

Melarsoprol-Free Drug Combinations for Second-Stage Gambian Sleeping Sickness: The Way to Go

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(See the article by Priotto et al. on pages 1435–42)

There is little doubt that human African trypanosomiasis (HAT) would stand on the podium of a most-neglected diseases contest, despite the dishearteningly high number of other candidates. The disease is present solely in sub-Saharan Africa. The vast majority of patients are very poor and live in remote rural areas of countries recently or currently affected by deep social unrest, such as Angola, the Democratic Republic of Congo, the Republic of Congo, Uganda, and Sudan. In these countries, HAT due to *Trypanosoma brucei gambiense* reached epidemic proportions during the 1990s, following decades of deficient surveillance and control activities. Fortunately, the improved political situation in some countries and the conjugated efforts of national disease-control programs, nongovernmental organizations, and the World Health Organization (WHO) allowed the trend to be reversed. Despite some major uncertainties (e.g., the proportion of patients who are not covered by existing control and surveillance programs is unknown), it is now estimated

by the WHO that 50,000–70,000 cases of *T. brucei gambiense* HAT occur annually in Africa [1].

The disease is transmitted via the bite of tsetse flies (*Glossina* species). *T. brucei gambiense* HAT is a slowly evolving disease (it progresses over months to years) that leads to death in the absence of treatment. After an initial stage during which the trypanosomes remain confined to the hemolymphatic system (first-stage disease), the parasites invade the CNS, leading to the various neuropsychiatric disorders, such as confusion, convulsions, speech and walking disturbances, sleep disturbances, and lethargy, of the second (or meningoencephalitic) stage.

The diagnosis of HAT is cumbersome and follows a 3-step approach: screening, parasitological confirmation (microscopic examination of lymph node and blood specimens), and staging (examination for trypanosomes and for increased WBC counts in the CSF). This staging step is essential, because the means of treating first- and second-stage disease differ widely. The treatment of first-stage illness relies on daily intramuscular injections of pentamidine for 7–10 days. This treatment is relatively safe and practical, allowing for ambulatory treatment of patients. Pafuramidine maleate (DB289), given orally for 10 days, is being developed as an alternative to pentamidine that may facilitate

home-based treatment of patients with first-stage disease.

The treatment of second-stage illness is much more problematic. It has relied on arsenical derivatives since the beginning of the 20th century; in particular, it has relied on melarsoprol since 1949. Melarsoprol is given by slow intravenous administration in 3–4 series of 3–4 injections (with the old schedules) or through 10 consecutive injections (with the modern schedule). With either schedule, 3%–6% patients die during or after treatment of an encephalopathic syndrome (severe cerebral edema or bleeding). Other adverse effects can also be life-threatening, including liver toxicity, severe enterocolitis, and diffuse peripheral neuropathy. The high toxicity of melarsoprol has been repetitively reported for decades. This may have induced a certain sense of tolerance or resignation among some, but certainly not among first-line caregivers who have to report patients' deaths to relatives. Moreover, high failure rates associated with melarsoprol have been reported from several endemic foci in Angola, the Democratic Republic of Congo, Sudan, Central African Republic, and Uganda [2].

Because the disease is fatal if left untreated, the use of melarsoprol was acceptable in the absence of safer alternatives. This is no longer the case. Eflornithine (difluoro-methyl-ornithine), an ornithine decarboxylase inhibitor, was

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first used to treat patients with HAT due to *T. brucei gambiense* >20 years ago [3]. The recommended dosage of 400 mg/kg divided in 6-hourly intravenous infusions for 14 days was shown to be efficient in adults, but higher doses must be given in children [4]. For almost 2 decades, patients with HAT had no access to eflornithine because of high price or lack of production. This unacceptable situation fueled a strong advocacy campaign led by Médecins Sans Frontières and other organizations in the late 1990s. Aventis Pharma (now Sanofi-Aventis) and the WHO signed 2 consecutive 5-year agreements in 2001 and 2006 that included financial support for control and research programs and the donation of the key antitrypanosomal drugs (pentamidine, melarsoprol, and eflornithine). Eflornithine has therefore been available in the field and widely used in control programs run by nongovernmental organizations since 2001. In southern Sudan, 4222 patients with second-stage HAT were treated with eflornithine by Médecins Sans Frontières and Malteser during the period 2001–2006. In these settings, the treatment was safe (in-hospital case-fatality rate, 1.1%) and effective (relapse rate, <10%) (unpublished data). Two studies demonstrated the significantly lower rates of death and severe adverse effects with eflornithine, compared with melarsoprol, in consecutive cohorts of Congolese and Sudanese patients [5, 6]. Therefore, eflornithine is the drug of choice for second-stage *T. brucei gambiense* HAT. However, it remains to be seen whether these good results can be replicated in the more simple settings of government-run treatment centers.

The introduction of eflornithine as first-line treatment to replace melarsoprol for patients with second-stage disease who are receiving treatment in hospitals or health centers run by national control programs is progressing slowly. This slowness is mainly associated with factors that are inherent to the complex mode of eflornithine administration, which involves

substantial logistic constraints and indirect costs (e.g., acquisition and transport of infusion materials from the capital to the field), and the need for sufficient and trained human resources to assume adequate round-the-clock nursing care. Training workshops for regional nurses have been organized by the WHO. Medical kits containing all necessary drugs and infusion materials have been prepared and will be available at no cost for national control programs. These initiatives should facilitate—to some extent—wider field use of eflornithine, but its complicated treatment regimen (56 slow infusions administered over 14 days) will remain a challenge to its widespread implementation.

There is another concern with eflornithine. Sooner or later, the widespread—and, therefore, less controlled—use of eflornithine as monotherapy is likely to lead to parasite resistance, which would have catastrophic consequences. It is thus vital to protect the efficacy of this drug by using it in combination regimens, an approach that has been successful for numerous infectious diseases, such as HIV infection, tuberculosis, and malaria. The most promising option today is the combination of eflornithine with oral nifurtimox, a nitrofurantoin compound registered for treatment of American trypanosomiasis. Nifurtimox has shown some degree of effectiveness against second-stage HAT, but its use as monotherapy should be discouraged, because most studies have reported high treatment failure rates [7, 8]. Nifurtimox has also been used in combination with melarsoprol but published data are very limited. The melarsoprol-nifurtimox combination was shown to be associated with a lower risk of relapse than melarsoprol alone in one study [8], but there are serious concerns about the safety of this combination [9].

Preliminary data on eflornithine-nifurtimox combination therapy originate from 2 studies (an aborted 3-arm randomized study and a case series) led by Epicentre in northwestern Uganda [9, 10]. In total, 48 patients received 7 days of in-

travenous eflornithine (400 mg/kg per day given in 4 infusions) and 10 days of oral nifurtimox (15–20 mg/kg per day). The treatment was well tolerated, with no relapses observed during the 24-month follow-up period. These promising results led Epicentre, Médecins Sans Frontières, and the Ministry of Health of the Republic of Congo to launch, in Nkayi, a randomized phase III study called the Nifurtimox-Eflornithine Clinical Trial (NECT), which compared eflornithine-nifurtimox therapy with the standard 14-day course of eflornithine therapy. The total dose of eflornithine in the eflornithine-nifurtimox arm was the same as that used in the 2 preliminary studies, but the drug was administered in 2 infusions per day only. This decision was justified by the potentially large beneficial impact on feasibility—and, therefore, on field application—of a simplified treatment schedule that does not require full-time presence of qualified nurses (14 eflornithine infusions were given over 7 days, as opposed to 56 infusions given over 14 days).

The NECT was designed as a randomized, open-label, noninferiority trial with a sample size calculated at 280 patients. This objective was not reached in Nkayi because of a low enrollment rate. The publication of partial data in this issue of *Clinical Infectious Diseases* may raise some critical voices, but the researchers' decision must be interpreted in the light of the atypical context of HAT and the urgent need for data on treatment of second-stage illness [11]. The authors are to be congratulated for the excellent study design and for the exceptionally high rate of follow-up (95%), which highlights the dedication of the research team in the field. Fifty-two and 51 patients were treated with eflornithine-nifurtimox and standard eflornithine, respectively. Cure rates were excellent (> 94%) in both arms. No HAT- or treatment-related deaths occurred during hospitalization or during follow-up in the eflornithine-nifurtimox arm. The rate of hematologic (in particular, severe neutropenia) and neuropsychiatric adverse ef-

fects appeared to be low in the eflornithine-nifurtimox arm. As stated by the authors, for the time being, none of these findings should be considered as proof.

Since 2005, the NECT has become a multiple-center trial, with a gradual extension to 5 other field sites (3 in the Democratic Republic of Congo and 2 in Uganda), under the coordination of the Drugs for Neglected Diseases initiative and WHO–Tropical Diseases Research, with several other partners (Epicentre, Médecins Sans Frontières, the Swiss Tropical Institute, and the national HAT control programs of the Democratic Republic of Congo and Uganda). The NECT is the only ongoing clinical trial for second-stage HAT, and thus, it provides the only perspective toward improved treatment in the next 5 to 10 years. Research and development of new HAT drugs have been revived—for instance, through the efforts of the Drugs for Neglected Diseases initiative and the University of North Carolina consortium—but no new drug candidate for treatment of for second-stage illness has reached clinical development. If the promising results presented by Priotto et al. [11] are confirmed at the other study sites (the definitive results of this multiple-center study will not be available before mid-2008), the eflornithine-nifurtimox com-

bination therapy should become the first-line treatment of choice for second-stage *T. brucei gambiense* HAT. In the meantime, standard eflornithine therapy should be more widely used. Nifurtimox, used as part of combination treatment, should already be available for compassionate use in patients who experience relapse who, otherwise, have nothing other than death to face.

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References

1. World Health Organization. Human African trypanosomiasis (sleeping sickness): epidemiological update. *Wkly Epidemiol Record* **2006**; 81:71–80.
2. Brun R, Schumacher R, Schmid C, Kunz C, Burri C. The phenomenon of treatment failures in human African Trypanosomiasis. *Trop Med Int Health* **2001**; 6:906–14.
3. Van Nieuwenhove S, Schechter PJ, Declercq J, Bone G, Burke J, Sjoerdsma A. Treatment of gambiense sleeping sickness in the Sudan with oral DFMO (DL-alpha-difluoromethylornithine), an inhibitor of ornithine decarboxylase; first field trial. *Trans R Soc Trop Med Hyg* **1985**; 79:692–8.
4. Pepin J, Khonde N, Maiso F, et al. Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *Bull World Health Organ* **2000**; 78: 1284–95.
5. Chappuis F, Udayraj N, Stietenroth K, Meussen A, Bovier PA. Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. *Clin Infect Dis* **2005**; 41: 748–51.
6. Balasegaram M, Harris S, Checchi F, Ghorashian S, Hamel C, Karunakara U. Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo. *Bull World Health Organ* **2006**; 84:783–91.
7. Pepin J, Milord F, Meurice F, Ethier L, Loko L, Mpia B. High-dose nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness: an open trial in central Zaire. *Trans R Soc Trop Med Hyg* **1992**; 86:254–6.
8. Bisser S, N'Siesi FX, Lejon V, et al. Equivalence trial of melarsoprol and nifurtimox monotherapy and combination therapy for the treatment of second-stage *Trypanosoma brucei gambiense* sleeping sickness. *J Infect Dis* **2007**; 195:322–9.
9. Priotto G, Fogg C, Balasegaram M, et al. Three drug combinations for late-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Uganda. *PLoS Clin Trials* **2006**; 1:e39.
10. Checchi F, Piola P, Ayikoru H, Thomas F, Legros D, Priotto G. Nifurtimox plus eflornithine for late-stage *Trypanosoma brucei gambiense* sleeping sickness in Uganda: a case-series. *PLoS Neglected Dis* (in press).
11. Priotto G, Kasparian S, Nguouama D, et al. Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* **2007**; 45: 1435–42 (in this issue).