Sleeping sickness in West and Central Africa: is eradication just skin deep?

Fexinidazole promises to be a breakthrough in the treatment of African sleeping sickness and could help eliminate it. But it might be too early to proclaim victory just yet. There could be a previously unnoticed reservoir of disease. Adrian Burton investigates.

For the **major fexinidazole trial** see **Articles** *Lancet* 2018; **391:** 144–54

For more on the **hope surrounding fexinidazole** see https://stories.dndi.org/sleepingsickness-doctors-dream/#group-intro-752cq70HVt

For more on the **symptoms of African sleeping sickness** see **Seminar** *Lancet* 2017; **390:** 2397–409

For more on **historical treatments for African sleeping sickness** see *PLoS Negl Trop Dis* 2010; **4:** e720

For more on the **indications and effectiveness of fexinidazole** see https://www.dndi.org/achievements/fexinidazole/ and https://www.ema.europa.eu/documents/medicine-outside-eu/fexinidazole-winthrop-assessment-report_en.pdf

For more on **parasites in the skin of asymptomatic individuals** see *PLOS Biol* 2019; **17:** e3000105

For more on the **possibility of asymptomatic carriers of sleeping sickness** see *Microbes Infect* 2011; **13:** 943-52 and *PLoS Negl Trop Dis* 2014; **8:** e3349

Following the results of clinical trials published last year, the Drugs for Neglected Diseases *initiative* (DND*i*) announced on Nov 16, 2018, that fexinidazole, the first oral treatment for African sleeping sickness (or human African trypanosomiasis), had received a positive opinion from the European Medicines Agency. The product of a decade of development by the DND*i*, Sanofi, and African partners, there is hope that this new drug will not only make sleeping sickness much easier to treat, but that it will also, alongside programmes that have successfully targeted its tsetse-fly vector, finally help eradicate it. But sleeping sickness has a way of coming back just when you think it has disappeared forever. A group of researchers now believes it has discovered why—and it might just put any celebrations on hold for a while.

The approval of fexinidazole in the Democratic Republic of the Congo, communicated Jan 30, 2019, means that other West and Central African countries, where collectively about 97% of all cases of African sleeping sickness occur, might soon follow suit. This would arm health workers for the first time with a simple, safe, orally administered treatment for a condition with alarming neurological symptoms: choreiform, athetoid, oscillatory movements of the limbs or trunk, muscle fasciculation, motor weakness, ataxia, akinesia, speech disorder, and perioral and cheiro-oral reflexes, accompanied by irresistible daytime somnolescence, night-time insomnia, hallucinations, delirium, violent behaviour, agitation, rage, and mania, eventually leading to death. Treatment for the first stage of the disease (peripheral parasitaemia), as triggered by *Trypanosoma brucei gambiense*—the parasitic causal agent encountered in West and Central Africa—has until now relied on injected or infused pentamidine, a treatment that can have unpleasant side effects, including sudden hypotension, hypoglycaemia, hypocalcaemia, and tachycardia, and requiring some medical infrastructure to administer. Treatment for second-stage disease (ie, with CNS involvement) was until recently limited to the use of the arsenical compound melarsoprol—which is so toxic that 10% of patients thus treated developed post-treatment encephalopathy, half of whom died. A safer alternative that became available in the 1990s, eflornithine, demanded 56 intravenous infusions—which is impractical in many African settings. In 2009, nifurtimox-eflornithine combination therapy (NECT) started to be used, needing only 14 infusions over 7 days plus 10 days of further oral treatment, but still requiring that patients spend 10 days in hospital. Against this backdrop, fexinidazole is something of a game-changer. Administered as 24 tablets over a 10-day period, it can be curative for both first-stage and second-stage disease, although for late second-stage disease it is less effective than NECT, which remains the treatment of choice for patients with the most serious neurological symptoms. Furthermore, it has not been tested in small children or in people with very advanced disease.

Encouraging as it sounds, however, it might not be the definitive solution against sleeping sickness. "Just when you think the incidence is so low that you've broken the transmission cycle, and that mathematically the disease has got to die out, the numbers can go back up", explains Annette MacLeod, professor of parasitology at the University of Glasgow (Glasgow, UK). "Right now, fewer than 1500 new cases are being reported from Africa per year, a testimony to the effort to eliminate the disease. But we reached a similar situation back in the 1960s, and sleeping sickness sprang back after elimination measures became prohibitive for many African countries, especially those stricken with war and civil unrest. We used to think that livestock provided a reservoir of disease, but while this may be the case in some areas, we know through intensive sampling that this is not universally so for *T b gambiense*-induced disease. There could be a wild animal reservoir. But there appears to be another one that we have missed—and right under our noses. It looks like there could be a large population of asymptomatic people that no-one knew about, with the parasite hanging out in their skin."

Most textbooks suggest that those who have been bitten by an infected tsetse fly develop symptoms of first-stage disease within 3 weeks. But it is now becoming clear that people could remain asymptomatic for years, maybe decades. One report describes

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The tsetse fly, the vector of African sleeping sickness

a 62 year-old Sierra Leone-born UK resident, who last visited Africa 30 years ago, suddenly developing second-stage sleeping sickness. "Tsetse flies are not like mosquitoes that puncture you and suck your blood", explains Hamidou Ilboudo, researcher at the Institut de Recherche en Sciences de la Santé, Unité de Recherche Clinique de Nanoro (Nanoro, Burkina Faso). "Rather, they slice up your skin and suck out whatever comes…blood, lymphatic fluid, interstitial fluid, etc. So they can pick up skin dwelling parasites and transmit the disease. We believe that some people can have parasites in their skin for years but only have very low numbers of parasites in their blood. These individuals could act as asymptomatic carriers. This means that our present surveillance system, which largely relies on blood serology and parasitology tests, is not going to pick up these asymptomatic individuals, who could contribute to parasite dissemination."

MacLeod's team reports finding extravascular parasites in skin biopsies of undiagnosed individuals, and that under experimental conditions, at least, skin-infected mice are able to transmit the disease. Additionally, in field work performed in Guinea they detected the parasites consistently in the skin of people with no parasitaemia—findings reported anecdotally for now in their sponsor's magazine. This could have implications for the way surveillance of the disease is performed. Passive surveillance records only those patients who turn up sick at clinics, whereas active surveillance involves testing all people in known disease foci. "Financial pressure has resulted in a decline in active surveillance in some countries but relying on passive surveillance and neglecting the asymptomatic population could leave behind an important reservoir of disease", explains MacLeod. "It might be necessary to increase rather than decrease active surveillance. Perhaps we should be actively screening the population and treating those who are found to have asymptomatic disease, maybe with fexinidazole." This approach, however, would not be easy. Skin-biopsy screening everyone over huge areas would be a massive undertaking even in high-income countries. And how many trained personnel would then be needed to process and examine the samples collected? "We would clearly need a much simpler detection tool", concedes MacLeod. Her team is, however, already working on a rapid skin test involving the use of Raman spectroscopy. Their aim is to detect parasites by simply scanning the skin, removing the need for laboratories and trained histology technicians, and all the associated costs. "We are working hard on this and hope to have a working test by 2020."

But there is another snag. Although fexinidazole has been shown to be effective against first-stage and second-stage sleeping sickness, no clinical trials have been done to assess whether it works against parasites in the skin. However, "in preclinical studies, fexinidazole was shown to have a good distribution in the skin, so we can expect that skin parasites, assuming they are viable, would be neutralised", says Olaf Valverde, *Trypanosoma brucei rhodesiense* Research Leader with DND*i* (Geneva, Switzerland) who was involved with the preapproval clinical trial of the drug against *T b gambiense*. But even if screening millions of people with a hand-held Raman instrument were possible, and even if fexinidazole does work against skin parasites, would it not just be easier and cheaper to eradicate the tsetse fly? "But could you kill every tsetse fly across Africa?" asks Enock Matovu, Associate Professor at the College of Veterinary Medicine, Animal Resources and Bio-Security, Makerere University in Kampala, Uganda, a country where *T b gambiense* and its East African counterpart *T b rhodesiense* (for which trials with fexinidazole have not yet been undertaken) can occur together. "What happens if there are pockets we miss, and in our complacency we then lay down our tools, thinking our work done? There would still be a ready reservoir of disease in these asymptomatic individuals for any resurgent flies to spread."

Given these concerns, is a change of surveillance and elimination policy warranted? "Maybe not yet", says José Ramón Franco, Department of Control of Neglected Tropical Diseases, WHO (Geneva, Switzerland). "We need more data on the frequency of skin carriers among serologically positive, non-confirmed, and serologically negative individuals in different epidemiological situations before considering adapting our control and elimination strategies. Sleeping sickness [is currently] low-burden in terms of cases and has become a minor priority in countries suffering many other problems. Maintaining sustainable funding for this disease therefore becomes more complicated. In this context, integrating elimination activities as much as possible into regular health system activities is currently the best way to maintain elimination efforts."

A change in elimination policy might well be warranted, however, should acoziborole, a new, single-dose drug being developed by the DND*i*, live up to its promise. "If it works against skin parasites too, a single tablet might be given to everyone, along the lines of a vaccination programme, effectively wiping out every form of the disease—asymptomatic, first stage, and second stage. No need for testing, no need for anything", says MacLeod. "But that's the future."

However, a small black cloud hangs over even that bright future. New findings are beginning to suggest that animals might have asymptomatic dermal infections too. "The question is, can we treat every domestic animal?" asks MacLeod. "And what about wild animals? Putting this disease to sleep might just be a little trickier than anyone had imagined."

Adrian Burton

For more on **skin-living parasites in undiagnosed individuals** see *eLife* 2016; **5:** e17716