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Research

Treatment outcomes and risk factors for relapse in patients with early-stage human African trypanosomiasis (HAT) in the Republic of the Congo

Manica Balasegaram, Steve Harris, Francesco Checchi, Catherine Hamel, & Unni Karunakara

Objective In 2002–03, the Republic of the Congo increased the threshold separating stage 1 and 2 cases of human African trypanosomiasis (HAT) from a cerebrospinal fluid (CSF) white cell count of 5 cells/mm³ to 10 cells/mm³. We aimed to assess whether the increased threshold of 10 cells/mm³ is a safe indicator of stage 2 disease.

Methods We assessed patients treated for stage 1 HAT caused by Trypanosoma brucei gambiense in the Republic of the Congo between April 2001 and April 2005. Patients with 0–10 cells/mm³ in CSF were classed as stage 1 and treated with pentamidine. Patients with CSF of > 10 cells/mm³ were classed as stage 2 and treated with either melarsoprol or eflornithine. We did a retrospective analysis of all patients treated after the September 2002 increase in threshold for classification of HAT disease stage 2, and who were eligible for at least 1 year of follow-up. Primary outcome was survival without death or relapse within 1 year of discharge. Risk factors for treatment failure, in particular CSF white cell count on diagnosis, were assessed.

Findings Between September 2002 to April 2004, 692 patients eligible for our analysis were treated with pentamidine. All were discharged alive. Relapse rate was 5% (n = 33). The only identified risk factor for relapse was a CSF white cell count of 6–10 cells/mm³ rather than 0–5 cells/mm³ (adjusted hazard ratio 3.27 (95% confidence interval, 1.52–7.01); P = 0.002).

Conclusion A threshold of 5 white cells/mm³ in CSF is safer than 10 cells/mm³ to determine stage 2 HAT and reduce risk of relapse.

Introduction

Human African trypanosomiasis (sleeping sickness) caused by the parasite Trypanosoma brucei gambiense is endemic in the Republic of the Congo. The disease is transmitted by the tsetse fly (Glossina genus) and manifests itself in two stages. The early stage (stage 1) occurs shortly after initial infection and can present as a haemolymphatic illness with fever, headache, lymphadenopathy, and organomegaly. The late stage (stage 2) presents several months or even years after infection and is characterized by central nervous system involvement. The disease is fatal if untreated.

The early and late stages of sleeping sickness are differentiated by visualization of the parasite in cerebrospinal fluid (CSF) or the proxy indicator of white cell count in CSF. Treatment varies according to stage. Pentamidine is currently the standard recommended treatment for the early stage of the disease. This drug is a water-soluble compound given at a dose of 4 mg/kg once daily for 7 days either intramuscularly or by slow intravenous injection. Maximum plasma concentrations are attained within 1 hour of an intramuscular injection, but the drug is largely bound to plasma proteins and has a long-lasting action with a slow rate of excretion. Important, only very low concentrations of the drug are achieved in CSF, making it unsuitable for use in confirmed stage 2 cases.

 Médecins Sans Frontières (MSF) has run three trypanosomiasis intervention programmes in conjunction with the Republic of the Congo National Programme (the Programme National de lutte contre la Trypanosomiase Humaine Africaine (PNLTHA)) in Gamboma (from April 2001), Nkayi (September 2002), and Mossaka (July 2003) in the Plateaux, Bouenza, and Cuvette regions, respectively. The programmes ended in April 2005.

In September 2002, the MSF programmes, in accordance with a recommendation by the PNLTHA, increased the threshold separating stage 1 and 2 cases from 5 cells/mm³ to 10 cells/mm³. This change was accompanied by a formal revision to the PNLTHA protocol in 2003. We did a retrospective analysis in a cohort of stage 1 patients treated for human African trypanosomiasis caused by T.b. gambiense in the Republic of the Congo. We aimed to assess whether the use of a higher CSF white cell count threshold increased the risk of relapse.

Methods

Patients were originally enrolled through passive case detection at fixed sites, as well as by active case detection by mobile

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teams systematically screening villages. The national protocol of the PNLTHA guided diagnosis and treatment.

Diagnosis (Fig. 1) involved screening (card agglutination trypanosomiasis test (CATT) with whole blood), confirmation (visualization of the parasite in blood or lymph, or a positive result with CATT dilution of 1 in 8), and staging (parasite found in CSF or CSF white cell count).

We analysed risk factors for treatment failure during the first year of follow-up using Cox proportional hazards regression. Patients were included in the analysis if they had a stage 1 diagnosis, were treated with pentamidine (4mg/kg by intramuscular (IM) injection once daily for 7 days), admitted on or after September 2002 (the month when the stage 1 to stage 2 white cell count threshold was raised), and eligible for 1 year of follow up. Patients were excluded if they had not attended at least one follow-up visit or if baseline variables such as age, sex, parasitological findings and treatment outcome were not in their records.

We restricted our analysis to the first year of follow-up, since follow-up rates were unacceptably low for longer periods. We took any visit from month 10 (day 304) to month 14 (day 425) after discharge as the 1-year follow-up visit. We defined failure as death attributable to any cause after discharge, recurrence of parasites in any body fluid, CSF white cell count > 50 cells/mm³ and at least doubled from the previous measurement, or white cell count 11–49 cells/mm³ with either a significant increase from the previous measurement or with symptoms suggestive of sleeping sickness. 3, 5

Potential risk factors (treatment centre, sex, age, screening mode, technique on which parasitological confirmation was based (i.e. visualization of parasite or serological alone), CSF white cell count) and confounders (period during which the patient was admitted) were entered in the multivariate model if associated with the outcome at the P<0.20 level in a univariate analysis. We forced semester of admission into the final model since pentamidine relapse rates varied over the duration of the project (data not shown). We also tested for interactions between covariates and verified the proportionality assumption.

Data were entered at programme locations into either an Excel database (Gamboma) or YoTryps (Nkayi and Mossaka), a Microsoft Access-based software designed for human African trypanosomiasis programmes. Data were analysed with Stata version 8.0 (Stata Corp, College Station, Texas, USA).

Ethical approval
The study was a retrospective analysis on Médecins Sans Frontiéres’ operational medical work in the Republic of the Congo. Approval for data exportation, analysis and reporting was obtained from the PNLTHA of the Republic of the Congo. The data sets extracted and used for analysis were anonymized through removal of all patients’ names, separation into a new dataset, and analysis by a statistician unconnected with the programmes.

Results
Between April 2001 and March 2005, 1980 patients were diagnosed with primary stage 1 human African trypanosomiasis. Criteria for selection of the cohort retained for analysis is shown in Fig. 2. Of 692 patients discharged alive after treatment with pentamidine, 454 (66%) and 371 (54%) attended follow-up at 6 months (± 2 months) and one year (± 2 months), respectively. Overall, 652 patients (94%) attended at least one follow-up visit and were included in the multivariate analysis. Table 1 shows their baseline characteristics.

Patients not attending at 1-year follow-up differed significantly from those who did attend in the semester of admission: 159 of 228 patients (70%) admitted in September 2002 to March 2003 were seen, compared with 212 of 424 (50%) later; P<0.001. Groups did not differ with respect to any other baseline characteristics.

There were 33 treatment failures (5% of 652 eligible for analysis). Age, sex, mode of screening and technique of diagnosis (parasitological or serological) did not affect risk of failure (Table 1). The proportion of failures was higher in patients with a white cell count of 6–10 cells/mm³ than in those with white cell count of 0–5 cells/mm³ (10 of 84 (12%) versus 23 of 568 (4%) eligible for analysis). Patients with a white cell count of 6–10 cells/mm³ had a similar median duration of follow-up to those with white cell count of 0–5 cells/mm³ (316 versus 338 days; P=0.880). Among the 41 defaulters, 18 diagnoses (44%) were serological in the 6–10 cells/mm³ group compared with 165 of 240 (69%) in the 0–5 cells/mm³ group (P=0.004);
defaulters in the two exposure groups were otherwise similar.

Patients treated with pentamidine with a raised white cell count (6–10 cells/mm$^3$) had a significantly higher risk of failure (adjusted hazard ratio 3.27; $P=0.002$) than did those with a white cell count of 0–5 cells/mm$^3$ (Table 1). The association remained significant when stratified by treatment centre: 2.75 (95% confidence interval (CI), 0.99–7.67) in Nkayi and 4.48 (95% CI: 1.29–15.52) in Mossaka.

**Discussion**

Our results show that the risk of treatment failure in patients with a CSF white cell count of 6–10 cells/mm$^3$ is three times higher than in those with a count of 0–5 cells/mm$^3$. This difference may be because some of these patients had late stage or stage 2 disease for which pentamidine treatment is ineffective.

Attempts have been made to use pentamidine to treat patients with a mild elevation of CSF white cell count. Doua et al. in Côte d’Ivoire, for example, showed that pentamidine could be effective in “intermediate” cases with a CSF white cell count between 6 cells/mm$^3$ and 20 cells/mm$^3$. However, Lejon et al. in Uganda noted a higher risk of relapse for these patients treated with pentamidine and went on to recommend a value of 10 cells/mm$^3$ as a more appropriate cut off. Ruiz et al. indeed found that a CSF white cell count of 6–10 cells/mm$^3$ was not associated with a higher risk of relapse in patients treated with pentamidine. Our results somewhat contradict outcomes from these studies and indicate that a lower threshold of 5 cells/mm$^3$ may be advisable in the Republic of the Congo.

A CSF white cell count cut-off of 10 cells/mm$^3$ to differentiate stage 1 and 2 cases is a feature of the national diagnostic protocol of the PNLTHA. Many protocols use a cut-off point of 5 cells/mm$^3$. The reason for adopting a high threshold is because melarsoprol, which is highly toxic, was initially used for the treatment of stage 2 cases. This higher threshold seems justified in view of the fact that if the lower threshold of 5 cells/mm$^3$ had been used, an additional 84 patients (in the analysed group) would have been treated with potentially toxic stage 2 medication. Since about 5% of all patients treated with melarsoprol die from severe adverse events, we calculate that treatment of these 84 extra patients with melarsoprol would have resulted in 4 additional deaths to prevent 10 relapses.

However, we feel that where an alternative to melarsoprol, such as eflornithine, is available, use of a higher threshold is not justified. In our programme in the Republic of the Congo we also found a relatively low case fatality rate of 1.7% ($n=5$) among 288 patients treated with eflornithine. Furthermore, the idea that one can have a positive risk–benefit with a higher CSF white cell count is based on the assumption that all patients can be followed up and any extra relapses can be retreated. In our programme, despite additional resources not normally available to the PNLTHA, only 54% of patients attended follow-up at 1 year. In areas where good follow-up rates can not be guaranteed, additional deaths in the community may occur in patients who relapse or who are lost or unable to attend follow-up.

Overall, the treatment failure rate (5%) in our programme was acceptable and similar to levels noted in other studies. A high proportion (62%) of patients entered in the analysis of relapse risk were diagnosed serologically, in the absence of visualized parasites. This low rate of parasite detection may be related to poor laboratory performance. As such, the treatment of serological cases with a CATT end titre > 1/8 has been proposed as a control strategy in areas with a high prevalence of sleeping sickness. Howi et al. have reported 10 relapses (when CSF white cell count cut-off point changed) of 618 patients treated with melarsoprol.

**Fig. 2. Criteria used for selecting the cohort retained for analysis**

- 1986 patients with primary stage 1 HAT$^a$ diagnosis
- 619 admitted before September 2002 (when CSF white cell count threshold for stage 1 treatment was changed)
- 499 discharged in the last year of the intervention (insufficient follow-up time)
- 175 with one or more missing variables
- 1 died during admission
- 692 discharged alive within period of interest
- 652 attended follow-up at 6 months ($n=454$) and/or 12 months ($n=371$) and hence retained for analysis
- 619 remained disease free
- 33 treatment failures
- 40 did not attend a control visit during the first year

$^a$ HAT = human African trypanosomiasis.
$^b$ CSF = cerebrospinal fluid.
cases having been treated several years ago. There is evidence of immunity following *T. b. gambiense* infection and it is also known that results of the CATT may remain positive for some time.\(^\text{14,15}\)

Furthermore, the positive predictive value of the CATT dilutions is unknown and may vary over the length of a control programme. Perhaps a higher threshold of even 1/16 or 1/32 should be considered especially when the overall prevalence of the disease is moderate to low.

Our results should be interpreted with some caution since they are derived from a retrospective analysis, and are not from a randomized study but from a field-based medical intervention. Additionally, our data were insufficient to analyse outcomes beyond 1 year of follow-up; patients can relapse up to 3 years after initial treatment.\(^\text{11}\)

### Conclusion

Overall, pentamidine was safe and well tolerated. However, a CSF white cell count of 10 cells/mm\(^3\) as the threshold between stage 1 and 2 cases seems to be associated with a higher risk of relapse. Therefore, we recommended that stage 1 should be defined by a CSF white cell count of 0–5 cells/mm\(^3\) (with absence of trypanosomes in the CSF) and that a count of 6 cells/mm\(^3\) and greater should be treated as a stage 2 case, especially if the alternative stage 2 drug eflornithine is available and can be safely administered. In view of a higher risk of relapse, a higher threshold should be used in the context where good follow-up is possible. Surveillance of treated cases is important to monitor development of possible resistance to pentamidine.

### Acknowledgements

We thank the field teams of Médecins Sans Frontières and Dr Claude Rudy Manthelot, director of the PNLTWA, for their work and assistance in the Republic of the Congo.

### Competing interests: none declared.

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### Table 1. Baseline characteristics of patients and risk factors for treatment failure within first year after discharge in stage 1 patients treated with pentamidine

<table>
<thead>
<tr>
<th>Baseline characteristic/ potential risk factor</th>
<th>Patients (n = 652)</th>
<th>Relapses</th>
<th>Crude hazard ratio (95%CI(^a))</th>
<th>Adjusted hazard ratio(^a) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment centre</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nkayi</td>
<td>457 (70%)</td>
<td>23</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Mossaka</td>
<td>195 (30%)</td>
<td>10</td>
<td>1.15 (0.54–2.42)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Semester of admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>September 2002 to March 2003</td>
<td>228 (35%)</td>
<td>13</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>April to September 2003</td>
<td>217 (33%)</td>
<td>13</td>
<td>1.04 (0.48–2.27)</td>
<td>0.86 (0.39–1.91)</td>
</tr>
<tr>
<td>October 2003 to March 2004</td>
<td>207 (32%)</td>
<td>7</td>
<td>0.66 (0.26–1.65)</td>
<td>0.55 (0.22–1.40)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>351 (54%)</td>
<td>19</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Female</td>
<td>301 (46%)</td>
<td>14</td>
<td>0.90 (0.45–1.77)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥ 15 years</td>
<td>504 (77%)</td>
<td>23</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td>148 (23%)</td>
<td>10</td>
<td>1.47 (0.70–3.09)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Mode of screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>490 (75%)</td>
<td>26</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Passive</td>
<td>162 (25%)</td>
<td>7</td>
<td>0.69 (0.30–1.60)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Technique on which diagnosis and staging was based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct gland puncture</td>
<td>157 (24%)</td>
<td>9</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Centrifugation (Woo or QBC(^c))</td>
<td>98 (15%)</td>
<td>7</td>
<td>1.11 (0.41–3.00)</td>
<td>–</td>
</tr>
<tr>
<td>CATT positive at dilution 1/8 or higher</td>
<td>396 (61%)</td>
<td>17</td>
<td>0.83 (0.37–1.87)</td>
<td>–</td>
</tr>
<tr>
<td><strong>White cell count in CSF(^d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 cells/ mm(^3)</td>
<td>568 (87%)</td>
<td>23</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>6–10 cells/ mm(^3)</td>
<td>84 (13%)</td>
<td>10</td>
<td>3.05 (1.45–6.40)</td>
<td>3.27 (1.52–7.01)</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted hazard ratios based on Cox regression model with \(P = 0.030\) (goodness of fit).

\(^b\) CI = confidence interval.

\(^c\) QBC = quantitative buffy coat.

\(^d\) CSF = cerebrospinal fluid.
Résumé
Résultats du traitement et facteurs de risque de rechute chez les personnes atteintes de trypanosomiase africaine humaine (TAH) à un stade avancé en République du Congo

Objectif Dans les années 2002-2003, les responsables sanitaires de la République du Congo ont fait passer de 5 leucocytes/mm³ à 10 leucocytes/mm³ le seuil de séparation des stades 1 et 2 de la trypanosomiase africaine humaine (TAH) d’après la numération leucocytaire dans le liquide céphalorachidien. On s’est efforcé d’évaluer la sécurité du tri effectué à partir du seuil augmenté de 10 leucocytes/mm³ en tant qu’indicateur du stade 2 de la maladie.

Méthodes On a évalué des patients traités pour une TAH au stade 1 due à Trypanosoma brucei gambiense en République du Congo entre avril en 2001 et avril 2005. Les patients dont la numération leucocytaire dans le liquide céphalorachidien se situait entre 0 et 10 leucocytes/mm³ ont été classés « stade 1 » et traités par la pentamidine. Ceux dont la numération était > 10 leucocytes/mm³ ont été classés « stade 2 » et traités par du mélasoprol ou de l’éflornithine. Une étude rétrospective a été réalisée sur l’ensemble des patients traités après l’augmentation du seuil de classification de la TAH en stade 2 effectuée en septembre 2002 et répondant aux critères d’inclusion dans un suivi d’un an au moins. Les deux principaux résultats du traitement pris en compte étaient la survie sans décès ou la rechute dans l’année suivant la sortie de l’établissement de soins. Les facteurs de risque d’échec thérapeutique, notamment la numération leucocytaire dans le liquide céphalorachidien, ont été évalués.

Résultats Entre septembre 2002 et avril 2004, 692 patients remplissant les critères d’inclusion dans l’analyse ont été traités par la pentamidine. Tous ont quitté l’établissement de soins vivants. Le taux de rechute était de 5 % (n = 33). Le seul facteur de risque de rechute identifié était une numération leucocytaire située entre 6 et 10 leucocytes/mm³, par comparaison avec une valeur de 10 leucocytes/mm³ (rapport de risque ajusté 3,27; intervalle de confiance à 95 % : 1,52 - 7,01; p = 0,002).

Conclusion Le seuil de 5 leucocytes/mm³ dans le liquide céphalorachidien est plus sûr que celui de 10 leucocytes/mm³ pour définir une TAH au stade 2 et réduire le risque de rechute.

Resumen
Resultados terapéuticos y factores de riesgo de recaída en pacientes con tripanosomiasis africana humana (TAH) en fase inicial en la República del Congo

Objetivo En 2002–2003, la República del Congo aumentó el umbral de separación de los casos de fase 1 y 2 de tripanosomiasis africana humana (TAH) de un recuento de leucocitos en líquido cefalorraquideo (LCR) de 5 células/mm³ a 10 células/mm³. Decidimos determinar si ese mayor umbral, de 10 células/mm³, es un indicador seguro de la fase 2 de la enfermedad.

Métodos Evaluamos a pacientes tratados contra la TAH por Trypanosoma brucei gambiense en fase 1 en la República del Congo entre abril de 2001 y abril de 2005. Los pacientes con 0–10 células/mm³ en LCR se clasificaron como fase 1 y fueron tratados con pentamidina. Los pacientes con más de 10 células/mm³ en LCR se clasificaron como fase 2 y fueron tratados con melarsoprol o eflornitina. Hicimos un análisis retrospectivo de todos los pacientes tratados después de aumentar el umbral de definición de la fase 2, en septiembre de 2002, y considerados aptos para un seguimiento de al menos un año. Como variable principal de valoración se empleó la supervivencia sin defunción o recaída durante el primer año tras el alta. Se evaluaron los factores de riesgo de fracaso terapéutico, en particular el recuento de leucocitos en LCR en el momento del diagnóstico.

Resultados Entre septiembre de 2002 y abril de 2004, 692 pacientes aptos para nuestro análisis fueron tratados con pentamidina. Todos sobrevivieron y recibieron el alta. La tasa de recaídas fue del 5 % (n=33). El único factor de riesgo conocido fue un recuento de leucocitos en LCR de 6–10 células/mm³ en lugar de 0–5 células/mm³ (razón de riesgos instantáneos ajustada = 3,27 (intervalo de confianza del 95 % = 1,52–7,01; P = 0,002).

Conclusiones La cifra de 5 leucocitos/mm³ en el LCR es más segura que 10 leucocitos/mm³ como umbral para determinar la fase 2 de la TAH y reducir el riesgo de recaída.
References


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ینعيب 5 خلايا لكل مليمتر مكعب من السائل النخاعي أكثر آمناً من 10 خلايا لكل مليمتر مكعب من السائل النخاعي في تشخيص المرحلة الثانية من داء المثقبيات البشري الأفريقي، وهذه العتبة ستؤدي من خطر النكس.

الاستنتاج: إن عتبة 5 خلايا لكل مليمتر مكعب من السائل النخاعي أكثر آمناً من 10 خلايا لكل مليمتر مكعب من السائل النخاعي في تشخيص المرحلة الثانية من داء المثقبيات البشري الأفريقي، وهذه العتبة ستؤدي من خطر النكس.

Tخرج جميعهم من المستشفى أحياءً، وكان معدل النكس 3.3% (33 مريضاً) وكان عامل الخطر الوحيد للنكس هو عدد الكريات البيض الذي يتراوح بين 6-10 خلايا لكل مليمتر مكعب بدلاً من 5-0 خلايا/مليمتر مكعب. إذ بلغ معدل الخطر المُصَحَّح 3.27 (فاصلة ثقة 95% لقيم تتراوح بين 1.52 و0.7، وقيمة احتمال 0.05).

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Sleeping sickness in the Republic of the Congo
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References