The battle is not over until it is won

Sleeping sickness, or human African trypanosomiasis, threatens millions of people in 36 countries across sub-Saharan Africa. The Democratic Republic of the Congo bears the brunt, accounting for 83% of all cases. In the 1960s there were less than 5,000 patients suffering from the disease in the whole of the continent. However, the end of the 20th century – with internal conflict, competing health priorities, and decolonization – witnessed a halt in the successful control methods, and the number of cases reported rose steeply, peaking in 1998 with over 37,000 cases reported in that year. Nowadays, thanks to the combined efforts of WHO, National Sleeping Sickness Control Programmes, NGOs and other partners, the disease has once more been brought under control, and since 2010 the number of reported cases has fallen below 8,000.

The WHO has laid out a roadmap to eliminate the disease as a public health problem by 2020, when less than one case per 10,000 inhabitants in at least 90% of endemic foci is expected. Maximizing efficiency through a ‘WHO network’ of partners and stakeholders in order to achieve elimination is currently underway.

The most advanced stage of the disease is determined after multiple and complex diagnostic procedures, including a painful lumbar puncture, and is treated with a combination of oral and intravenously administered drugs. Nifurtimox-eflornithine combination treatment (NECT), introduced by DNDi and partners in 2009, was the first improved treatment option for patients with advanced sleeping sickness to be developed in 25 years, and has reduced the time required to spend in hospital during administration, from 14 to 10 days. By the end of 2012, NECT, which features on the WHO Essential Medicines Lists for adults and children, was being used to treat 96% of late-stage T.b. gambiense HAT patients in endemic countries, thus virtually replacing the previous and toxic arsenic-based treatment, melarsoprol. The latter, however, is still the first-line treatment for the less common T.b. rhodesiense HAT.

To contribute to the WHO elimination goal, a ‘test and treat’ strategy that would be implemented at the primary healthcare level is on the horizon, with potential simple oral pills for both the early and late stage as well as both types of HAT, that are currently in development, along with new rapid diagnostics, which together would remove the need for painful and dangerous lumbar punctures. This would mean that rural health centres, rather than hospitals, will play an increasingly important role, especially as the number of reported cases continues to dwindle.

Ideal Target Product Profile for HAT

A new treatment for adults and children:

- Effective against both stages of the disease
- Active against both causative parasite sub-species: Trypanosoma brucei gambiense and T.b. rhodesiense
- Less than 0.1% drug-related mortality
- At least 95% efficacy at 18 months follow-up
- Safe for pregnant and breastfeeding women
- Easy to use: short-course (7, maximum 10 days), oral, once a day, requiring no monitoring
- Affordable
- Adapted to tropical climates (three-year shelf-life)

WHAT IS THE IMPACT OF HAT?
The number of reported cases in 2012 was fewer than 8,000, but the actual number of cases is estimated to be 20,000.\(^1\) Fatal if untreated, the disease affects mainly those living in remote areas with limited access to adequate health services. The disease is found in 36 countries in sub-Saharan Africa, but 8 countries report 97% of all cases (see map), and over two-thirds of those are reported in the Democratic Republic of the Congo.\(^2\) Almost eliminated in the 1960s, transmission increased again as a result of war, population displacement, poverty, and the collapse of adequate support to the control activities conducted within health systems. Recent successes and an impressive drop in the number of reported cases call for renewed hope, but there is still work to be done, as some areas are not covered by surveillance and control efforts.

HOW IS HAT TRANSMITTED?
HAT is transmitted to humans by two sub-species of the parasite Trypanosoma brucei (T. b.) through the bite of the tsetse fly: T. b. gambiense (West and Central Africa, responsible for the vast majority of cases) and T.b. rhodesiense (East Africa). Man is the essential reservoir for T. b. gambiense.

WHAT ARE THE SYMPTOMS?
HAT occurs in two stages:

→ **Stage 1:** the haemolymphatic stage – includes non-specific symptoms like headaches and bouts of fever (and generally goes undiagnosed without active HAT surveillance).

→ **Stage 2:** the later, neurologic stage – occurs when the parasite crosses the blood-brain barrier and is characterized by serious sleep cycle disruptions, paralysis, progressive mental deterioration, and ultimately, without effective treatment, death.

A lumbar puncture is needed to differentiate between the two stages to choose an appropriate treatment.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Available treatments have limitations, are difficult to administer, often toxic, and are stage-specific.

→ **Stage 1:** pentamidine and suramin, require injections and are ineffective for stage 2.

→ **Stage 2:** NECT (nifurtimox-eflornithine combination therapy), available since 2009, is a simplified therapy option for stage 2 T.b. gambiense sleeping sickness, with only 14 injections of eflornithine over 7 days and 10 days of oral treatment with nifurtimox. While not the most appropriate treatment to support elimination efforts as it requires a hospital setting, NECT does provide a major improvement in case management.

Melarsoprol, still the only drug available for stage 2 T. b. rhodesiense, is a toxic arsenic derivative that causes pain and fatal encephalopathies in up to 5% of patients who receive it,\(^3\) and is increasingly ineffective, with reports of drug resistance and treatment failure.

Eflornithine, today rarely used alone, is difficult to administer as treatment requires trained health staff and an extended hospital stay (56 intravenous infusions taking two hours each to administer, over 14 days, four times per day).

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
At its inception, DNDi’s short-term strategy was to make better use of existing treatments by combining drugs already in use. In September 2009, DNDi and partners launched the first new treatment for sleeping sickness in 25 years: nifurtimox and eflornithine combination therapy (NECT). NECT was included on the WHO Essential Medicines List (EML) in 2009, and extended to the EML for children in 2013. Since June 2013, all countries endemic to T.b. gambiense are using NECT as first-line treatment for second stage HAT, with the exception of Nigeria.

As a medium-term strategy, DNDi initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases. This resulted in the rediscovery of fenixinidazole, which completed Phase I clinical development in 2011. Fenixinidazole entered a pivotal Phase II/III study in 2012 and is currently recruiting patients in the DRC. Two complementary studies will examine efficacy and safety in adults with stage 1 and early stage 2 HAT, and children aged 6-14 years. Sanofi is the industrial partner for this project.

In order to build a strong pipeline for long-term drug discovery, DNDi initially established a HAT Lead Optimization Consortium resulting in the identification of the Oxaborole SCYX-7158. SCYX-7158 successfully progressed through pre-clinical development, entering Phase I clinical development in early 2012, which is nearing completion. Other backup compounds were evaluated by the consortium and remain available for further development if necessary.

In addition, DNDi supports the HAT Platform that was launched in Kinshasa, Democratic Republic of the Congo (DRC) in 2005. The HAT Platform is a clinical research and access-supporting network that brings together key players in the fight against sleeping sickness from Angola, the Central African Republic, Chad, DRC, Republic of the Congo, Sudan, South Sudan, Uganda and those involved in HAT from the international research arena.

By 2018, DNDi aims to deliver from its HAT-specific portfolio:

→ An oral, safe, effective treatment to be used for both stage 2 and stage 1 HAT

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