Tropical Medicine and International Health doi:10.1111/j.1365-3156.2007.01999.x

VOLUME 13 NO 2 PP 265–271 FEBRUARY 2008

# Eflornithine is a cost-effective alternative to melarsoprol for the treatment of second-stage human West African trypanosomiasis in Caxito, Angola

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**Summary**

OBJECTIVE To compare the cost-effectiveness of eflornithine and melarsoprol in the treatment of human African trypanosomiasis.

METHOD We used data from a Médecins Sans Frontières treatment project in Caxito, Angola to do a formal cost-effectiveness analysis, comparing the efficiency of an eflornithine-based approach with melarsoprol. Endpoints calculated were: cost per death avoided; incremental cost per additional life saved; cost per years of life lost (YLL) averted; incremental cost per YLL averted. Sensitivity analysis was done for all parameters for which uncertainty existed over the plausible range. We did an analysis with and without cost of trypanocidal drugs included.

RESULTS Effectiveness was 95.6% for melarsoprol and 98.7% for eflornithine. Cost/patient was 504.6 for melarsoprol and 552.3 for eflornithine, cost per life saved was 527.5 USD for melarsoprol and 559.8 USD for eflornithine without cost of trypanocidal drugs but it increases to 600.4 USD and 844.6 USD per patient saved and 627.6 USD and 856.1 USD per life saved when cost of trypanocidal drugs are included. Incremental cost-effectiveness ratio is 1596 USD per additional life saved and 58 USD per additional life year saved in the baseline scenario without cost of trypanocidal drugs but it increases to 8169 USD per additional life saved and 299 USD per additional life year saved if costs of trypanocidal drugs are included.

CONCLUSION Eflornithine saves more lives than melarsoprol, but melarsoprol is slightly more cost-effective. Switching from melarsoprol to eflornithine can be considered as a cost-effective option according to the WHO choice criteria.

**keywords** human African trypanosomiasis, *Trypanosoma brucei gambiense,* eflornithine, melarsoprol, cost-effectiveness

## Introduction

Melarsoprol is still the most widely used drug for treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis (HAT) despite its toxicity, with an iatrogenic mortality between 3% and 10%. An alternative short-course melarsoprol regimen showed equal effectiveness but also similar encephalopathy and death rates (Burri *et al.* 2000; Schmid *et al.* 2004, 2005). Robays *et al.* (2007) in a qualitative study on perception of HAT control in Democratic Republic of Congo (DRC) showed how people's awareness of melarsoprol toxicity leads to poor acceptance of active screening programmes, and may partly explain why HAT control programmes are ineffective in a number of high prevalence settings such as the provinces of Bandundu and Kasai in the DRC.

DL-Alpha-difluoromethylornithine (DFMO) (eflornithine) was proposed as an alternative to melarsoprol, but decision makers long objected against its use as first-line drug in the treatment of second-stage HAT (Louis *et al.* 2003). Main arguments put forward were its allegedly prohibitive cost, partly due to the need for a substantial number of infusions, the high cost of the drug and the need for additional skilled staff to maintain IV perfusions around the clock in a ward full of HAT patients. Other arguments evoked are the risks of sepsis when nursing care is suboptimal and the danger of emerging resistance if eflornithine is used in monotherapy. Politi *et al.* (1995) considered first-line treatment with eflornithine not a

cost-effective option. Feasibility of eflornithine-based treatment in field centres was demonstrated by Médicins Sans Frontières (MSF) in Kiri, Kajo-Keji County, Southern Sudan (Chappuis *et al.* 2005). Free donation of eflornithine by the drug company Aventis, now Sanofi Aventis removed one of the main obstacles. Also the recently emerging high relapse rates with melarsoprol documented in Uganda (Legros *et al.* 1999; Matovu *et al.* 2001), and in M'banza Congo in Angola (Stanghellini & Josenando 2001) push programmes to reconsider their treatment strategies, as recently done in Angola and the Central African Republic. We used data from a Médecins Sans Frontières treatment project in Caxito, Angola to do a formal cost-effectiveness analysis (CEA), comparing the efficiency of an eflornithine-based approach with melarsoprol.

## Methods

### Study site and background

Between 2002 and 2006 MSF Belgium implemented a HAT control programme in Caxito, Angola, treating 1200 sleeping sickness patients, of whom 690 were in second stage. In 2004, eflornithine was introduced for treatment of second-stage HAT because the high toxicity of melarsoprol was considered unacceptable. The sources for the data were programme input and output data provided by the MSF programme in Angola. As the sleeping sickness ward in Caxito was managed separately from the other wards in the hospital, all reported data on staff and cost items were specifically related to the care for sleeping sickness patients. We compared formally the efficiency of HAT treatment based on a regimen of 14 days IV (100 mg/kg q.i.d.) eflornithine (Sanofi Aventis) compared to melarsoprol (Sanofi Aventis), three series of four injections with 5 days of rest between each series, with a total dose of 32.4 mg/kg, together with prednisone 1 mg/kg/day. We assumed that a case of relapse would be retreated with the other drug. For the CEA, we used a health care system perspective and only examined the cost of patient care for HAT. This did not include the cost of active case finding and diagnosis. Only blinded routinely available data were used for the study. Permission was granted by the Ministry of Health of Angola.

### Costing of HAT care

All costs were converted to 2005 US dollars.

We conducted the baseline CEA assuming that the HAT-specific drugs (trypanocides) were free of charge, as Sanofi Aventis has been donating them since 2001 to the HAT control programmes per 5 year agreement. But, in the sensitivity analysis, we checked a scenario that included the cost of the trypanocides, rated at the preferential pricing level that was charged before the donation programme existed: 64 USD per average adult course for melarsoprol (plausible range 50–100 USD) and 288 USD (plausible range 250–400 USD) for eflornithine (Lutumba 2005). The cost and quantities of all non-HAT-related drugs was obtained from records kept by the MSF supply-centre at the prices of 2005.

Transportation costs for most drugs were estimated at 7% of their value based on MSF freight reports. Because IV fluids and eflornithine are bulkier and heavier than other drugs, we used a freight cost per kg for those two items based on the prices from the actual freight reports (€ 1 per kg). The MSF technical guideline on HAT was used to estimate the quantities of drugs and medical supplies (infusion sets, dressing material, etc.) used per patient, including the treatment for major complications (arsenical encephalopathy). Data obtained from the suppliers were cross-checked with the data on the actual drug consumption and the trends in patient case load, obtained from the pharmacy records in Caxito.

Information on number and function of staff over the years, wages and benefits were taken from the MSF administration records. As first- and second-stage HAT patients were treated in the same ward by the same staff and first-stage patients are treated with pentamidine, have few side effects and need little nursing care. Therefore, we assumed that 80% of staff time was devoted to the treatment of second-stage patients. The HAT care centre was staffed by one-half Full Time Equivalent (FTE) medical doctor, one-fourth FTE nurse and one-fourth FTE logistician.

Initially HAT patients were admitted in hospital tents while a ward was being built. The building became only operational at the end of the programme, but we included its cost evenly over the period for our cost estimation. The real building cost for this ward was spread over 20 years and we used an annualization factor with a discount rate of 10%. We assumed a bed occupancy rate of 80%.

### Effectiveness

Data on clinical outcomes (cure, side effects, mortality) and patient characteristics such as age and sex had been entered in Caxito by the clinician in charge in a database specially developed for the care of sleeping sickness (Epitryp, V.3, EPICENTRE). For the CEA we could extract all relevant outcome data from this database. For all clinical outcomes except for the relapse rate, we used the actual value observed in Caxito in the baseline CEA analysis, and obtained a range of

plausible values from the literature (Burri *et al.* 2000; Blum *et al.* 2001; Burri & Brun 2003). We used a baseline case fatality rate of 1% (plausible range 0.5–2%) for eflornithine. For melarsoprol treatment we used a proportion of encephalopathy of 10% (plausible range 3–20%) and a case fatality rate due to the encephalopathy of 40% (plausible range 20–100%). For the model we assumed that all melarsoprol-related deaths were caused by arsenical encephalopathy.

Because clinical follow-up was incomplete in the Caxito treatment centre, we could not derive the relapse rates for melarsoprol and eflornithine directly from the data. Therefore, we used published relapse rates from the literature in the base case scenario. As published relapse rates vary, we used a baseline of 7% for both drugs with a plausible range of 1–10 for eflornithine and of 3–30 for melarsoprol (Pepin *et al.* 1994, 1989, 2000; Burri *et al.* 2000; Blum *et al.* 2001; Burri & Brun 2003).

Years of life lost averted (equivalent to years of life gained) was used as the endpoint for the effectiveness evaluation, as there was insufficient information on HAT-related disability to use the Disability Adjusted Life Year as an endpoint. To establish YLL due to HAT disease, we used the age distribution of our patients and used the formula with non-zero discounting and age weighting given by Murray and Lopez (1996) and used in the Global Burden of Disease project (GBD) as follows:

$$\mathrm{YLL} = NCe^{(ra)} \Big/ (\beta + r)^2 \Big[ e^{(\beta+r)(L+a)}[-(\beta + r)(L + a) - 1] - e^{(\beta+r)a}[(\beta r)a - 1] \Big]$$

where $r$ is the discount rate (GBD standard value is 0.03), $C$ is the age-weighting correction constant (GBD standard value is 0.1658), $\beta$ is the parameter from the age-weighting function (GBD standard value is 0.04). We used the spreadsheet available from the WHO website (http://www.who.int/evidence).

### Model

We built a decision tree using the software TREEAGE PRO 2006© (TreeAge Software, Inc., Figure 1). Sensitivity of all parameters for which uncertainty existed was analysed over the plausible range (mentioned between brackets in the Results and Methods section). As endpoints we calculated cost per death avoided; incremental cost per additional life saved; cost per YLL averted; and incremental cost per YLL averted.

## Results

### Costing

In case of melarsoprol treatment, the cost of baseline adjuvant drugs was 19.7 USD, mainly due to oral prednisolone (plausible range 10–30 USD). An episode of encephalopathy required an additional 37.8 USD for specific drugs (plausible range 20–50 USD). Eflornithine treatment, on the other hand, required baseline adjuvant drugs and medical supplies at a cost of 92.2 USD. We increased the transportation cost to compensate for the 16 kg extra weight of eflornithine and IV solutions.

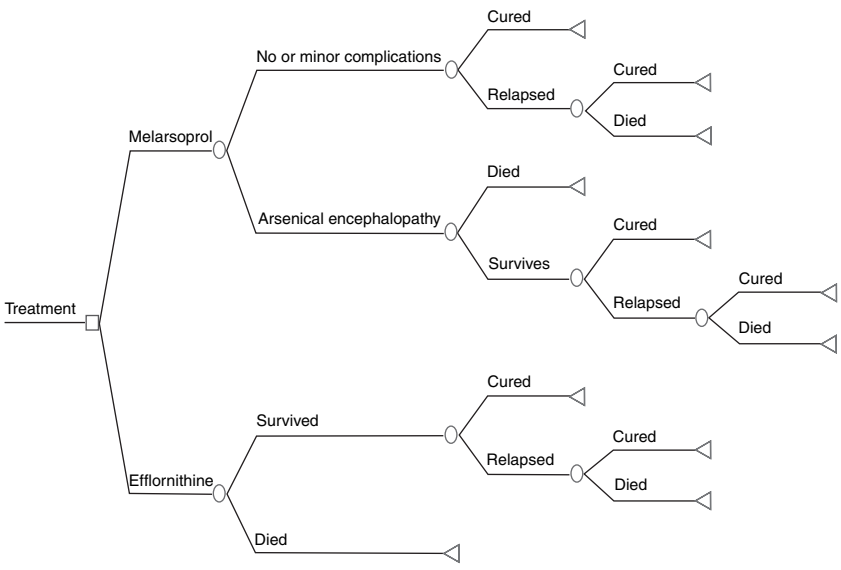


**Figure 1** Decision tree used during the analysis.

The number of staff in the Caxito HAT treatment centre rose after introduction of eflornithine. For melarsoprol the cost of auxiliary nursing staff per patient was estimated at 209 USD per patient (USD 6.3/patient/day, plausible range 5–15 USD). For eflornithine cost of auxiliary nursing staff per patient was estimated at 306 USD (USD 15/patient/day, plausible range 5–20 USD). The cost of the expatriate staff was estimated at USD 5.7/patient/day, plausible range 0–10 USD based on real cost, including wages, social security and travel, as budgeted by MSF.

Cost for the building was estimated at 1.6 USD/patient/day.

### Cost-effectiveness

Cost per death avoided, incremental cost per additional live saved, cost per YLL avoided and incremental cost per YLL avoided including and excluding the cost of melarsoprol and eflornithine are presented in Table 1. It shows that eflornithine saves more lives than melarsoprol, but the latter is slightly more cost-effective. Incremental cost-effectiveness ratio (ICER) is the cost of saving one additional life if the treatment policy would change from melarsoprol to eflornithine. ICER is 1596 USD per additional life saved and 58 USD per additional life year saved in the baseline scenario without cost of trypanocidal drugs but it increases to 8169 USD per additional life saved and 299 USD per additional life year saved if costs of trypanocidal drugs are included.

Sensitivity was analysed including and excluding the cost of trypanocidal drugs. Figure 2 shows that treatment with eflornithine becomes more cost-effective when relapse rates for melarsoprol exceed 16%. Eflornithine also becomes the most cost-effective option when the lethality of encephalopathy exceeds 70% (i.e. when the death rate due to melarsoprol exceeds 7%).

## Discussion

Both eflornithine and melarsoprol are effective and cost-effective treatments for HAT, even if melarsoprol is cheaper and its cost-effectiveness in second-stage HAT care is slightly better in the baseline scenario. Eflornithine is a cost-effective treatment, with 560 USD per life saved and 20 USD per life year saved. This is considered very good value for money according to the WHO CHOICE criteria (http://www.who.int/choice).

Higher adjuvant drug cost accounted for about half of the increased cost of eflornithine, increased staffing for the other half. The additional workload of administering 24 h perfusions was partly compensated by the fact that patients needed less intensive monitoring for arsenical encephalopathy. There is discussion on how to decide whether an intervention is cost-effective or not. An ICER of 1595 USD per additional life saved and USD 60 per additional life year saved would still be considered cost-effective according to the WHO choice criteria (Evans *et al.* 2005) and is comparable to adding measles immunization and treatment of active pneumonia to child care programmes (Edejer *et al.* 2005) and tetanus vaccination in antenatal care (Adam *et al.* 2005). It is definitely more cost-effective than a lot of commonly implemented interventions, such as meningitis vaccination, tetanus treatment and intensive feeding programmes, while it is considerably cheaper than ARV treatment for HIV. Another approach, proposed by Murray *et al.* (2003) and Goldie *et al.* (2006), based on the report of Commission for Macroeconomics and Health (2001), investing in health for economic development is to consider all intervention that cost less than the per capita gross domestic product (GDP) for any given country as

**Table 1** Cost per death avoided, incremental cost per additional live saved, cost per year life lost avoided and incremental cost (USD) per year life lost avoided including and excluding the drug cost of melarsoprol and eflornithine

| | Cost of drug not included | | Cost of drug included | |
|---|---|---|---|---|
| | Melarsoprol | Eflornithine | Melarsoprol | Eflornithine |
| Cost/patient | 504.6 | 552.3 | 600.4 | 844.6 |
| Effectiveness (%) | 95.6 | 98.70 | 95.6 | 98.70 |
| Cost/life saved | 527.5 | 559.8 | 627.6 | 856.1 |
| Cost/YLL averted | 19.3 | 20.1 | 23.0 | 31.4 |
| Incremental cost | | 47.7 | | 244.2 |
| Incremental effectiveness (%) | | 3 | | 3 |
| Incremental cost per additional life saved | | 1595.6 | | 8168.8 |
| Incremental cost per additional YLL averted | | 58.4 | | 299.2 |

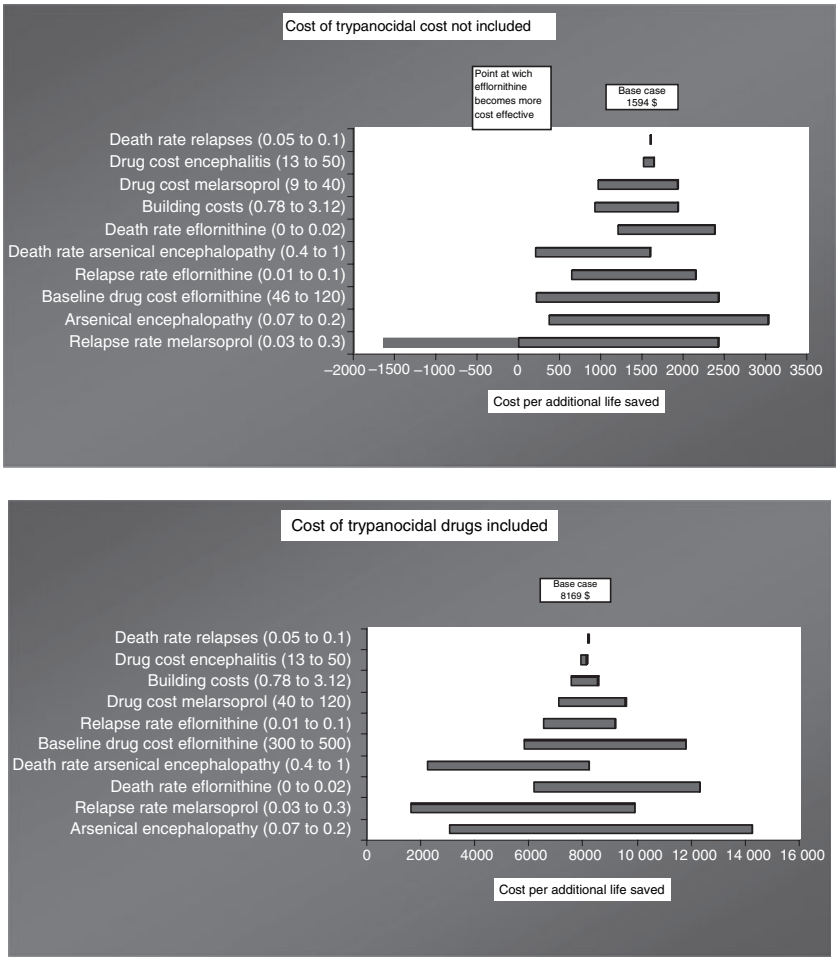


**Figure 2** Tornado diagrams displaying results on sensitivity analysis, incremental cost effectiveness varying in function of the plausible range for a number of parameters, including and excluding cost of trypanocidal drugs.

very cost-effective and all interventions that cost less than three times GDP as cost-effective. For Angola (GDP 4300 USD) and Congo (GDP 700 USD) up this would mean that the intervention can be considered as very cost-effective.

The main argument for switching from melarsoprol to eflornithine should not be searched for in CEA, it should be done in the first place because it avoids the melarsoprol-related iatrogenic mortality. Robays *et al.* (2007) showed that the mortality caused by melarsoprol has a profound impact on the acceptability of the treatment and control programmes, especially because people die who were without symptoms but diagnosed infected by a screening programme. Discussions with health staff in DRC revealed that they did not dare to treat pregnant women because they feared for their own security in case of complications.

We chose not to put the cost of eflornithine and melarsoprol in the baseline calculations because free donation of these products is assured at least until 2011. Eflornithine is more difficult to produce than melarsoprol, but production of melarsoprol causes more environmental hazard and environmental regulations make its production difficult if not impossible in Europe. National programmes are unable to procure either without external support and we strongly plead for a continuation of the donation programme as long as it is needed. However, even if Sanofi Aventis gives both drugs for free for the moment, costs will be incurred eventually. Therefore, we also made the calculations using the preferential prices in use before 2000. Our results differ considerably from Politi *et al.* (1995), who included the cost of eflornithine in the baseline calculations, assumed much lower hospitalization costs and used a baseline where relapsing patients were not retreated, which we did not consider acceptable. In Caxito, the long melarsoprol regimen was used, while the new short regimen requires less

hospitalization days. We do not have information on the admission duration and on the implications for the workload. The number of injections that need to be given is comparable and the patient needs to be monitored in the new regiment after the injections.

Cost of hospitalization is comparable with hospitalization costs for Angola put forward by WHO on their WHO CHOICE website despite the fact that we also included the cost for expatriate staff. We included expatriate staff because a transfer of competence is needed to implement eflornithine treatment. Skills and capacity needed to administer melarsoprol and dealing with its complications are very specific for HAT treatment and favour treatment in specialized centres. In contrast, the technical capacity that is needed to administer eflornithine is more generic, managing and safely administering perfusions should be a basic skill in all district hospital settings and efforts to achieve this also help to increase the overall quality of primary health care. Results of implementation of eflornithine may be less good when implemented outside a structure managed by an international NGO. On the other hand, the 3% death rate for melarsoprol in our study may also be lower than what could be achieved in a more natural setting. A cost-effectiveness study based on data coming from national programmes would be useful.

Mortality rates for HAT treatment were relatively low in Caxito compared to the death rates of 6% reported by Burri *et al.* (2000) and Schmid *et al.* (2005) in a clinical trial setting. In our sensitivity analysis we found that eflornithine becomes equally cost-effective if the death rate exceeds 7%. Eflornithine treatment is the most cost-effective option when relapse rates exceed 16% and continuing melarsoprol treatment in those circumstances is, apart from being unethical, a waste of money. The combination eflornithine/nifurtimox showed promising preliminary results (Priotto *et al.* 2006) and an equivalence trial is ongoing. This regimen is likely to be more feasible and cost-effective and may prevent the emergence of parasite resistance to eflornithine.

## References

Adam T, Lim SS, Mehta S *et al.* (2005) Achieving the millennium development goals for health – cost effectiveness analysis of strategies for maternal and neonatal health in developing countries. *British Medical Journal* **331**, 1107–1110.

Blum J, Nkunku S & Burri C (2001) Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. *Tropical Medicine & International Health* **6**, 390–400.

Burri C & Brun R (2003) Eflornithine for the treatment of human African trypanosomiasis. *Parasitology Research* **90**(Suppl. 1), S49–S52.

Burri C, Nkunku S, Merolle A *et al.* (2000) Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by *Trypanosoma brucei gambiense*: a randomised trial. *Lancet* **355**, 1419–1425.

Chappuis F, Udayraj N, Stietenroth K, Meussen A & Bovier PA (2005) Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. *Clinical Infectious Disease* **41**, 748–751.

Commission for Macroeconomics and Health (2001) *Macroeconomics and Health, Investing in Health for Economic Development*. WHO, Geneva.

Edejer TTT, Aikins M, Black R *et al.* (2005) Achieving the millennium development goals for health – cost effectiveness analysis of strategies for child health in developing countries. *British Medical Journal* **331**, 1177–1180.

Evans DB, Lim SS, Adam T & Edejer TTT (2005) Achieving the millennium development goals for health – evaluation of current strategies and future priorities for improving health in developing countries. *British Medical Journal* **331**, 1457–1461.

Goldie SJ, Yazdanpanah Y, Losina E *et al.* (2006) Cost-effectiveness of HIV treatment in resource-poor settings – the case of Cote d'Ivoire. *New England Journal of Medicine* **355**, 1141–1153.

Legros D, Fournier C, Gastellu EM, Maiso F & Szumilin E (1999) Therapeutic failure of melarsoprol among patients treated for late stage *T. b. gambiense* human African trypanosomiasis in Uganda. *Bulletin de la Société de Pathologie Exotique* **92**, 171–172.

Louis FJ, Keiser J, Simarro P, Schmid C & Jannin J (2003) L'Eflornithine dans le traitement de la maladie du sommeil. *Médecine Tropicale* **63**, 559–563.

Lutumba P (2005) Trypanosomiasis control, Democratic Republic of Congo 1993–2003. *Emerging Infectious Diseases* **11**, 1382–1389.

Matovu E, Enyaru JC, Legros D *et al.* (2001) Melarsoprol refractory *T. b. gambiense* from Omugo, north-western Uganda. *Tropical Medicine & International Health* **6**, 407–411.

Murray CJL & Lopez AD (1996) *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability From Diseases, Injuries and Risk Factors in 1990 and Projected to 2020. Global Burden of Disease and Injury Series*, **Vol. 1.** Harvard University Press, Cambridge.

Murray CJL, Lauer JA, Hutubessy RCW *et al.* (2003) Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* **361**, 717–725.

Pepin J, Milord F, Guern C *et al.* (1989) Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* **1**, 1246–1250.

Pepin J, Milord F, Khonde A *et al.* (1994) Gambiense trypanosomiasis – frequency of, and risk-factors for, failure of melarsoprol therapy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 447–452.

Pepin J, Khonde N, Maiso F *et al.* (2000) Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *Bulletin of the World Health Organization* **78**, 1284–1295.

Politi C, Carrin G, Evans D, Kuzoe FA & Cattand PD (1995) Cost-effectiveness analysis of alternative treatments of African gambiense trypanosomiasis in Uganda. *Health Economics* **4**, 273–287.

Priotto G, Fogg C, Balasegaram M *et al.* (2006) Three drug combinations for late-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Uganda. *PLoS Clinical Trials* **1**, e39. doi:10.1371/journal.pctr.0010039.

Robays J, Lefèvre P, Lutumba P *et al.* (2007) Drug toxicity and cost as barriers to community participation in HAT control in the Democratic Republic of Congo. *Tropical Medicine & International Health* **12**, 290.

Schmid C, Nkunku S, Merolle A, Vounatsou P & Burri C (2004) Efficacy of 10-day melarsoprol schedule 2 years after treatment for late-stage gambiense sleeping sickness. *Lancet* **364**, 789–790.

Schmid C, Richer M, Bilenge CM *et al.* (2005) Effectiveness of a 10-day melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: confirmation from a multinational study (IMPAMEL II). *The Journal of Infectious Diseases* **191**, 1922–1931.

Stanghellini A & Josenando T (2001) The situation of sleeping sickness in Angola: a calamity. *Tropical Medicine & International Health* **6**, 330–334.

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