

Opinion

The Long Wait for a New Drug for Human African Trypanosomiasis

Catriona H. Baker^{1,3} and Susan C. Welburn^{1,2,3,*}

Human African trypanosomiasis (HAT) is responsible for around 3000 reported cases each year. Treatments for HAT are expensive and problematic to administer, and available drugs are old and less than ideal, some with high levels of toxicity that result in debilitating and, in some cases, fatal side effects. Treatment options are limited, with only one drug, eflornithine, introduced in the last 28 years. Here we examine the limitations of current chemotherapeutic approaches to manage HAT, the constraints to new drug development exploring drug failures and new drugs on the horizon, and consider the epidemiological, political, social, and economic factors influencing drug development.

HAT – Two Different Diseases

HAT, or sleeping sickness, is caused by two subspecies of the haemoflagellate parasite *Trypanosoma brucei sensu lato* (see [Glossary](#)). *Trypanosoma brucei rhodesiense* (*T. b. rhodesiense*) causes acute infection, and infection with *Trypanosoma brucei gambiense* (*T. b. gambiense*) results in a chronic infection [1]. In the absence of treatment, infection with either form of HAT results in death.

The epidemic nature of the two forms of HAT presents a major public health risk within the 36 sub-Saharan countries with endemic disease foci [2], with an estimated 70 million people at risk of infection [3]. The majority of reported HAT cases (97%) are for *T. b. gambiense* (g-HAT) (the Democratic Republic of Congo (DRC) contributing 75% of cases), with acute *T. b. rhodesiense* HAT (r-HAT) contributing 3% of HAT cases¹. The level of under-reporting is significant for both forms of HAT [4,5], and while reported case numbers have been falling (3796 HAT cases in 2014, and 2804 cases in 2015²), most HAT foci are not under surveillance [5–8] and the number of cases will range from three times the number reported [8] to far higher [5].

Since none of the drugs currently available for HAT treatment are recommended for prophylaxis³, HAT control focuses on early diagnosis and treatment (to remove infected cases) and vector control (to interrupt transmission). For r-HAT, in endemic foci where there is a significant domestic animal reservoir of infection, identifying and eliminating *T. b. rhodesiense* parasites from that reservoir is important [9–12]. In wildlife-protected zones, where a wide range of species harbour *T. b. rhodesiense* parasites [13], vector control may be deployed to prevent spill-over into human and domestic animal populations.

The causal agents of HAT can be horizontally transmitted by tsetse [14], vertically transmitted from mother to offspring [15], and sexually transmitted in semen [16]. The parasites multiply in the host bloodstream prior to migrating into the cerebrospinal fluid (CSF). Early clinical signs of infection may be a trypanosomal chancre and lymphadenopathy at the site of fly bite [17], but often a chancre is not observed (particularly for *T. b. gambiense* infection). As infection progresses, intermittent fever, headache, and joint pain are experienced [18,19]. When

Highlights

Drugs currently available for the treatment of HAT are unacceptable against a range of benchmarks. The ideal drug is a safe, oral compound with 95% efficacy against both stages of HAT, and a drug meeting these requirements could be used to prevent maternal transmission and prophylactically.

Significant investment for the identification and development of drug candidates for HAT over the last decade has resulted in several promising drugs that are progressing through clinical development. However, a range of political and social barriers prevent clinical trials from being conducted effectively. An estimated 90% of cases occur in countries enduring conflict and political/social instability, which negatively impacts on health expenditure, infrastructure, and the ability to conduct clinical trials.

During interepidemic periods, the few available HAT patients are thinly distributed, and while two promising new drugs are in the last stage of testing, the lack of patients available for recruitment into trials is problematic.

¹The University of Edinburgh, Deanery of Biomedical Sciences, Edinburgh Medical School, College of Medicine & Veterinary Medicine, 1 George Square, Edinburgh, EH8 9JZ, UK

²Zhejiang University – University of Edinburgh Institute, Zhejiang University School of Medicine Zhejiang University, International Campus, 718 East Haizhou Road, Haining, 314400, China

³Orcid ID: <https://orcid.org/0000-0002-9903-7086>

*Correspondence: sue.welburn@ed.ac.uk, s1403768@sms.ed.ac.uk (S.C. Welburn).

parasites are detected only in blood and lymph but not in CSF, the disease is considered **haemolymphatic** or stage 1.

The **meningoencephalitic** or late (stage 2) phase of infection is characterised by parasites crossing the blood–brain barrier (BBB) into the central nervous system (CNS) [17]. This is diagnosed by the visual presence of trypanosomes in the CSF or the patient having more than 5 lymphocytes/ μl in the CNS [19–21]. Trypanosomes disrupt circadian rhythm and sleep patterns, and common neurological symptoms include somnolence and confusion with tremor and sensory dysfunction [21]. Progression of r-HAT to stage 2 may occur within weeks [21] while g-HAT infection progresses more slowly with lymphadenopathy and hepatosplenomegaly observed months to many years after infection [21].

For both forms of HAT, a rapid diagnosis is essential. BMJ Best Practice guidelinesⁱⁱ suggest a three-step approach: (i) screen population at risk, (ii) confirm the presence of parasites, and (iii) stage the disease. For *T. b. rhodesiense* a thick blood film is examined microscopically [21,22]. Since, individuals infected with g-HAT may remain asymptomatic for years [11,21,23] screening is undertaken using the serologic card agglutination test for trypanosomiasis (CATT)ⁱⁱⁱ [22,23]. A molecular marker is available to detect r-HAT parasites [24], and several rapid diagnostic tests are under trial for g-HAT [22,25]. As new detection methods are introduced the key issue of clinical follow-up or treatment of silent carriers of *T. b. gambiense* infection (individuals positive by PCR and/or other sensitive methods but showing no clinical signs of g-HAT) will need to be addressed [11,23].

While improvements have been made in diagnostics for HAT screening, vector control, public health, and treatment of domestic animal reservoirs, no new drug has been introduced for routine clinical treatment of HAT for almost 30 years [26].

Drugs Currently Available for HAT

Four drugs are currently registered for HAT treatment: suramin, pentamidine, melarsoprol, and eflornithine. A nifurtimox–eflornithine combination therapy (NECT), while not approved in all HAT affected countries, has been on the WHO list of essential medicines since 2009 [27] (Table 1). A timeline of early HAT drug development is shown in Figure 1.

Suramin (synthesised in 1917 as Bayer 205) [27] disrupts glucose synthesis [28]. Suramin is used to treat stage 1 HAT but is ineffective for stage 2 infection since it does not cross the BBB^{iv}. Suramin is administered intravenously and requires prolonged hospital admission (21

Glossary

Haemolymphatic: blood and lymphatic fluid.

Intramuscular (IM): situated or taking place within, or administered into, a muscle.

Intravenous (IV): existing or taking place within, or administered into, a vein or veins.

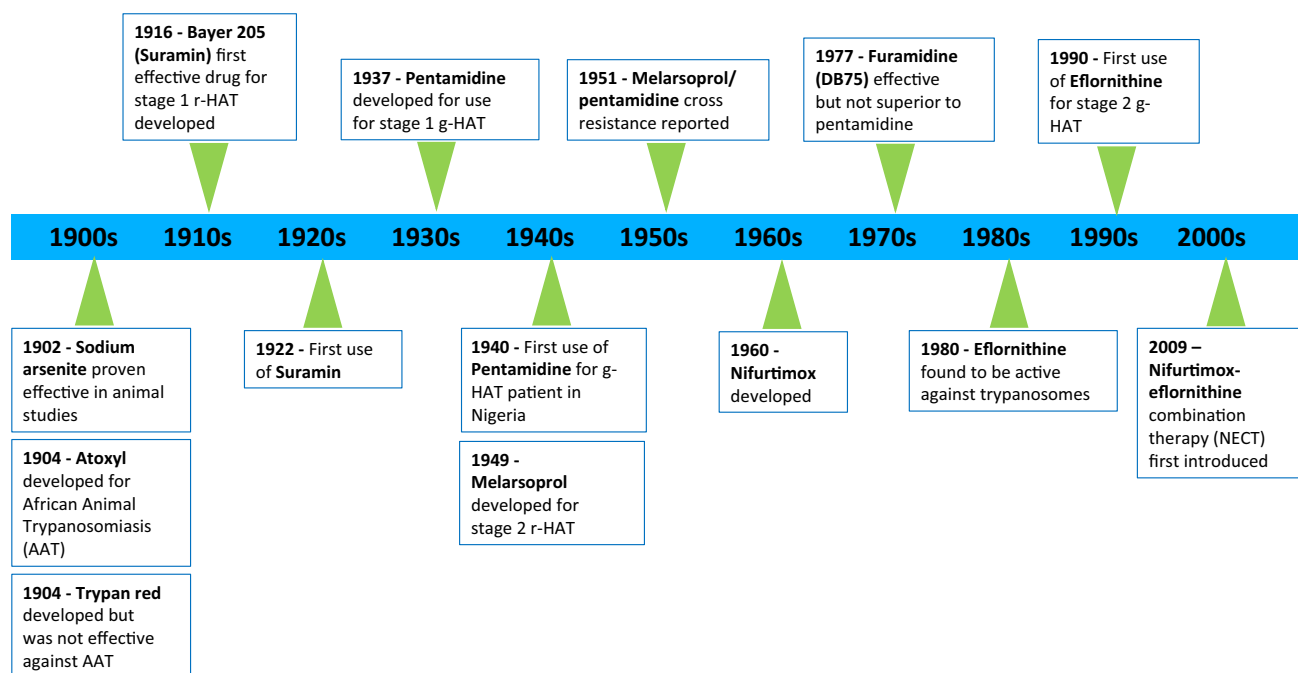
Meningoencephalitic: brain and meninges.

Per os (PO): from Latin 'by opening' or 'by way of the opening'. The expression is used in medicine to describe a treatment that is taken orally.

Sensu lato: in a broad sense, used especially with names of taxa to indicate that the name is used more inclusively than sanctioned by current practice.

Table 1. Summary of Current Drug Dose Regimens for Each Stage of g-HAT and r-HAT^{iv}

Infection	Stage	Drug	Mode of application	Adult dose
g-HAT	Stage 1	Pentamidine	IM or IV	4 mg/kg/day for 7–10 days
		Suramin	IV	1 g on days 1, 3, 7, 14, and 21
	Stage 2	Melarsoprol	IV	2.2 mg/kg/day for 14 days
		Eflornithine	IV	4 × 100 mg/kg/day for 14 days
		NECT	IV Eflornithine PO Nifurtimox	2 × 200 mg/kg/day for 7 days 15 mg/kg/day for 10 days
r-HAT	Stage 1	Suramin	IV	1 g on days 1, 3, 7, 14, and 21
	Stage 2	Melarsoprol	IV	2.2 mg/kg/day for 10 days



Trends in Parasitology

Figure 1. Early HAT Drug Development, 1900s to 2000. HAT drugs currently in clinical use, pentamidine and suramin, used for stage 1 HAT treatment, were developed in the early part of the last century. Melarsoprol, eflornithine and nifurtimox, used for stage 2 HAT, were developed in the latter part of the last century. Adapted from [31].

days). While there are indications of eflornithine, nifurtimox, and melarsoprol synergies with suramin, combination therapies have not been successfully implemented [19].

Pentamidine (discovered in 1937) [29] binds to nucleotides and disrupts the mitochondrial genome [30,31]. Pentamidine has been used to treat stage 1 g-HAT since 1940 but is less effective against stage 1 r-HAT than suramin^{iv}. Pentamidine is not effective for stage 2 HAT [32]. The standard dose of pentamidine is 4 mg/kg/day administered by the **intramuscular (IM)** or **intravenous (IV)** route, for 7–10 days^{iv}. Pentamidine is supplied as a powder and, once in solution, must be used within 24 h [33].

Melarsoprol (developed in 1949) is effective against both stages of g-HAT and r-HAT [19]. Since safer alternatives exist for stage 1 HAT, the use of melarsoprol is restricted to stage 2 disease [34] and it is the only treatment for stage 2 r-HAT. Relapses occur in 10–30% of melarsoprol-treated patients, and cure rates have fallen dramatically from 89.7–97.2% pre-1999 to 62.9–92% post-1999 [34]. *T. b. gambiense* is considered to be increasingly melarsoprol-resistant [27,35]. Administration originally required a daily IV dose of 1.2 mg/kg increasing to 3.6 mg/kg for 3–4 days followed by a 7-day treatment break, repeated two or three times^{iv}. A shorter regimen of 2.2 mg/kg/day IV for 10 consecutive days is now recommended^{iv} [36]. Melarsoprol is highly toxic, and since adverse effects are common (5–10% of patients develop a reactive encephalopathy which is fatal in 50% of cases [34]), administration must be given in hospital.

Eflornithine (α -DFMO) was developed in the 1970s for cancer chemotherapy [37]. Trypanostatic action was observed in 1980 [19], and eflornithine was approved for stage 2 g-HAT treatment in 1990 [18]. Eflornithine inhibits trypanosome ornithine decarboxylase (ODC) [34] in *T. b. gambiense*

but not in *T. b. rhodesiense* [34]. Eflornithine is effective in both stages of g-HAT as it penetrates the BBB^{iv} [19,29]. However, drug administration is problematic; the drug half-life is short (3 h) and a 100 mg/kg dose is required every 6 h^{iv}. Administration of 56 IV injections over 14 days is labour-intensive^{iv}. Production was stopped by Sanofi in 1999 [37] but restarted by Aventis in 2001.

NECT combination therapy was developed to overcome the problems associated with eflornithine monotherapy [34]. Nifurtimox, or 5-nitrofurantoin is cytotoxic to both forms of HAT [34] but is not registered as a stand-alone compound for HAT [27]. A trial of three combination therapies: nifurtimox–eflornithine; melarsoprol–nifurtimox and melarsoprol–eflornithine on patients with stage 2 g-HAT concluded that nifurtimox–eflornithine was the most effective with less adverse effects when compared to eflornithine monotherapy [38]. NECT is now recommended for stage 2 g-HAT infection [39,40].

Issues with Existing Drugs

Adverse side effects, poor efficacy, emerging drug resistance and complex treatment, and administration protocols make HAT treatment problematic, and the toxicity of current chemotherapies negates their use for prophylaxisⁱⁱ. Melarsoprol is considered particularly toxic, but even HAT drugs which do not cross the BBB, have adverse effects [18,41,42]. All current treatments, aside from nifurtimox, which is administered **per os (PO)**, require IV or IM administration [43]. Melarsoprol, administered in propylene glycol, is a particularly painful treatment which affects compliance [44]. The requirement for eflornithine to be administered every 6 h for 14 days makes it an impractical treatment in areas with poor infrastructure [43]. The shorter (10 day) melarsoprol treatment shows higher mortality and relapse rates than both the standard melarsoprol and eflornithine treatments [45]. While combination therapies offer short-term solutions to the current lack of available therapies for HAT, the 7 days of treatment required for NECT is not ideal [45]. The relapse rate for melarsoprol in some HAT foci is as high as 30% and reduces treatment options in many HAT foci [42,46,47].

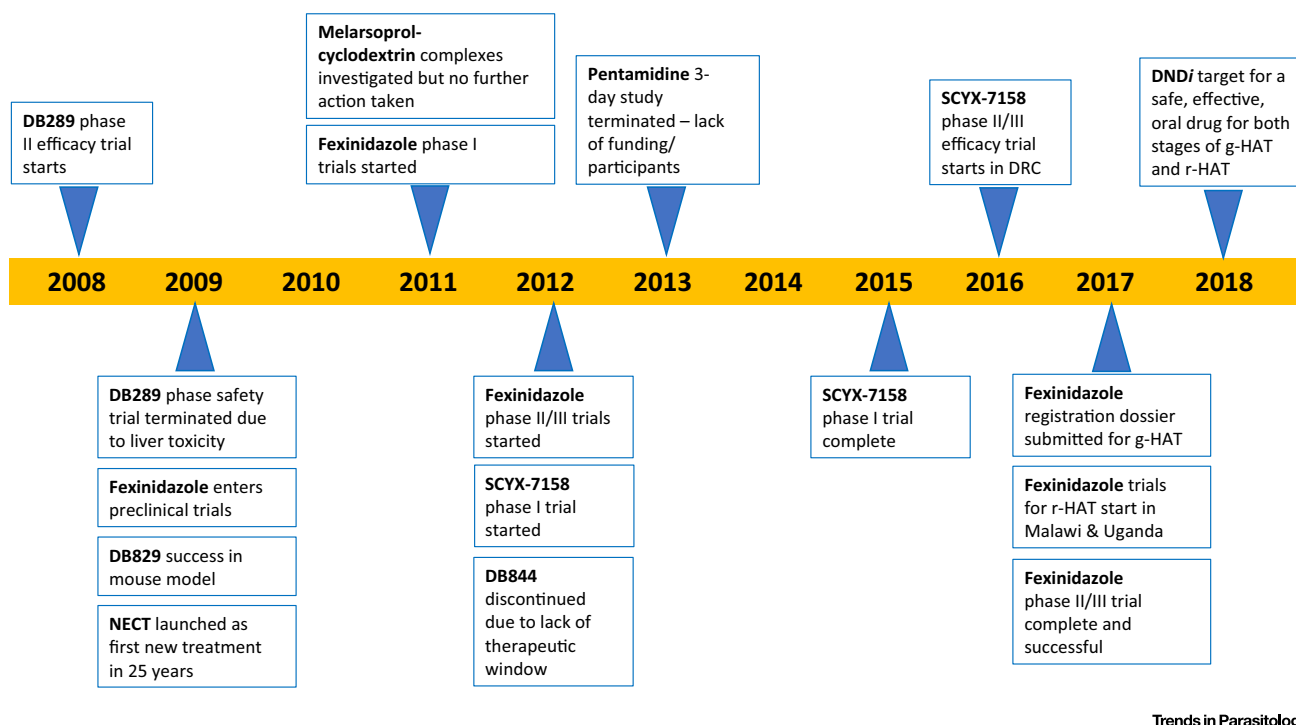
Drug Development

The WHO donates HAT drugs to affected countries, but HAT drugs are expensive to produce and distribute. NECT, at US \$357 per treatment, is considerably cheaper than eflornithine (US \$675) but these costs by far exceed the target of US \$37 per course proposed by the Drugs for Neglected Diseases initiative (DNDi)^v.

Drug development is a lengthy process with high attrition rates. Only 12% of drugs that enter clinical development will reach the market [48], and drug registration in developing countries is challenging [49]. Several early HAT drug candidates entered clinical development but most failed to reach full approval and 90% failed to reach production and distribution [27] (Figure 2).

Furamide (DB75), a diamine analogue, was shown to be effective against HAT in 1977, but was found inferior to pentamidine. Pafuramide maleate (DB289), a prodrug of DB75, showed high levels of hepatotoxicity and nephrotoxicity in Phase I safety trials, and the study was terminated in 2009 [19,27]. DB844 and its active metabolite DB820 were considered possible candidates for treatment of stage 2 HAT but their development was discontinued [50]. The diamidine, DB829, and its prodrug DB686, showed improvements over DB289 in terms of efficacy and without the liver toxicity, and performed strongly in mouse models (even for stage 2 HAT) and further trials were recommended [51,52].

The economies of countries affected by HAT are not sufficiently strong to support investment in new drug development and, as only a relatively small number of people get sleeping sickness



Trends in Parasitology

Figure 2. Major Drug Development Stages Occurring since 2008. Progress in the last decade towards a safe, oral compound with 95% efficacy against both stages of HAT.

compared to many other diseases, this has until relatively recently discouraged drug company involvement. HAT drugs have a low potential for profit due to the relatively small number of reported cases and this has impeded investment in drug development [53,54]. DNDi aimed to accelerate replenishing the dwindling HAT drug pipeline with new drugs with some success [55] (Figure 2). Support for research has been garnered over the past decade with engagement from the Bill and Melinda Gates Foundation, UK Medical Research Council, National Institutes of Health, Wellcome Trust, Médecins Sans Frontières, WHO, DNDi and drug companies, many of which also donate unlimited, registered HAT drugs free of charge.

DNDi established a set of goals to guide the push in HAT drug research (Table 2) with the overall aim for HAT being a safe oral drug with 95% efficacy against both stages of HAT infection (and possibly a combination therapy to reduce toxicity) by 2018. One candidate, SCYX-7158 (acoziborole), an oxoborole with a long half-life (400 h) has the potential to be administered as a single oral dose. Acoziborole was admitted to Phase I efficacy trials in 2015 to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral ascending doses in healthy human volunteers and results confirmed penetration of the BBB. A DNDi phase II/III trial of single-dose acoziborole was initiated in DRC in 2016 for stage 2 g-HAT^{vi}.

The nitroimidazole fexinidazole, effective against both stages of g-HAT and r-HAT [19] can also be orally administered. A DNDi^{vii}-supported clinical trial used a loading dose of 1800 mg/day for 4 days followed by a 1200 mg/day regimen for 6 days administered with a meal. Fexinidazole was shown to be an effective (and safe) treatment for g-HAT [56]. Trials for efficacy for r-HAT were rolled out in Uganda and Malawi in 2017^{vii}. Fexinidazole shows promise as the first oral treatment shown to be effective against second-stage g-HAT, and the drug could possibly be

Table 2. DNDi Target Product Profile for the Ideal New Drug for HAT^{viii}

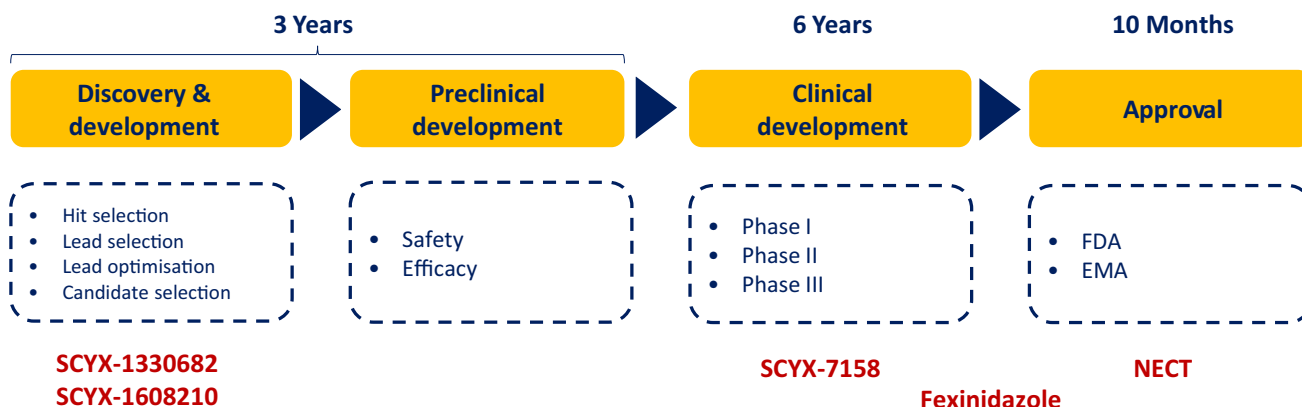
Feature	Ideal drug	NECT ^a
HAT stage	Both stages 1 + 2	Stage 1 and 2, but only used for stage 2
Subspecies causing HAT	<i>T. b. gambiense</i> and <i>T. b. rhodesiense</i>	<i>T. b. gambiense</i>
Clinical efficacy	>95% after 18 months	96.5%
Efficacy in melarsoprol-resistant cases	Effective	Effective
% Drug-related mortality	<0.1%	1.2%
Monitoring for adverse effects	Not required	Hospitalisation required
Cost for donor agencies	<US \$37/course	US \$276/course
Treatment duration	<7 Days PO once daily <7 Days IM once daily	10 Days PO 7 Days IV infusion
Administration route	PO	IV and PO

^aNifurtimox–eflornithine combination therapy.

administered in a home setting [57]; registration for a 10-day treatment programme of fexinidazole for g-HAT was submitted to the European Medicines Agency (EMA) in 2017^{vii} and the EMA accepted the application under ‘Article 58’^{viii}.

Drug candidates undergo an extensive development process of preclinical development, clinical development, and approval before implementation in endemic areas (Figure 3). Finally, some success is being seen for HAT, as demonstrated by candidates SCYX-7158, fexinidazole, and NECT in approval and implementation stages. Several other compounds – SCYX-1330682, SCYX-1608210, and SCYX-2035811 – are on hold and will only be pursued, and development continued, if more advanced candidates fail in clinical trials^{ix,x}.

A safe oral drug treatment opens the possibility for prevention of maternal transmission, treatment of silent carriers of infection, and in prophylaxis. The fexinidazole phase II/III, open-label, noninferiority trial did not include children under 15 or pregnant or lactating women



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Figure 3. Drug Development Process. Estimated time frame from basic research to the drug reaching patients. HAT drug candidates (in red) are in the pipeline. FDA, Food and Drug Administration; EMA, European Medicines Agency; NECT, nifurtimox–eflornithine combination therapy.

[56], and a Phase IIIb trial on special population groups, excluded from previous studies, has been initiated^{xi}. A drug that can be used in pregnant and lactating women is needed if maternal transmission of HAT is to be addressed and prevented [11]. If fexinidazole safety is confirmed for these groups, importantly, patients could be treated without visualisation of parasite infection in blood or spinal fluid, which would permit screening of populations at scale, and silent carriers of infection to be treated [11,23].

Routes to Drug Discovery

Successes have followed a number of different drug discovery routes. Compound repositioning, in which existing drugs were screened for HAT, was used in the development of nifurtimox and eflornithine and for the re-discovery of fexinidazole in 2005 [19].

Target-based approaches to identify compounds that act as inhibitors against a molecular target also offer promise, given the unique characteristics of trypanosomatids and advanced technologies that facilitate target-based discovery (structure-based drug design or high-throughput genetic RIT-seq screening) [58–61]. Compounds can be identified by high-throughput library screens to find a suitable inhibitor based on its potency, selectivity, and pharmacokinetic properties [62]. Deconvolution of eflornithine led to the discovery of ornithine decarboxylase, the only fully validated drug target for HAT [63]. N-myristoyltransferase has been identified as a target, and a number of trypanocidal inhibitors, most notably DDD85646, are now being explored [64].

There are inherent difficulties in translating target inhibition in cell-free systems to inhibition of parasite proliferation *in vivo* [65]. Phenotypic and cellular screening of inhibitors against whole parasites (rather than isolated targets) has been successfully applied in HAT drug discovery for fexinidazole and SCYX-7158. *In vitro* assays, however, remain challenging for *T. b. gambiense*, which is difficult to isolate and culture, requiring adaptation to screen against the nonhuman infective forms of *T. b. brucei* [66].

Political, Social, and Economic Factors Influencing Drug Development

HAT is a neglected tropical disease (NTD) that affects the poorest and most remote communities in sub-Saharan Africa and, as for all NTDs, multiple political, social, and economic factors feed into the drug discovery, development, and deployment landscape. HAT incidence has been decreasing since 2000, and this directly impacts on political will and commitment for long-term investment in HAT.

HAT outbreaks and epidemics are intrinsically linked to displacement of populations, particularly during conflicts. Social disruption impacts on resources for surveillance and health care provision [67–69]. Solutions require to be tailored to the settings in which they will be deployed, hence the requirement for a safe, all-oral treatment, for both first and second stages of HAT.

Across the HAT foci in sub-Saharan Africa, we are experiencing an interepidemic period, characterised by low case numbers. The successful trials of fexinidazole in the DRC and the Central African Republic offer hope for a major step forward in treatment of g-HAT, but the falling case numbers over the past decade directly impacted on the ability to conduct clinical trials for HAT. Recruitment into the Phase II/III SCYX-7158 trial was problematic, and by the end of 2016 only 11 patients (out of a target 350) were enrolled. Similarly, only 6 patients, of a target of 174, agreed to participate in the trials of fexinidazole^{vi,xii}, and clinical trials for NECT in Uganda were terminated^{xiii} due to low case numbers.

Infection with HAT brings considerable social stigma to the infected individual and their families. Communities are inherently superstitious of individuals afflicted with HAT, in part due to the extraordinary behavioural changes and neurological symptoms typical of stage 2 infection. When r-HAT first emerged in Kabaramiadi District, Uganda, in 2005, the New Vision newspaper commented 'Sleeping sickness has hit Kabaramiadi however residents are ignorant of the disease because of their traditions and superstitions' [10]. This stigma impacts directly on health-seeking behaviour: suspected cases are fearful of diagnosis and treatment and do not present for screening. This has a direct impact on recruitment of cases for participation in clinical trials [70].

Concluding Remarks

The epidemiology of HAT suggests that we are at present experiencing an interepidemic period, characterised by low case numbers. With the apparent decrease in cases for a neglected disease, such as HAT, there is a risk that both political and donor support for the current drive in investment for drug development could contract. This would be an expensive mistake.

HAT is a disease characterised by epidemics; we have experienced interepidemic periods many times before [11] and should now be preparing for the next HAT epidemic (see Outstanding Questions). The present parasite populations of *T. b. gambiense* Group 1 have arisen from a single individual within the last 10 000 years [71]. It has been suggested that the *T. b. gambiense* Group 1 clone is normally transmitted maternally from infected mothers to their offspring [11]. Transmission in the absence of tsetse vectors has fiscal implications for programmes designed to eliminate g-HAT. The goal posts have moved, and the criteria needed for new drugs may need to adapt to be acceptable for treatment of women of childbearing age and young children.

An arsenal of 'safe oral drugs with 95% efficacy against both stages of HAT infection' is needed that can be used to eliminate the human reservoir of HAT infection across established foci, if we are finally to be able to confine the long and sorry saga of HAT to the history books.

Acknowledgments

The authors would like to thank Dr Kevin Read, Professor Peter Kennedy, Professor Michael Field, Dr Charles Mowbray, Professor Michael Ferguson, Professor Simon Croft, Professor David Horn, Professor Harry de Koning, Professor Malcolm Walkinshaw, and Professor Reto Brun for their insightful inputs and communication of their understanding of the reasons behind the wait for new drugs. We are also grateful to DNDi for providing access to the latest news from the HAT clinical trials.

We acknowledge research support from Tackling Infections to Benefit Africa, National Institute for Health Research, using Official Development Assistance (ODA) funding 16/136/33. The funders had no role in the study design, data collection and analysis, decision to publish, or in preparation of the manuscript.

Resources

ⁱwww.who.int/mediacentre/factsheets/fs259/e/

ⁱⁱ<http://bestpractice.bmj.com/best-practice/monograph/9999/diagnosis/step-by-step.html>

ⁱⁱⁱwww.cdc.gov/parasites/sleepingsickness/health_professionals/

^{iv}www.who.int/trypanosomiasis_african/drugs/en/

^vwww.dndi.org/diseases-projects/hat/hat-target-product-profile/

^{vi}www.dndi.org/diseases-projects/portfolio/scyx-7158/

^{vii}www.dndi.org/diseases-projects/portfolio/fexinidazole/

^{viii}www.dndi.org/2018/media-centre/press-releases/sanofi-dndi-seek-ema-review-for-sleeping-sickness-treatment/

Outstanding Questions

During interepidemic periods, when HAT case incidence is low, how can the financial sustainability of platforms that support research and translation for continuous evolution of the drug-discovery pipeline be maintained? Can social finance models play a role [72]?

There is an urgent need to address the obstacles to recruiting patients in the field for current trials. Can new diagnostic tools be deployed for mass screening to address both under-reporting of cases and identify patients for recruitment into trials?

The mounting evidence for maternal transmission of g-HAT demands a new approach to enable early identification and treatment of g-HAT infection. Can a safer, orally administered drug be used in pregnant and lactating women? Could this drug be used prophylactically to eliminate *T. b. gambiense* from human reservoirs in HAT foci?

^{ix}www.dndi.org/diseases-projects/portfolio/completed-projects/nitroimidazole-backup/

^xwww.dndi.org/diseases-projects/portfolio/scyx-1330682/

^{xi}www.dndi.org/2017/media-centre/news-views-stories/news/hat_rnd_status_feb_2017/?utmsource=DNDi&utm_campaign=b9fa73585e-ENEWS_SCIENTIFIC_2017_02_17&utm_medium=email&utm_term=0_4c3dd201d2-b9fa73585e-277304533

^{xii}<https://clinicaltrials.gov/ct2/show/NCT01685827>

^{xiii}<https://clinicaltrials.gov/ct2/show/NCT00489658>

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