A sleeping sickness patient rests in the HAT ward in Katanda, Kasai, DRC.

› **Sleeping sickness** is usually deadly without treatment. Patient numbers have fluctuated with time, with disease outbreaks occurring intermittently, particularly when surveillance and control measures were relaxed. In the mid-1960s fewer than 5,000 cases were reported in the whole African continent, but the disease re-emerged, with a major epidemic from 1970, peaking in 1998 with over 38,000 cases detected. Since then, numbers have been falling consistently thanks to the combined efforts of WHO, National Control Programmes, NGOs, and Belgian and French bilateral aid. The most recent figures show that fewer than 3,000 new cases of *T.b. gambiense* HAT (g-HAT) were reported in 2015, the lowest figure ever recorded by WHO; 117 cases of *T.b.* rhodesiense (r-HAT) were recorded in 2014.

Available treatment options depend on the stage of the disease and the parasite subspecies causing the infection, making the invasive and feared lumbar puncture – to determine if the parasite has entered the brain – mandatory for every patient diagnosed. Nifurtimox-eflornithine combination therapy (NECT), developed by Epicentre, MSF, DND*i*, and partners for treating stage 2 g-HAT, replaced melarsoprol, a highly toxic arsenic-containing drug which killed 1 in 20 patients. Eflornithine was initially introduced as a slow-infusion treatment administered 56 times (every 6 hours for 14 days). In NECT, the number of eflornithine infusions is reduced to 14, in combination with orally administered nifurtimox, shortening the time spent in hospital and reducing the burden on resources. For stage 1 disease, pentamidine (discovered in 1940) remains the current treatment for g-HAT and suramin (discovered in 1920) for r-HAT. The arsenic-derivate melarsoprol is still the only treatment available for stage 2 r-HAT.

WHO aims to eliminate g-HAT as a public health problem by 2020. A paradigm shift in diagnosis and treatment is therefore needed, with patients screened at home, referred to a nearby centre for diagnostic confirmation and sent back home with an oral treatment, obviating the need for staging of the disease by lumbar puncture. This will require a simple, reliable, rapid test, coupled with a safe and effective treatment that is easy to administer for both disease stages in g-HAT and r-HAT.

Sustained disease elimination requires new tools

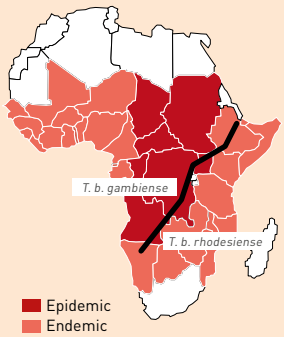
DND*i* has advanced oral candidates for HAT treatment in clinical development that are new chemical entities: fexinidazole, a 10-day treatment, and SCYX-7158, a potential single-dose treatment. The fexinidazole pivotal trial in adults with stage 2 g-HAT, and additional trials in adults with stage 1 disease and in children with both disease stages, had finished recruitment by the beginning of 2016. In addition, an implementation study to determine safety and efficacy in a 'real world' setting will provide further data on the use of fexinidazole for treating outpatients, including at home. This will inform HAT endemic countries on the widest possible use of the drug and guide treatment policy. A study is planned for fexinidazole in r-HAT. SCYX-7158 has completed studies in healthy human volunteers and DND*i* will start recruiting patients into a phase II/III trial in 2016.

During recruitment into the fexinidazole trials in the DRC, mobile teams from the National Control Programme for HAT, supported by DND*i*, travel to endemic villages to identify infected people who are then sent to specialized district hospitals for diagnosis confirmation and treatment. Mobile teams tested approximately 25% of the nearly 4 million people screened for g-HAT in the entire country in 2014 and 2015. As such, DND*i* is making a real contribution to the control and elimination of HAT through the work of mobile teams and conduct of clinical trials.

With the exciting prospect of wiping out this deadly disease, it is vital that funding is maintained to sustain elimination efforts and avoid previous scenarios where control and surveillance lapsed and the disease re-emerged.

HUMAN AFRICAN TRYPANOSOMIASIS / SLEEPING SICKNESS

13.1 million people were estimated to live in areas at moderate to very high risk in 2012 (more than one case per 10,000 population)



Disease is caused by two subspecies of *Trypanosoma brucei (T. b.) gambiense* (g-HAT; 98% of reported sleeping sickness cases) and *T. b. rhodesiense* (r-HAT), and occurs in two stages: the early stage has non-specific symptoms and is often un- or misdiagnosed, and the late stage, where the parasite crosses the blood-brain barrier, causing serious neurological disorders including sleep cycle disruptions, paralysis, and progressive mental deterioration. Without effective treatment, the disease usually leads to death. A lumbar puncture is needed to differentiate between stages in order to choose the appropriate treatment.

Current treatments are difficult to administer, and stage-specific:

TREATMENT OF STAGE 1 HAT

Pentamidine (1940) for g-HAT and suramin (1920s) for r-HAT, require injections and are ineffective for stage 2.

TREATMENT OF STAGE 2 HAT

NECT – nifurtimox-eflornithine combination therapy (2009): for stage 2 g-HAT, requires 14 slow intravenous infusions of eflornithine of 2 hours each over 7 days, together with three times a day oral nifurtimox for 10 days. Requires specialized hospital administration and trained staff. Since its addition to the EML, NECT is first-line treatment for stage 2 g-HAT.

Eflornithine (1981): today seldom used alone, requires an extended stay in hospital during administration (56 intravenous infusions – four times per day, over 14 days).

Melarsoprol (1949): No longer used for g-HAT. Remains the only drug available for stage 2 r-HAT – a toxic arsenic derivative that causes pain and fatal encephalopathy in up to 5% of patients who receive it.

T. b. gambiense is endemic in

24 countries

of West and Central Africa • Less than 3,000 new cases reported (2015)

T. b. rhodesiense is endemic in

13 countries

of Eastern and Southern Africa • 117 cases (2014)

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

At its inception, DND*i*'s short-term strategy was to make better use of existing treatments by combining drugs already in use. In September 2009, DND*i* and partners launched the first new treatment option for sleeping sickness in 25 years: nifurtimox and eflornithine combination therapy (NECT). NECT is included on the WHO Essential Medicines Lists (EML) for adults (since 2009) and children (since 2013), and virtually all *T. b. gambiense* endemic countries are now using NECT as first-line treatment for stage 2 g-HAT.

As a medium-term strategy, DND*i* initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases, resulting in the rediscovery of fexinidazole. After a complete Phase I programme, DND*i* engaged in g-HAT patient studies. Inclusion into a pivotal Phase II/III study in stage 2 g-HAT is complete and patient follow-up is ongoing. Two complementary studies will examine efficacy and safety in adults with stage 1 and early stage 2 g-HAT, in children aged 6-14 years, and a third one is being planned for r-HAT patients. Additional information will be obtained from a study in special population groups and to provide preliminary evidence on treatment compliance and effectiveness in ambulatory patients. Sanofi is the industrial partner.

In order to build a strong pipeline for long-term drug discovery, DND*i* established a HAT Lead Optimization Consortium resulting in identification of the oxaborole SCYX-7158, which successfully progressed through pre-clinical development. Phase I clinical development was completed in 2015 and preparations are underway for a prospective Phase II/III efficacy study in patients, to be initiated in 2016. Other backup compounds were evaluated by the consortium and remain available for further development if necessary.

In addition, DND*i* supports the HAT Platform (see p.59) that was launched in Kinshasa, Democratic Republic of the Congo (DRC) in 2005. The HAT Platform is a clinical research and access-supporting network for HAT endemic countries that brings together key players in the research on sleeping sickness in endemic countries and those involved in HAT from the international research arena, with partners having a role in developing HAT health policy participating in the Platform.

Ideally a new treatment for adults and children would be effective against both stages of the disease and both parasite sub-species, non-toxic, have at least 95% efficacy at 18 months post end of dosing follow-up examination, be safe for pregnant and breastfeeding women, easy to use (short-course or once a day), oral, require no monitoring, affordable, and adapted to tropical climates.

By 2018, DND*i* aims to deliver from its HAT-specific portfolio: An oral, safe, effective treatment to be used for both stage 2 and stage 1 HAT.