only rarely come across actual gHAT cases.

Vector control for gHAT has historically been considered too expensive and logistically challenging [29]. The breakthrough came when researchers discovered the effectiveness of using small ($\sim$0.13m^2) targets for gHAT vectors [30]. This discovery led to the development of Tiny Targets [31,32]. Tiny Targets are small, 25 cm × 50 cm, used in Central Africa and the Nile catchment of East Africa where *Glossina fuscipes* are the predominant vectors, or 75 cm × 50 cm, used in West Africa where *Glossina palpalis* predominate, insecticide-treated visual baits constituting a blue panel, which attracts the flies. The blue panel is flanked by a black mesh, which is invisible to tsetse; tsetse collide with the mesh and take up a lethal dose of insecticide. This novel technology was found to be more cost-effective than previous control operations for gHAT vectors, and it is now widely used in Uganda, Chad, Côte d'Ivoire, Guinea, and DRC [33–35]. (supplementary material picture 1,Tiny Target DRC, picture 2, Tiny Target Uganda). Entomological surveys demonstrate that Tiny Targets can achieve reductions to more than 80% in tsetse densities [36–39]. Analyses have shown that Tiny Target operations can significantly reduce the incidence of gHAT, thus demonstrating the value of adding vector control to screening and treatment efforts [37,38,40▪].

ENABLING FACTORS AND INNOVATIONS

Currently there are several factors that make it possible to consider interruption of gHAT transmission, despite all the obstacles mentioned. Even at times of

high prevalence, gHAT has always been known for its very focal distribution. Approximately 300 gHAT foci have been described, distributed across 24 countries in sub-Saharan Africa [41]. This opens up perspectives for permanent disease elimination as interrupting transmission from these foci and keeping them under postelimination surveillance is at least theoretically feasible. In 2012, WHO formulated a strategy for elimination of gHAT as a public health problem, defined as the detection of less than 1 new case per 10 000 population in at least 90% of these endemic foci and fewer than 2000 cases reported annually by 2020 [41]. These targets have by and large been achieved [42]. The new target set for 2030 is interruption of transmission of *T. brucei gambiense* [5].

We are now at an all-time low with less than 1000 cases reported across the African continent in 2019, before the start of the COVID-19 pandemic. Importantly, the current low is a different low from that of 1960. As shown in Fig. 1, screening coverage for HAT in DRC has consistently been very high for the past 20 years; even during the pandemic years, approximately two million people were screened each year. Despite such intensive screening, numbers of cases detected have continued to drop. Moreover, recent innovations in diagnostics and treatment now make it possible to consider alternative strategies that could lead to interruption of transmission.

In the field of diagnostics, there have been some important innovations. Since the mid-1990s, the card agglutination test for trypanosomiasis (CATT), an antibody detection test requiring a cold chain and a battery operated rotator, has been used extensively as serological screening tool [43]. More recently, two rapid diagnostic tests (RDTs) based on native antigen (HAT Sero-K-SeT and SD Bioline HAT) have been developed and validated [44,45]. These RDTs are thermostable and do not require any equipment or source of electricity. A phase 2 study on stored plasma samples comparing two RDTs showed a sensitivity of 99.6% for SD Bioline HAT and 99.1% for HAT Sero-K-Set [46]. A case–control study that prospectively enrolled 134 gHAT cases showed a sensitivity of 98.5% for HAT Sero-K-SeT [44]. However, in two recent phase 3 studies, sensitivity estimates were much lower: 69.1% for CATT versus 92.0% for SD Bioline HAT and 62.5% for CATT versus 59.0% for SD Bioline HAT [45,47]. RDTs based on recombinant antigens have now also been developed, a prototype of one has already been evaluated under field conditions [47]. Importantly, these are all screening tests. Out of 1 621 170 people actively screened in DRC in 2021, 9794 (0.6%) tested positive to either RDT or CATT, among them 303 were confirmed gHAT cases (Data PNLTHA of DRC). Thus, despite excellent specificity, their positive-predictive value in population screening was only in the order of 3%.

Until recently in DRC, there were so many villages to be screened that the available screening capacity was largely surpassed. With only 421 cases reported in 2021 (active and passive case detection combined), this is no longer the case. At this stage, quality rather than quantity becomes of crucial importance. Diagnostic confirmation tests are not only highly specific but also complex, and errors do occur [48] Quality-assured diagnosis remains of crucial importance [49]. With the drugs currently available, overtreatment is less of an issue, but it is important not to waste scarce resources on screening villages that are nonendemic.

A shift from active to passive screening may seem a logical next step once no more cases are found. Yet, because of the constraints described earlier, this will not be sufficient to achieve permanent elimination of gHAT. Some form of active screening will always be required to reach and sustain interruption of transmission. In a postelimination phase, such active surveillance can focus on historic foci, villages that have been endemic in the past. They will need to be screened actively once every 5–10 years to ensure that there is no resurgence. There may also be blind spots, villages that are suspected to be endemic but from which no data is available. Such villages should be screened at least once to rule out gHAT endemicity.

In all probability, the greatest breakthrough in recent years is a nontoxic single-dose oral drug acoziborole that has recently passed phase 3 clinical evaluation [50,51▪]. Publication of the final results is eagerly awaited (ClinicalTrials.gov Identifier: NCT03087955), because this novel treatment would make it possible to consider entirely different approaches to achieve interruption of transmission. As acoziborole can be used to treat HAT irrespective of disease stage, stage determination would become redundant.

The combination of highly specific screening tests (>99% specificity in DRC in 2021) and a single-dose oral treatment, now makes it possible to consider a screen-and-treat approach, skipping the on-the-spot diagnostic confirmation step. A phase 3A study exploring safety of acoziborole in serological suspects is currently ongoing (ClinicalTrials.gov Identifier: NCT05256017). If one were to screen HAT endemic villages with an RDT and presumptively treat all those testing positive, there would probably be a major reduction in numbers of dropouts during the diagnostic procedures [23]. The fact that treatment is provided on the spot and that the dreaded lumbar puncture is no longer required would almost certainly result in increased participation in

screening [52]. Such a screen-and-treat strategy could also be applied in passive screening.

With fewer than 10 000 serological suspects identified in DRC last year, treating all presumptively is far from impossible. There would still be a need for post hoc diagnostic confirmation to decide whether a village should be kept under active surveillance and eventually to confirm whether or not *T. brucei gambiense* is still circulating. For *a posteriori* diagnostic confirmation too, there have been some promising innovations. A highly specific inhibition ELISA, as well as a molecular test, are currently being validated for use in regional hospitals [53,54▪].

The combination of a screen-and-treat strategy with well targeted vector control using Tiny Targets is already showing great promise [33]. There is no need to permanently eliminate tsetse flies, reducing their density by more than 70%, as achieved in various settings, is sufficient to interrupt transmission [35–39]. Rather than aiming to control tsetse everywhere, efforts can be targeted to foci with active transmission. Combining tsetse control with the treatment of all potential sources of infection, including humans testing positive to serological tests would accelerate the interruption of transmission and ultimately eradicate the disease.

There is plenty of reason for optimism, but some word of caution is also required. Even though gHAT is assumed to be anthroponotic, there have been reports of pigs and other livestock being infected with *T. brucei gambiense*, and potentially playing a role in transmission [55]. At this stage, the existence of cryptic reservoirs in animals cannot be excluded with certainty. If they do exist, Tiny Targets could offer a solution to this threat. There have also been reports of humans carrying parasites in the skin but not in the blood and remaining asymptomatic [56]. So far, such asymptomatic carriers were identified among serological gHAT suspects, and thus would only strengthen the case for presumptive treatment based on serology. But we need to know more about this group, in particular whether the serological tests used in gHAT screening are sufficiently sensitive to pick them up or not, and whether current drugs are able to reach those parasites residing in the skin or not.

In a screen-and-treat strategy, sensitivity of serological tests becomes of crucial importance, and results from most studies seem to be reassuring [44,46]. However, there were also two phase 3 studies showing poor sensitivity of CATT and three RDTs [45,47]. Unfortunately, further research into sensitivity of screening tests is hampered by low numbers of new gHAT cases being identified and by the fact that existing specimen banks have very much been preselected on CATT.

CONCLUSION

Over the past 20 years, the combination of improved control tools and their implementation in screening of gHAT-endemic villages, followed by treating all diagnosed patients, has greatly reduced gHAT transmission. The targets of elimination of gHAT as a public health problem by 2020 have been achieved. Thanks to further innovations in diagnostics, vector control, and treatment in particular, the new target of interruption of transmission by 2030 is well within reach. Even if there was an animal or a cryptic human reservoir, based on the current epidemiological developments, it does not appear to play a major role. If transmission from the known human reservoir can be interrupted and historic foci kept under surveillance, a full-scale resurgence of gHAT as we have repeatedly witnessed in the past becomes highly unlikely. This will require sustained commitment from all stakeholders as well as adaptation of gHAT control strategies, making optimal use of available innovations.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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