Combination Therapy for Sleeping Sickness: A Wake-Up Call

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(See the article by Bisser et al., on pages 322–9.)

Ours is a smaller world than that of previous generations. Given humankind’s insatiable desire to change places for all kinds of reasons and through all kinds of routes, clinicians in developed countries are increasingly exposed to diseases that used to be considered “exotic.” Cases of African trypanosomiasis, the archetype of such diseases ever since Joseph Conrad’s *Heart of Darkness*, are now seen in the Western world—albeit rarely—in tourists who have visited the game parks of East and southern Africa [1], where they acquired *Trypanosoma brucei rhodesiense* infection, and in asylum seekers or long-term expatriates from Central Africa, where *T. brucei gambiense* sleeping sickness reemerged 10 years ago [2].

*T. brucei rhodesiense* trypanosomiasis is a zoonosis, with cattle being the main reservoir, and humans are occasionally infected through an animal-fly-human cycle; interhuman transmission is rare, except during epidemics, such as in the Busoga focus of Uganda 20 years ago [3]. The disease is characterized by a short incubation period, a high degree of parasitemia (which facilitates parasitological diagnosis by use of blood smears), early complications, and rapid progression (within weeks) to central nervous system infection. Thus, this subspecies kills its human hosts too rapidly for its own interest, but cattle and game animals, which tolerate it fairly well, allow it to prosper [4]. *T. brucei rhodesiense* trypanosomiasis is found only in East and southern Africa, and <1000 cases are reported each year to the World Health Organization (WHO) [5]. In recent years, most cases among tourists were acquired in Serengeti Park [1].

In contrast, *T. brucei gambiense* shares with HIV a key epidemiological parameter: a very long duration of infection, which explains its ability to cause dramatic epidemics [4]. Most humans are infected through a human-fly-human cycle, and animals (mostly pigs) probably contribute to the dynamics of sleeping sickness only at the very end of an epidemic, when the human reservoir has dwindled. After a long (months or years) asymptomatic period, patients initially develop intermittent fevers (corresponding to successive waves of parasites expressing new variant surface glycoproteins, a process known as “antigenic variation”) and then slowly develop classical sleeping sickness, which is characterized by somnolence, persistent headaches, occasional psychiatric symptoms, and a chronic lymphocytic meningoen cephalitis. Because the parasitemia is low grade and intermittent, it may be difficult to document trypanosomes in blood smears, but cervical lymph-node aspirates and the cerebrospinal fluid (CSF) can be examined for trypanosomes. During the early 20th century, after mass migrations organized to satisfy the need of the European colonizers for manpower, *T. brucei gambiense* trypanosomiasis wiped out entire communities in Central Africa. After decades of active case finding to reduce the human reservoir, it was nearly eliminated by the late 1950s. During the mid-1990s, it reemerged in the 2 Congos, Angola, Sudan, and northern Uganda, where civil wars or strife hampered disease control long enough for the human reservoir to expand [4, 6, 7]. After sustained efforts by the WHO, national control programs, nongovernmental organizations, and the private sector, this trend has fortunately been reversed: the number of cases reported in the Democratic Republic of Congo (DRC), which peaked at 26,318 in 1998, decreased to 10,369 in 2004, and Angola, which had notified 8291 cases in 1997, reported 2280 cases in 2004 [5]. This indicates, along with the similar results attained during the first half of the 20th century, that *T. brucei gambiense* trypanosomiasis could be eliminated, provided that control efforts are maintained long enough (i.e., even after the incidence reaches low levels, when the cost per case detected will be high) and that a serious
effort is made at some point to address the persistence of infections in domestic animals.

Diagnosing African trypanosomiasis requires the documentation of trypanosomes in blood smears, lymph node aspirates, or CSF. For *T. brucei gambiense* trypanosomiasis, a card agglutination serological assay, available from the Institute of Tropical Medicine in Antwerp, Belgium, can also be used. To select the appropriate treatment, 2 questions need to be addressed. First, whether the infecting pathogen is *T. brucei gambiense* or *T. brucei rhodesiense* (the 2 subspecies are morphologically identical) can easily be sorted out through geography, because Uganda is the only country where both *T. brucei rhodesiense* (in the southeast) and *T. brucei gambiense* (in the northwest) are found. When in doubt (e.g., a traveler visits several countries of endemicity), identification of the serum-resistance-associated gene provides definitive proof of *T. brucei rhodesiense* infection [8]. Second, CSF needs to be examined in all patients, to distinguish late-stage (CSF white blood cell count >5 cells/μL and/or CSF trypanosomes) from early-stage (normal CSF) disease. For patients with *T. brucei rhodesiense* trypanosomiasis, the lumbar puncture (LP) is delayed until after 1 or 2 doses of suramin have been administered, to avoid iatrogenically seeding the CSF.

Patients with early-stage disease are treated with suramin (*T. brucei rhodesiense*) or pentamidine (*T. brucei gambiense*). For late-stage *T. brucei rhodesiense* sleeping sickness, melarsoprol is the only effective drug. Patients with late-stage Gambian trypanosomiasis can be treated with either eflornithine (available from the WHO) or melarsoprol. Details on various regimens have been given elsewhere [9]. After treatment, patients need to be followed up with LPs every 6 months for 2 years, to identify relapses requiring further treatment. Melarsoprol, a trivalent arsenical drug developed single-handedly by Ernst Friedheim after World War II, remains extremely effective against trypanosomes but is quite toxic: 5%–10% of patients develop a reactive encephalopathy, probably because the rapid destruction of trypanosomes induces an autoimmune CNS vasculitis [10]. Eflornithine, the only addition to the short list of trypanocidal drugs in 60 years, is as effective as melarsoprol but, presumably because it kills parasites more slowly, is much better tolerated [11]. Its major drawback is the need for intravenous administration every 6 h for 14 days—not a big issue in Manhattan, but more problematic in rural hospitals of the DRC or southern Sudan. Furthermore, as for many infectious diseases, the emergence of resistance to these drugs is causing considerable concern: high frequencies of treatment failure have been reported for melarsoprol in Angola, Uganda, and Sudan and for eflornithine in Uganda [7, 11]. Thus, the addition of novel treatments would be most welcome, if only as second-line options for patients who experience relapse.

The idea of using nifurtimox for the treatment of African trypanosomiasis has been around for a long time. If it works against *Trypanosoma cruzi* infection, then perhaps it will be effective against African trypanosomes? Nifurtimox has the advantage of being administered orally. Unfortunately, when used as monotherapy, nifurtimox has been disappointing, with approximately half of patients experiencing relapse after treatment [12]. Nifurtimox also has substantial gastrointestinal and neurological toxicity. This unfavorable therapeutic index led to benznidazole being preferred to nifurtimox in the treatment of Chagas disease, and nifurtimox is no longer marketed in several South American countries [13, 14].

Thus, the potential niche for nifurtimox in the treatment of African trypanosomiasis would be as a component of combination therapy, with either melarsoprol or eflornithine. Combination therapy could lead to lower doses of trypanocidal drugs being used, perhaps decreasing their toxicity, or avoiding altogether the use of intravenously administered drugs, should the combination of nifurtimox and oral eflornithine prove to be more effective than monotherapy with either drug. Moreover, combination therapy might provide solutions for areas of endemicity in which failures of melarsoprol or eflornithine monotherapy are common.

The authors of the randomized controlled trial whose results are reported in the current issue of the *Journal* [15] are to be congratulated for conducting an important trial in the very difficult field conditions of the DRC (then at war) and for using sound analytical methods such as the Kaplan-Meier plot, which allows the duration of follow-up for each patient to be taken into consideration. This approach is infinitely better than considering all patients who never come for follow-up LP as being cured, especially when half the patients never show up [16]. Four important findings need to be emphasized. First, the combination of nifurtimox and melarsoprol was more effective than what used to be the standard regimen of melarsoprol monotherapy. Despite many drug combinations having been shown to be additive in murine models, this is the first time that the superiority of a drug combination has been documented in human African trypanosomiasis. Second, nifurtimox given for only 8 days was much better tolerated than were the longer courses (30–60 days) used in previous trials and in the treatment of American trypanosomiasis [12, 13]. Third, one-third of the patients experiencing relapse (as in previous trials), nifurtimox monotherapy should be definitively abandoned. Fourth, Bisser et al.’s trial adds to the existing evidence that graded dosing of melarsoprol monotherapy is associated with a higher frequency of relapses [17], and such regimens should also be abandoned.

What should be the next steps taken in defining more precisely the potential contribution of nifurtimox-melarsoprol combinations in the treatment of African trypanosomiasis? First and foremost, a larger 2-arm randomized controlled trial should be organized to compare the combination
with the melarsoprol monotherapy regimen now seen as the standard one (2.2 mg/kg daily for 10 consecutive days) [18], to confirm Bisser et al.’s findings and to delineate with narrower confidence intervals the failure rate associated with the nifurtimox-melarsoprol combination (Bisser et al.’s estimate is based on only 64 observations). Second, the combination should be tested in areas in which resistance to melarsoprol is common: it is in these foci that the combination could be truly life-saving, and the relative resistance of local T. brucei gambiense strains to melarsoprol could potentially hamper the additive or synergistic effect of the combination. Third, the combination should be tested among those rare but unfortunate patients with T. brucei rhodesiense trypanosomiasis who experience relapse twice after courses of melarsoprol, for whom there is, at the moment, no effective treatment. There is some urgency in pushing ahead this research agenda, not only for the sake of patients who could benefit from better treatments but also to avoid the production of nifurtimox being abandoned. Fortunately, Bayer is already supporting efforts to control African trypanosomiasis by donating suramin to the WHO and has indicated its willingness to support a label extension for nifurtimox and make it available for patients with African trypanosomiasis.

References