



## Fexinidazole recommended for sleeping sickness

The approval of an oral treatment for human African trypanosomiasis could be one of the last milestones en route to ambitious elimination targets. Talha Burki reports.

For the trial of fexinidazole see  
Articles *Lancet* 2018;  
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On Nov 16, 2018, the European Medicines Agency (EMA) announced that it had adopted a positive scientific opinion of fexinidazole. The treatment for human African trypanosomiasis caused by *Trypanosoma brucei gambiense* is the first new chemical entity to be developed by the Drugs for Neglected Disease Initiative (DNDi). It is the tenth medication to be recommended by the EMA under article 58, a mechanism designed for drugs intended for use outside the EU. As *The Lancet Infectious Diseases* went to press, a meeting at WHO was scheduled to discuss how to incorporate fexinidazole within new interim guidelines for the treatment of human African trypanosomiasis.

"When we started working on fexinidazole, melarsoprol was still the main drug to treat the second stage of gambiense sleeping sickness", recalls Olaf Valverde Mordt (DNDi, Geneva, Switzerland). Melarsoprol is a highly toxic arsenic derivative; it entails intravenous injections for at least 10 days and patients run the risk of reactive encephalopathy, which is often fatal. It remains the first-line treatment for the advanced stage of the rhodesiense form of sleeping sickness that accounts for roughly 2% of the total burden of disease.

The introduction of nifurtimox and eflornithine combination therapy (NECT) in 2009, transformed the outlook for gambiense sleeping sickness. However, it requires multiple intravenous infusions, which means that it can only be administered by specialised staff, hardly ideal for a disease that affects remote rural districts of sub-Saharan Africa, and its bulk makes it difficult to transport and store. Fexinidazole is an oral treatment. It comes in a small box of 24 tablets, to be taken once per day with food for 10 days.

A 2017 trial published in *The Lancet* compared fexinidazole with NECT in late-stage gambiense human African trypanosomiasis. At 18 months, treatment success rates were 98% for NECT and 91% for fexinidazole. This met the criteria for non-inferiority. "Fexinidazole shows superb efficacy in stage one and early stage two disease; there are some relapses in very advanced disease, but those patients can be cured by NECT", explains Valverde. Fexinidazole might soon be superseded—DNDi is running clinical trials on acoziborole, a new drug to treat gambiense sleeping sickness with a single course of three pills.

24 nations in sub-Saharan Africa are endemic for gambiense human African trypanosomiasis. About 80% of all cases occur in the Democratic Republic of the Congo (DR Congo). The 2012 London Declaration on Neglected Tropical Diseases targeted the elimination of gambiense human African trypanosomiasis as a public health problem by 2020. This aim was defined as cutting prevalence to less than one case per 10 000 population in 90% of endemic foci and reducing the global burden to fewer than 2000 cases. The latter goal has already

been attained and progress towards the former is very encouraging.

In 1998, reported cases of sleeping sickness had reached 37 385. The actual disease burden was estimated to be somewhere around 300 000. By 2017, the number of reported cases had fallen to 1447, a figure that probably represents about a third of the true burden. "The decrease in cases is real; there has been a strong effort to reinforce surveillance of the disease and our knowledge of the epidemiological situation is much better now", explains José Ramón Franco Minguell (WHO, Geneva, Switzerland). Experts are confident that the endemic areas have mostly been mapped. "With the current surveillance system, we do not think there are hidden spots with large numbers of undiscovered cases", said Minguell.

More than 1300 facilities in endemic regions are now equipped to diagnose and treat sleeping sickness. In many foci, prevalence has fallen below the one in 10 000 target. "In the last few years, vector control has started to play a large role", notes Stephen Torr (Liverpool School of Tropical Medicine, UK). "It has been used in Chad, Guinea, Uganda, and DR Congo, countries which represent a large number of cases of the disease, and the epidemiological and empirical evidence suggests that it can make an important contribution to controlling gambiense sleeping sickness."

The advent of so-called tiny targets has greatly simplified vector control. By contrast with the man-sized traps of the past, tiny targets are about the size of a handkerchief. They are impregnated with insecticide and dotted at regular intervals along the banks of rivers rich in tsetse flies. Studies have found that the



A Crump. Tid. Who/Science Photo Library

introduction of tiny targets led to reductions in the vector populations of 80% in Guinea and 90% in Uganda. "Tsetse flies have a very slow reproduction rate so you do not have to kill that many to have a big impact on the population, and the transmission dynamics are such that you do not have to get rid of all the flies to have a big impact on the disease", said Torr.

During the 2014–16 Ebola virus disease epidemic in Guinea, active screening campaigns for sleeping sickness were halted. This resulted in a sharp rise in prevalence of the disease, but not in the areas covered by tiny targets. "It is a sustainable community intervention that offers something of a safety net when things go wrong", said Torr.

Certain regions will struggle to attain the one in 10 000 target by 2020. Unrest is partly to blame. "Insecurity in the trypanosomiasis-endemic health zone does not

facilitate control work with mobile teams", said Victor Kande, former director of the sleeping sickness programme at the DR Congo Ministry of Health and lead investigator in the fexinidazole trial. Militia activities have disrupted control efforts in DRC and the Central African Republic. The London declaration also outlined a target of zero transmission of *T brucei gambiense* by 2030. "Vector control could be crucial in helping to push us over the finishing line in terms of the 2012 goals", said Torr.

As the cases continue to fall, it will be necessary to clarify the role of asymptomatic carriers of the disease. Could they act as a source of potential infection? Unlike rhodesiense human African trypanosomiasis, the gambiense disease is assumed to be an anthroponosis. However, if it turns out that there is indeed an animal reservoir, control efforts would be complicated. There remains a need for improved diagnostics.

"We need simpler, sensitive, specific, and inexpensive tools for detecting the disease", said Minguell. "That is an important gap—the current tools are cumbersome to use with limited specificity and sensitivity." Minguell added that containment activities will have to be integrated into public health-care networks. This could be challenging, given the weakness of the health-care systems in endemic areas. Surveillance programmes will have to be maintained, which means ensuring that political engagement does not falter. Then, there is the issue of the rhodesiense form of disease. "It would be great if we could find an oral medication that could be made freely available to everyone who contracts sleeping sickness", said Torr. A trial of fexinidazole in rhodesiense human African trypanosomiasis in Malawi and Uganda is planned for 2019.

Talha Burki

## Infectious disease surveillance update

### Syphilis in Japan

6096 cases of syphilis were reported in Japan this year, as of Nov 19. This is the first time in 50 years that the annual number of cases has exceeded 6000. The highest number of cases were reported in Tokyo (1548), followed by Osaka (1043), Aichi (399), Kanagawa (314), and Fukuoka (272). The sharpest increase has been in heterosexual individuals. Authorities have been unable to identify the cause of the increase in cases; however, prevention activities continue.

### Ebola in DR Congo update

Six new confirmed cases of Ebola virus disease were reported from North Kivu province in DR Congo between Nov 24 and 30. In the same week, four deaths were reported and seven patients recovered. Since August, 2018, 434 cases have been reported as of Nov 30: 386 confirmed

and 48 probable, making it the second largest outbreak in history. Overall, 134 people have recovered and 252 have died from their illness. There continues to be some community resistance to response activities due to mistrust and false rumours.

### Yellow fever in Nigeria

A new cluster of yellow fever cases was reported in Edo state, Nigeria, on Nov 22. Since Sept 9, 2018, 36 suspected cases and eight deaths have been reported. A further 13 samples from Edo state were sent to a laboratory outside the yellow fever laboratory network. Nine of the samples tested positive and have been sent for confirmation to the WHO yellow fever reference laboratory in Senegal. Rapid response teams have been deployed to help with active case finding, sensitising health-care

workers, and determining the appropriate response. The outbreak began in September, 2017, and as of Nov 25, 3510 suspected cases have been reported across Nigeria. Of those, 74 deaths have been reported, giving a case fatality rate of 2.1%.

### Diphyllobothriasis in Chile

Six cases of diphyllobothriasis have been reported at a hospital in Puerto Octay, Chile. The infection is acquired by consuming raw fish containing tapeworms of the *Diphyllobothrium* genus. All patients reported regularly consuming raw fish, specifically ceviche. The infection causes abdominal pain, nausea, vomiting, and diarrhoea. Authorities are encouraging individuals with these symptoms to visit a health-care facility.

Ruth Zwizwai



For more on **syphilis in Japan** see <https://www.promedmail.org/post/6175741>

For more on **Ebola virus disease in DR Congo** see <https://www.promedmail.org/post/6176037>

For more on **yellow fever in Nigeria** see <https://ncdc.gov.ng/diseases/sitreps/?cat=10&name=An%20update%20of%20Yellow%20Fever%20outbreak%20in%20Nigeria>

For more on **diphyllobothriasis** see <http://outbreaknewstoday.com/fish-tapeworm-outbreak-reported-los-lagos-chile-28029/>