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Effectiveness of melarsoprol and eflornithine as first-line regimens for gambiense sleeping sickness in nine Médecins Sans Frontières programmes

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Summary   This paper describes the effectiveness of first-line regimens for stage 2 human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* infection in nine Médecins Sans Frontières HAT treatment programmes in Angola, Republic of Congo, Sudan and Uganda. Regimens included eflornithine and standard- and short-course melarsoprol. Outcomes for 10 461 naïve stage 2 patients fitting a standardised case definition and allocated to one of the above regimens were analysed by intention-to-treat analysis. Effectiveness was quantified by the case fatality rate (CFR) during treatment, the proportion probably and definitely cured and the Kaplan—Meier probability of relapse-free survival at 12 months and 24 months post admission. The CFR was similar for the standard- and short-course melarsoprol regimens (4.9% and 4.2%, respectively). The CFR for eflornithine was 1.2%. Kaplan—Meier survival probabilities varied from 71.4—91.8% at 1 year and 56.5—87.9% at 2 years for standard-course melarsoprol, to 73.0—91.1% at 1 year for short-course melarsoprol, and 79.9—97.4% at 1 year and 68.6—93.7% at 2 years for eflornithine. With the exception of one programme, survival at 12 months was >90% for eflornithine, whilst for melarsoprol it was <90% except in two sites. Eflornithine is recommended where feasible, especially in areas with low melarsoprol effectiveness.
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1. Introduction

Human African trypanosomiasis (HAT), or sleeping sickness, is caused by *Trypanosoma brucei gambiense* and is transmitted by the tsetse fly (*Glossina* spp.). Over 200 foci of transmission occur in some of the most resource-poor and conflict-ridden areas of Africa; the most affected regions are the Democratic Republic of the Congo, Sudan, northwest Uganda and Angola. The WHO reports that approximately 17 000 gambiense cases were identified in 2004, but the true number may be considerably higher.[1]

Available drugs for stage 2 HAT include melarsoprol, a lipophilic organoarsenical, and eflornithine, an inhibitor of ornithine decarboxylase.[2] Melarsoprol is highly toxic, causing fatal reactive encephalopathy in up to 10% of cases.[3] Treatment failure with melarsoprol is common although localised, occurring in Angola, the Democratic Republic of the Congo, Sudan and Uganda.[4-10] The standard melarsoprol regimen consists of three weekly series of injections. A newer short-course alternative (10 days) shows equivalent effectiveness and is increasingly used.[11] Eflornithine requires numerous i.v. infusions, which hampers its feasibility in resource-poor settings. Generally, effectiveness appears to be high and the safety profile appears to be more favourable than that of melarsoprol.[12,13]

Médecins Sans Frontières (MSF) is a humanitarian medical relief agency that works in areas of conflict, neglect, disease outbreaks and natural disasters. Since 1986, MSF has responded to several HAT outbreaks. All these programmes collected individual patient data to monitor treatment and to facilitate follow-up. Here we present baseline data, end-of-treatment outcomes and various effectiveness measures for the three main first-line stage 2 treatment regimens (eflornithine and standard- and short-course melarsoprol) from nine MSF HAT programmes in four countries. We also investigate chronological trends in regimen effectiveness.

Effectiveness data on a proportion of patients treated in the Congo and Sudan programmes are already published elsewhere, although with heterogeneous durations of follow-up, inclusion and endpoint criteria, and analysis methods.[12-14] Specifically, in Ibba, Sudan, Priotto et al. performed a prospective cohort study of eflornithine-treated patients that included reinforced follow-up measures not applied to all patients in the programme.[13] Our aim here is to present a joint analysis of all MSF-treated patients in available data sets, using a common approach and comparing different effectiveness measurement methods.

2. Methods

2.1. Data sources

Individual patient data from the MSF HAT treatment programmes in the following locations were pooled: Caxito, Angola (2002—2006); Gamboma (2001—2003), Mossaka (2003—2005) and Nkayi (2002—2005), the Republic of the Congo; Adjumani (1991—1999), Arua (1995—2002) and Yumbe (2000—2002), Uganda; and Kiri (2000—2006) and Ibba (2000—2006), southern Sudan.

Data had originally been single-entered by field staff into Excel, YoTrypsI, YoTrypsII (both Microsoft Access-based) or EpiTryps databases. They were made anonymous, appended and cleaned on Stata 9.0 (StataCorp., College Station, TX, USA). Multiple records based on common variables (admission and discharge dates, sex, age, laboratory results, treatment regimen) were eliminated.

2.2. Diagnosis, treatment and follow-up

Patients were either actively or passively screened for HAT infection using the card agglutination test for trypanosomiasis (CATT). Programmes used different diagnostic algorithms and stage 2 definitions. The standard melarsoprol regimen was administered using one of the following schedules: (i) three series each comprising 4 days of increasing injections of 1.2 mg/kg on Day 1, 2.4 mg/kg on Day 2, 3.6 mg/kg on Day 3 and 3.6 mg/kg on Day 4, with a 7—10 day rest period between each series (Angola, Republic of Congo); (ii) three series of 3 days of injections at 3.6 mg/kg/day each, with series spaced by a 7—10 day rest period (Sudan); and (iii) another incremental scheme involving three 3-day injection series spaced by 7—10 day periods (series one, 1.8 mg/kg on Day 1, 2.16 mg/kg on Day 2 and 2.52 mg/kg on Day 3; series two, 2.52 mg/kg, 2.88 mg/kg and 3.42 mg/kg; series three, 3.6 mg/kg, 3.6 mg/kg and 3.6 mg/kg) (Uganda). The newer, short-course melarsoprol schedule consisted of 2.16 mg/kg injections every day for 10 days. Prednisolone was co-administered with any melarsoprol regimen to reduce the risk of reactive encephalopathy. Eflornithine was administered as four evenly spaced 100 mg/kg/day i.v. infusions (150 mg/kg in children aged <12 years) for 14 consecutive days.

If discharged alive, patients were invited back for follow-up visits at 3, 6, 12, 18 and 24 months or at 6, 12 and 24 months following discharge, depending on the programme.

2.3. Eligibility criteria

Patients were included in the analysis if they fulfilled the following stage 2 case definition: (i) parasites in the cerebrospinal fluid (CSF); and/or (ii) CSF white blood cell (WBC) count >5/μl in the presence of a positive parasitological test (Quantitative Buffy Coat, Capillary Tube Centrifugation or Woo test, microscopy of lymph tissue, mini-Anion Exchange Column Test) in blood or lymph gland aspirate; and/or (iii) CSF WBC count >20/μl in the presence of a positive CATT test at dilution ≥1:4. Furthermore, patients were included only if they had no record of prior HAT treatment and were allocated to one of the above regimens.

2.4. Effectiveness analysis

An intention-to-treat approach to the analysis was used since the aim was to establish effectiveness in field conditions. The following were considered as treatment failures: (i) death due to any cause between admission and discharge; (ii) incomplete treatment course due to any cause; (iii) death due to any cause during follow-up; (iv) microscopic observation of trypanosomes in any body tissues at any follow-up visit; (v) CSF WBC count at any follow-up visit >50/μl and greater than at admission; or (vi) programme's

Table 1 Profile of 6324 patients treated with melarsoprol (standard regimen) and eligible for analysis [n (%)]

	Caxito, Angola (n = 223)	Gamboma, Congo (n = 106)	Mossaka, Congo (n = 16)	Nkayi, Congo (n = 174)	Ibba, Sudan (n = 883)	Adjumani, Uganda (n = 3305)	Arua, Uganda (n = 1577)	Yumbe, Uganda (n = 40)
Baseline characteristics[a]								
Age (years)								
≤12	28 (12.6)	17 (16.0)	2 (12.5)	17 (9.8)	146 (16.5)	547 (16.6)	273 (17.3)	6 (15.0)
13—24	54 (24.2)	23 (21.7)	5 (31.3)	44 (25.3)	269 (30.5)	1196 (36.2)	498 (31.6)	11 (27.5)
25—44	96 (43.0)	38 (35.8)	8 (50.0)	73 (42.0)	311 (35.2)	1202 (36.4)	598 (37.9)	16 (40.0)
≥45	45 (20.2)	28 (26.4)	1 (6.3)	40 (23.0)	157 (17.8)	360 (10.9)	208 (13.2)	7 (17.5)
Female	95 (42.6)	54 (50.9)	6 (37.5)	76 (43.7)	447 (50.6)	1725 (52.2)	784 (49.7)	20 (50.0)
Screened actively	60 (26.9)	73 (68.9)	0	113 (64.9)	272 (30.8)	1108 (33.5)	284 (18.0)	7 (17.5)
GP-positive	147 (65.9)	57 (53.8)	7 (43.8)	116 (66.7)	636 (72.0)	2358 (71.3)	746 (47.3)	26 (65.0)
CTC-positive	63 (28.3)	37 (34.9)	5 (31.3)	41 (23.6)	157 (17.8)	600 (18.2)	458 (29.0)	13 (32.5)
mAECT-positive	ND	ND	ND	ND	ND	ND	ND	ND
QBC-positive	ND	ND	ND	ND	30 (3.4)	95 (2.9)	571 (36.2)	ND
Parasites in CSF	153 (68.6)	35 (33.0)	14 (87.5)	53 (30.5)	310 (35.1)	1604 (48.5)	1121 (71.1)	23 (57.5)
WBC in CSF (cells/μl)								
0	0	0	0	0	0	10 (0.3)	4 (0.3)	0
1—5	0	0	0	0	0	71 (2.1)	13 (0.8)	0
6—10	6 (2.7)	25 (23.6)	0	38 (21.8)	194 (22.0)	509 (15.4)	112 (7.1)	11 (27.5)
11—20	9 (4.0)	11 (10.4)	3 (18.8)	35 (20.1)	161 (18.2)	482 (14.6)	145 (9.2)	3 (7.5)
21—50	38 (17.0)	12 (11.3)	1 (6.3)	29 (16.7)	183 (20.7)	661 (20.0)	257 (16.3)	2 (5.0)
≥51	169 (75.8)	58 (54.7)	12 (75.0)	72 (41.4)	345 (39.1)	1566 (47.4)	1043 (66.1)	24 (60.0)
Follow-up attrition								
Completed treatment and discharged alive	214 (96.0)	98 (92.5)	16 (100)	163 (93.7)	843 (95.5)	3097 (93.7)	1506 (95.5)	40 (100)
Seen at least once after discharge[b]	181 (84.6)	81 (82.7)	16 (100)	162 (99.4)	552 (65.5)	1829 (59.1)	1325 (88.0)	36 (90.0)
Seen at 12 months[b]	86 (40.2)	25 (25.5)	7 (43.8)	118 (72.4)	42 (5.0)	611 (19.7)	725 (48.1)	12 (30.0)
Seen at 24 months[b]	43 (20.1)	5 (5.1)	0	67 (41.1)	87 (10.3)	293 (9.5)	512 (34.0)	4 (10.0)
Median no. of days followed up post discharge (IQR)[b]	424 (178—695)	220 (93—408)	532 (302—555)	571 (366—732)	204 (0—692)	185 (0—404)	391 (186—730)	259 (158—417)

GP: gland puncture; CTC: capillary tube centrifugation test; mAECT: mini-anion exchange centrifugation technique; QBC: quantitative buffy coat test; CSF: cerebrospinal fluid; WBC: white blood cells; IQR: interquartile range; ND: not done.

[a] Missing values as follows: sex (4 Adjumani, 1 Arua); screening mode (14 Adjumani); parasites in CSF (1 Caxito, 3 Ibba, 19 Adjumani); and WBC in CSF (1 Caxito, 6 Adjumani, 3 Arua).

[b] Of those who completed treatment and were discharged alive; includes patients discharged <24 months before the programme or data set's end.

Table 2   Profile of 973 patients treated with melarsoprol (short-course regimen) and eligible for analysis [n (%)][a]

	Gamboma, Congo (n = 44)	Kiri, Sudan (n = 929)
Baseline characteristics		
Age (years)		
≤12	1 (2.3)	193 (20.8)
13—24	13 (29.5)	292 (31.4)
25—44	21 (47.7)	313 (33.7)
≥45	9 (20.5)	131 (14.1)
Female	22 (50.0)	475 (51.1)
Screened actively	30 (68.2)	164 (17.7)
GP-positive	30 (68.2)	472 (50.8)
CTC-positive	8 (18.2)	59 (6.4)
mAECT-positive	ND	ND
QBC-positive	ND	315 (33.9)
Parasites in CSF	8 (18.2)	390 (42.0)
WBC in CSF (cells/μl)		
0	0	0
1—5	0	2 (0.2)
6—10	12 (27.3)	123 (13.2)
11—20	5 (11.4)	162 (17.4)
21—50	11 (25.0)	193 (20.8)
≥51	16 (36.4)	449 (48.3)
Follow-up attrition		
Completed treatment and discharged alive	38 (86.4)	885 (95.3)
Seen at least once after discharge[b]	34 (89.5)	708 (80.0)
Seen at 12 months[b]	1 (2.6)	296 (33.4)
Seen at 24 months[b]	0	158 (17.9)
Median no. of days followed up post discharge (IQR)[b]	210 (44—333)	358 (172—724)

GP: gland puncture; CTC: capillary tube centrifugation test; mAECT: mini-anion exchange centrifugation technique; QBC: quantitative buffy coat test; CSF: cerebrospinal fluid; WBC: white blood cells; IQR: interquartile range; ND: not done.
[a] Four patients treated in Mossaka, Congo, are not included in this table on the basis of small sample size.
[b] Of those who completed treatment and were discharged alive; includes patients discharged <24 months before the programme or data set's end.

decision to institute second-line treatment owing to clinical status and/or rising CSF cell counts on consecutive follow-up visits. Individual patient files could not be checked to verify that these instances of clinician discretion were indeed due to a relapsing infection, but it was assumed that they were. This was to accommodate cases where a HAT relapse is clinically evident despite no parasitological confirmation or WBC counts below the failure thresholds. Patients were considered cured at any follow-up visit if they were seen and did not meet any of the failure criteria.

Effectiveness was expressed in three ways. First, crude effectiveness proportions were calculated assuming that patients lost to follow-up were cured. Second, the same proportions were calculated excluding losses to follow-up both from the numerator and the denominator. For both of the above expressions, effectiveness was calculated at 12 months post discharge by excluding patients discharged <12 months before either the end of the programme or, for programmes that were ongoing at the time of analysis (Caxito, Angola; Kiri, Sudan; Ibba, Sudan), the last database update (since their follow-up might have been incomplete). Any follow-up visit occurring between 10—14 months after discharge was considered as a valid 12-month control. Effectiveness was also calculated at 24 months by excluding

patients discharged <24 months before the end of the programme or the last database update, and considering any visit between 22—26 months as a valid 24-month control.

Third, Kaplan—Meier probabilities of failure-free survival were computed by considering the date of admission as the start of the at-risk period, and censoring patients when they failed or at the last follow-up visit they attended. Survival probabilities at 12 months and 24 months were computed by censoring all observations at 14 months and 26 months, respectively. When the number of patients under follow-up at the last time point was low, the survival probability at the last time point when precision of the estimate lay within 15% was calculated as a more reliable Kaplan—Meier estimate. Note that some follow-ups and failures occurred >26 months after discharge. These are often considered novel infections.

We mostly abstained from statistical testing since patients were not randomly allocated to regimens and since the aim was merely to describe effectiveness. For programmes that treated considerable numbers of patients with the same regimen over a period of at least six semesters, the 12-month Kaplan—Meier survival probability was stratified by semester of admission, and a log-rank test for trend was performed.

Table 3 Profile of 3164 patients treated with eflornithine and eligible for analysis [n (%)]

	Caxito, Angola (n = 279)	Gamboma, Congo (n = 15)	Mossaka, Congo (n = 137)	Nkayi, Congo (n = 116)	Ibba, Sudan (n = 2090)	Kiri, Sudan (n = 482)	Arua, Uganda (n = 45)
Baseline characteristics[a]							
Age (years)							
≤12	21 (7.5)	10 (66.7)	19 (13.9)	31 (26.7)	327 (15.6)	104 (21.6)	4 (8.9)
13—24	60 (21.5)	2 (13.3)	30 (21.9)	25 (21.6)	823 (39.4)	144 (29.9)	15 (33.3)
25—44	123 (44.1)	2 (13.3)	59 (43.1)	39 (33.6)	714 (34.2)	171 (35.5)	20 (44.5)
≥45	75 (26.9)	1 (6.7)	29 (21.2)	21 (18.1)	226 (10.8)	63 (13.1)	6 (13.3)
Female	99 (35.5)	7 (46.7)	66 (48.2)	60 (51.7)	907 (43.4)	178 (36.9)	19 (42.2)
Screened actively	89 (31.9)	4 (26.7)	81 (59.1)	66 (56.9)	370 (17.7)	181 (37.6)	1 (2.2)
GP-positive	184 (65.9)	6 (40.0)	80 (58.4)	76 (65.5)	1163 (55.6)	229 (47.5)	18 (40.0)
CTC-positive	68 (24.4)	7 (46.7)	31 (22.6)	28 (24.1)	767 (36.7)	134 (27.8)	12 (26.7)
mAECT-positive	4 (1.4)	ND	ND	ND	ND	ND	9 (20.0)
QBC-positive	ND	ND	ND	8 (6.9)	49 (2.3)	56 (11.6)	ND
Parasites in CSF	206 (73.8)	11 (73.3)	93 (67.9)	54 (46.6)	729 (34.9)	257 (53.3)	40 (88.9)
WBC in CSF (cells/μl)							
0	0	0	0	0	0	0	0
1—5	0	0	0	1 (0.9)	0	0	0
6—10	13 (4.7)	1 (6.7)	1 (0.7)	1 (0.9)	495 (23.7)	50 (10.4)	0
11—20	32 (11.5)	2 (13.3)	32 (23.4)	32 (27.6)	347 (16.6)	59 (12.2)	3 (6.7)
21—50	37 (13.3)	0	19 (13.9)	21 (18.1)	311 (14.9)	57 (11.8)	3 (6.7)
≥51	197 (70.6)	12 (80.0)	85 (62.0)	61 (52.6)	937 (44.8)	316 (65.6)	39 (86.7)
Follow-up attrition							
Completed treatment and discharged alive	275 (98.6)	15 (100)	135 (98.5)	113 (97.4)	2057 (98.4)	478 (99.2)	44 (97.8)
Seen at least once after discharge[b]	128 (46.6)	12 (80.0)	105 (77.8)	75 (66.4)	1617 (78.6)	313 (65.5)	15 (34.1)
Seen at 12 months[b]	36 (13.1)	2 (13.3)	34 (25.2)	32 (28.3)	583 (28.3)	114 (23.8)	5 (11.4)
Seen at 24 months[b]	0	2 (13.3)	0	2 (1.8)	276 (13.4)	23 (4.8)	9 (20.5)
Median no. of days followed up post discharge (IQR)[b]	0 (0—216)	189 (91—368)	194 (98—363)	177 (0—360)	359 (184—683)	191 (0—372)	0 (0—213)

GP: gland puncture; CTC: capillary tube centrifugation test; mAECT: mini-anion exchange centrifugation technique; QBC: quantitative buffy coat test; CSF: cerebrospinal fluid; WBC: white blood cells; IQR: interquartile range; ND: not done.
[a] Missing values as follows: sex (1 Ibba); screening mode (3 Ibba); and parasites in CSF (1 Mossaka, 1 Ibba).
[b] Of those who completed treatment and were discharged alive; includes patients discharged <24 months before the programme or data set's end.

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Table 4 Endpoints and effectiveness measures for patients treated with melarsoprol (standard regimen)

	Caxito, Angola	Gamboma, Congo	Mossaka, Congo	Nkayi, Congo	Ibba, Sudan	Adjumani, Uganda	Arua, Uganda	Yumbe, Uganda
Case fatality rate during treatment								
Total dead/total admitted	8/223 (3.6%)	5/106 (4.7%)	0/16	10/174 (5.7%)	40/883 (4.5%)	179/3305 (5.4%)	66/1577 (4.2%)	0/40
Effectiveness at 12 months post discharge								
Discharged ≥12 months before programme/data set end	219	106	16	174	883	3181	1546	40
Lost to follow-up	115	72	6	25	704	2346	544	23
Cured	80	22	7	112	27	602	620	12
Failed	24	12	3	37	152	233	382	5
Total cured/total treated, assuming lost to follow-up are cured	195/219 (89.0%)	94/106 (88.7%)	13/16 (81.3%)	137/174 (78.7%)	731/883 (82.8%)	2948/3181 (92.7%)	1164/1546 (75.3%)	35/40 (87.5%)
Total cured/total treated, excluding lost to follow-up	80/104 (76.9%)	22/34 (64.7%)	7/10 (70.0%)	112/149 (75.2%)	27/179 (15.1%)	602/835 (72.1%)	620/1002 (61.9%)	12/17 (70.6%)
Survival probability in % (Kaplan—Meier)	86.2	73.3	80.8	77.8	75.6	91.8	71.4	85.3
Effectiveness at 24 months post discharge								
Discharged ≥24 months before programme/data set end	178	82	4	98	883	3044	1422	14
Lost to follow-up	106	68	1	19	612	2522	492	10
Cured	41	3	0	48	79	285	471	4
Failed	31	11	3	31	192	237	459	0
Total cured/total treated, assuming lost to follow-up are cured	147/178 (82.6%)	71/82 (86.6%)	1/4 (25.0%)	67/98 (68.4%)	691/883 (78.3%)	2807/3044 (92.2%)	963/1422 (67.7%)	14/14 (100%)
Total cured/total treated, excluding lost to follow-up	41/72 (56.9%)	3/14 (21.4%)	0/3	48/79 (60.8%)	79/271 (29.2%)	285/522 (54.6%)	471/930 (50.6%)	4/4 (100%)
Survival probability in % (Kaplan—Meier)	75.1	74.5	56.5 [b]	66.0	65.3	87.9	60.3	85.3
Reasons for failure (% of all failures)[a]								
Death during treatment	8 (23.5)	5 (35.7)	0	10 (20.4)	40 (19.3)	179 (70.5)	66 (13.4)	0
Treatment incomplete	1 (2.9)	3 (21.4)	0	1 (2.0)	0	29 (11.4)	5 (1.0)	0
Death during follow-up	0	0	0	2 (4.1)	6 (2.9)	0	38 (7.7)	0
Parasites during follow-up	10 (29.4)	1 (7.1)	5 (71.4)	7 (14.3)	128 (61.8)	22 (8.7)	282 (57.3)	5 (100)
WBC increase during follow-up	11 (32.4)	5 (35.7)	2 (28.6)	25 (51.0)	18 (8.7)	20 (7.9)	74 (15.0)	0
Clinician's decision during follow-up	4 (11.8)	0	0	4 (8.2)	15 (7.2)	4 (1.6)	27 (5.5)	0
Total failures	34	14	7	49	207	254	492	5

WBC: white blood cells.
[a] Includes failures that occurred after 24 months of discharge.
[b] Estimate unreliable due to small denominator.

Table 5 Endpoints and effectiveness measures for patients treated with melarsoprol (short-course regimen)[a]

	Gamboma, Congo	Kiri, Sudan
Case fatality rate during treatment		
Total dead/total admitted	3/44 (6.8%)	38/929 (4.1%)
Effectiveness at 12 months post discharge		
Discharged ≥12 months before programme/data set end	44	920
Lost to follow-up	26	554
Cured	7	293
Failed	11	73
Total cured/total treated, assuming lost to follow-up are cured	33/44 (75.0%)	847/920 (92.1%)
Total cured/total treated, excluding lost to follow-up	7/18 (38.9%)	293/366 (80.1%)
Survival probability in % (Kaplan—Meier)	64.8 [73.0 at 11 months][c]	91.1
Effectiveness at 24 months post discharge		
Discharged ≥24 months before programme/data set end	44	916
Lost to follow-up	32	682
Cured	0	158
Failed	12	76
Total cured/total treated, assuming lost to follow-up are cured	32/44 (72.7%)	840/916 (91.7%)
Total cured/total treated, excluding lost to follow-up	0/12	158/234 (67.5%)
Survival probability in % (Kaplan—Meier)	54.0 [73.0 at 11 months][c]	90.3
Reasons for failure (% of all failures)[b]		
Death during treatment	3 (25.0)	38 (49.4)
Treatment incomplete	3 (25.0)	6 (7.8)
Death during follow-up	0	11 (14.3)
Parasites during follow-up	0	16 (20.8)
WBC increase during follow-up	5 (41.7)	1 (1.3)
Clinician's decision during follow-up	1 (8.3)	5 (6.5)
Total failures	12	77

WBC: white blood cells.
[a] Four patients treated in Mossaka, Congo, are not included in this table on the basis of small sample size.
[b] Includes failures that occurred after 24 months of discharge.
[c] Estimate unreliable due to small numbers [refer to estimate in brackets].

3. Results

3.1. Patient profile

After pooling available data sets, 11 668 patients meeting the criteria of naïve stage 2 HAT were identified. Of these, 1109 received regimens other than standard- or short-course melarsoprol or 14-day eflornithine, including patients treated with pentamidine in Angola and the Republic of the Congo where the WBC threshold for stage 2 classification was higher than >5/μl, and participants in combination therapy trials. Another 94 could not be analysed owing to missing variables. Thus, 10 465 patients were eligible for analysis, of whom 6324 were allocated to standard-course melarsoprol, 977 to short-course melarsoprol (of whom a further 4 from Mossaka were omitted from the results owing to small sample size) and 3164 to eflornithine.

Baseline characteristics for all patients are shown by treatment given and treatment site in Tables 1—3. Only a minority of patients treated were children under the age of 12 years. In the Republic of the Congo, the majority of patients were detected through active screening; in Uganda and Sudan, passive screening was predominant. Gland puncture was an important means of confirming diagnosis, used in 61% of cases ($n = 6351$) and demonstrating persisting parasitaemia in the haemolymphatic system during stage 2 HAT. The presence of parasites in CSF was common (49%; $n = 5101$), as was a high WBC count (>50 cells/μl) in the CSF (52%; $n = 5401$), and the two stage 2 markers were strongly correlated [80.3% (4098/5101 patients) with parasites in CSF also had a WBC count >50/μl compared with 24.3% (1295/5334 patients) in those without; $P < 0.001$]. There was variation between sites and treatments for all baseline variables. For important indicators of severity such as CSF WBC count ≥51/μl, there were no striking differences between treatment groups. For example, for standard-course melarsoprol, the value ranged from 39.1% to 75.8% across the sites (overall mean 52%); for short-course melarsoprol it was 36.4% and 48.3% for the two sites (overall mean 49%); and for eflornithine it ranged between 44.8% and 86.7% (overall mean 52%). Only a total of 56 (0.5%) of 10 461 patients did not complete a full course of treatment. This included 39 (0.6%) in the standard-course melarsoprol, 9 (0.9%) in the short-course melarsoprol and 8 (0.3%) in the eflornithine regimens. Follow-up both at 12 months and 24 months was low and only exceeded 50% in the one site of Nkayi, although >50% of patients were followed-up at least once after discharge everywhere except for Caxito (eflornithine)

and Arua (eflornithine). Follow-up attendance declined over time. Follow-up for eflornithine-treated patients appears artificially low due to the fact that many were still under follow-up when the MSF programme was handed over to other agencies, or when the data sets for this analysis were captured.

3.2. Case fatality rates during treatment

For melarsoprol, some variation in case fatality rate (CFR) was observed due to the small sample sizes treated in some centres (Gamboma, Yumbe). However, where larger sample sizes existed (>150), the CFR was 3.6—5.7%. Rates for the standard- and short-course regimens were similar at 4.9% ($n = 308/6324$) and 4.2% ($n = 41/973$), respectively. Eflornithine CFRs varied between centres at 0—2.6%, and the overall CFR was 1.2% ($n = 39/3164$).

3.3. Effectiveness

Crude cure (effectiveness) rates varied strongly for each treatment regimen depending on whether patients lost to follow-up were assumed cured or were excluded from the analysis (Tables 4—6). For example, comparing the former assumption and the latter method, the cure rate at 12 months for the standard melarsoprol regimen was between 75.3—92.7% compared with 15.1—76.9%. For the short-course melarsoprol regimen the rates were 75.0—92.1% and 38.9—80.0%, respectively; and for eflornithine (12-month cure) they were 90.6—97.7% and 66.7—92.3%, respectively.

Kaplan—Meier survival probabilities for melarsoprol varied between 71.4—91.8% at 1 year and 56.5—87.9% at 2 years for the standard-course regimen to 73.0—91.1% at 1 year for the short-course regimen. For eflornithine, this varied from 79.9—97.4% at 1 year and 68.6—93.7% at 2 years. Estimates became unreliable at 24 months owing to heavy loss to follow-up. However, with the exception of Mossaka, survival at 12 months was >90% for eflornithine, whilst for melarsoprol it was <90% except in Kiri and Adjumani.

Of 854 relapses post discharge in the entire analysis group, 567 (66.4%) were diagnosed based on observation of parasites, 209 (24.5%) based on raised WBC count and 78 (9.1%) via clinician's discretion, with no differences among regimens (data not shown).

In a Cox proportional hazards model of the probability of failure up to the 12-month visit, after adjusting for project and treatment regimen, out of all baseline variables (Tables 1—3) age ≤12 years [hazard ratio (HR) 0.76, 95% CI 0.60—0.96], female gender (HR 0.77, 95% CI 0.65—0.90), passive case detection (HR 1.30, 95% CI 1.05—1.62), trypanosomes in the CSF (HR 1.30, 95% CI 1.06—1.59) and CSF WBC count >50/μl (HR 2.21, 95% CI 1.77—2.75) were associated with failure. From the above, only age ≤12 years (HR 0.86, 95% CI 0.80—0.94) and passive case detection (HR 1.15, 95% CI 1.08—1.23) were also associated with loss to follow-up before the 12-month visit in a similar survival model. There was no obvious correlation between the Kaplan—Meier probabilities of follow-up and failure-free survival at 12 months (see Figure 1) or 24 months (data not shown) across projects for the same regimen, although eflornithine cohorts
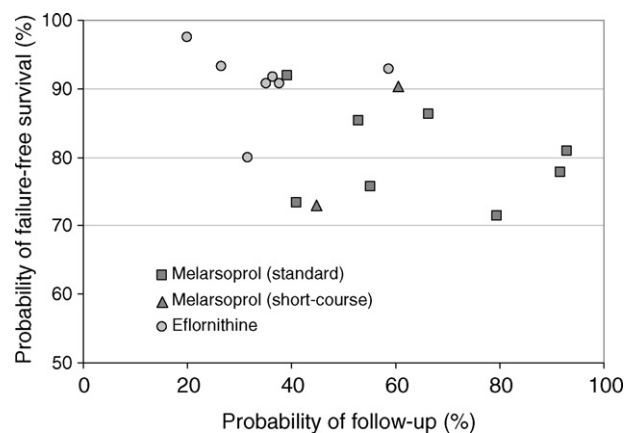

Figure 1   Correlation between the probabilities of failure-free survival and follow-up at the 12-month visit.

had worse follow-up and better observed effectiveness than the melarsoprol groups (Figure 1).

There was no evidence of a rising or declining trend in 12-month effectiveness in the four programmes that used any of the three regimens as first-line choice for at least six consecutive semesters. For example, with standard-course melarsoprol in Adjumani, survival was 93.2%, 89.6%, 92.0%, 92.2%, 94.2%, 90.7%, 90.6%, 91.4%, 91.8% and 98.3% for semesters 1 to 10, respectively (log-rank test for trend, $P = 0.406$). In Arua (also standard-course melarsoprol), survival was 80.2%, 69.1%, 63.4%, 71.9%, 77.6%, 61.1%, 66.7%, 67.2%, 73.1% and 67.1% for semesters 1 to 10, respectively (log-rank test for trend, $P = 0.839$ excluding semester 1). With short-course melarsoprol in Kiri, survival was 90.6%, 87.8%, 89.6%, 95.6%, 94.0% and 95.0% for semesters 1 to 6, respectively (log-rank test for trend, $P = 0.079$). With eflornithine in Ibba, survival was 94.7%, 91.8%, 91.9%, 94.5%, 91.1%, 93.6% and 90.0% for semesters 1 to 7, respectively (log-rank test for trend, $P = 0.457$).

4. Discussion

The data set presented is unique in being large and collected from a range of different locations. Our analysis consists of a large multicentre descriptive study presenting the outcome of the two main drugs used in HAT gambiense infections. Our analysis uses an alternative statistical method, Kaplan—Meier survival analysis, to what has typically been used in HAT treatment effectiveness analysis. In the past, various analytical approaches have been used to deal with incomplete follow-up attrition, ranging from only analysing patients who were followed-up to considering those lost to follow-up as cured. These methods calculate treatment failure rates as a percentage of treatment failures among the number of patients either treated or seen at follow-up.

The results show a lower CFR for patients treated with eflornithine compared with melarsoprol. The CFR for short-course melarsoprol in Kiri showed no difference from the standard regimen. The short-course melarsoprol patients in other centres are incomparable due to the low number of patients treated. These findings are in agreement with the current literature on efficacy and toxicity levels

Table 6 Endpoints and effectiveness measures for patients treated with eflornithine

	Caxito, Angola	Gamboma, Congo	Mossaka, Congo	Nkayi, Congo	Ibba, Sudan	Kiri, Sudan	Arua, Uganda
Case fatality rate during treatment							
Total dead/total admitted	4/279 (1.4%)	0/15	0/137	3/116 (2.6%)	27/2090 (1.3%)	4/482 (0.8%)	1/45 (2.2%)
Effectiveness at 12 months post discharge							
Discharged ≥12 months before programme/data set end	131	15	53	52	2082	369	12
Lost to follow-up	92	12	17	18	1421	248	6
Cured	36	2	31	30	554	105	5
Failed	3	1	5	4	107	16	1
Total cured/total treated, assuming lost to follow-up are cured	128/131 (97.7%)	14/15 (93.3%)	48/53 (90.6%)	48/52 (92.3%)	1975/2082 (94.9%)	353/369 (95.7%)	11/12 (91.7%)
Total cured/total treated, excluding lost to follow-up	36/39 (92.3%)	2/3 (66.7%)	31/36 (86.1%)	30/34 (88.2%)	554/661 (83.8%)	105/121 (86.8%)	5/6 (83.3%)
Survival probability in % (Kaplan–Meier)	97.4	91.7	79.9	90.7	92.9	90.7	93.3
Effectiveness at 24 months post discharge							
Discharged ≥24 months before programme/data set end	1	11	1	7	1448	198	10
Lost to follow-up	1	8	0	5	1064	163	1
Cured	0	2	0	0	255	18	8
Failed	0	1	1	2	129	17	1
Total cured/total treated, assuming lost to follow-up are cured	1/1 (100%)	10/11 (90.9%)	0/1	5/7 (71.4%)	1319/1448 (91.1%)	181/198 (91.4%)	9/10 (90.0%)
Total cured/total treated, excluding lost to follow-up	0/0	2/3 (66.7%)	0/1	0/2	255/384 (66.4%)	18/35 (51.4%)	8/9 (88.9%)
Survival probability in % (Kaplan–Meier)	93.7	91.7	71.7 [79.7 at 14 months][b]	25.9 [90.7 at 18 months][b]	85.2	68.6	83.0 [93.3 at 16 months][b]
Reasons for failure (% of all failures)[a]							
Death during treatment	4 (57.1)	0	0	3 (33.3)	27 (16.5)	4 (11.4)	1 (25.0)
Treatment incomplete	0	0	2 (20.0)	0	6 (3.7)	0	0
Death during follow-up	0	1 (100)	2 (20.0)	1 (11.1)	19 (11.6)	1 (2.9)	2 (50.0)
Parasites during follow-up	2 (28.6)	0	3 (30.0)	3 (33.3)	59 (36.0)	24 (68.6)	0
WBC increase during follow-up	0	0	3 (30.0)	2 (22.2)	36 (22.0)	6 (17.1)	1 (25.0)
Clinician's decision during follow-up	1 (14.3)	0	0	0	17 (10.4)	0	0
Total failures[a]	7	1	10	9	164	35	4

WBC: white blood cells.
[a] Includes failures that occurred after 24 months of discharge.
[b] Estimate unreliable due to small numbers [refer to estimate in brackets].

of melarsoprol and eflornithine.[15–20] Areas with documented melarsoprol refractoriness, such as Arua, Yumbe and Ibba, do not have particularly elevated CFRs compared with areas without documented resistance, showing that increased melarsoprol failure is not associated with fatality during treatment but with recurrence of disease during the follow-up period. For the four largest treatment centres, analysis by semester cohorts treated with the same drug regimen indicates that failure probability has remained consistent over the course of a programme.

In the first year of follow-up, the standard melarsoprol regimen has the overall lowest cure rates, but the values are spread across a wide range. Low cure rates of subfoci occur in Uganda; Arua and Yumbe have markedly higher failure rates, in contrast to the low rates in nearby Adjumani. South Sudan shows similar results between Kiri (low) and Ibba (high). Both situations appear to indicate that parasite populations followed the movements of human host populations, which in this area occur along a North–South axis across the border, both for war-related migrations and for ongoing commercial activity. These population flows connect Ibba with Arua and Yumbe on one axis, and Kiri with Adjumani (and Moyo) on another axis. Low melarsoprol cure probabilities in Mossaka are difficult to interpret owing to the low number of individuals studied.

Eflornithine has higher effectiveness than melarsoprol within 1 year of follow-up. In the second year, the cure probabilities decrease, demonstrating the importance of continued follow-up to 24 months. It is not possible to state whether failure probabilities increase more in the second year for any one drug regimen owing to limited follow-up rates. For example, Kiri is striking in that cure rates with eflornithine fall dramatically from 90.7% at 12 months to 68.6% at 24 months. Ibba also sees a fall in cure rates with eflornithine from 92.9% to 85.2%. However, the survival rate for eflornithine from Kiri at 2 years was strongly underestimated as a result of the very low follow-up rate, as shown by a recent analysis of an updated database from Kiri (F. Chappuis, unpublished observation). In general, our effectiveness estimates at 24 months should be interpreted with great caution owing to the considerable proportion of patients not followed up beyond 1 year. And whilst these decreases in cure rates with eflornithine appear dramatic, it must be borne in mind that cure rates with melarsoprol are already <90% at 12 months in all sites except Adjumani and Kiri (Adjumani has low melarsoprol failure rates, but it also has low rates of follow-up so the failure rates may have been underestimated).

Eflornithine treatment failures could have been associated with the age of patients, severe disease at admission or HIV co-infection.[21–23] Treatment failures with i.v. eflornithine are thought to occur disproportionately among children, who eliminate eflornithine at a faster rate. For this reason, higher doses have been recommended, particularly among naïve cases.[23] However, a recent publication on eflornithine safety and effectiveness now suggests that age plays a less important role as a risk factor and that higher doses do not improve effectiveness in children.[13] Advanced disease is a known risk factor for treatment failure.[11,13] The Kiri eflornithine group had 53.3% and 65.6% of patients with trypanosomes or a WBC count >50/µl in the CSF; the group averages were 43.9% and 52.1%, respectively. Case reports suggest that HIV-positive patients are less responsive to eflornithine, the hypothesis being that eflornithine's trypanostatic activity requires an active immune system to clear the parasites. We could not explore this issue as the HIV status of the patients was unknown.[11,13,21,22]

The Kaplan–Meier method yields failure estimates between the two crude methods, but is closer to the 'traditional' method of calculating the failure proportion as number failed/total treated and hence the assumption that cases lost to follow-up are cured. The main advantages of Kaplan–Meier are that patients with limited follow-up are included in the analysis group, resulting in less data loss and bias, more precision and no assumptions made about their final outcome. None the less, analysis is still subject to potential bias if patients not followed up feature a systematically different risk of treatment failure. Cost of travel/poor transport, days of missed income, fear of lumbar puncture and political instability can account for poor follow-up despite programme investment to improve it. Survival analysis suggested that children and actively screened cases had lower risk of failure and were overrepresented among patients followed up; however, the magnitude of these associations was small and both groups were a minority of all patients, suggesting a relatively mild overestimation of effectiveness. Melarsoprol-treated cohorts exhibited better follow-up and lower effectiveness than those receiving eflornithine, which may indicate selection bias and either overestimation or underestimation of effectiveness (those followed-up could either be the healthiest or, more probably, the sickest, i.e. relapsing patients). However, there was no apparent correlation between follow-up and effectiveness across projects, for the same regimen, suggesting little systematic bias related to differential follow-up, which would increase the reliability of our findings (see Figure 1). The reality may be more complex: certain groups of both healthy and relapsing patients might adhere to or default from the follow-up schedule, creating conflicting biases; the profile of these groups might vary across sites; and the above could be further confounded by site-specific effectiveness patterns. Investigation of patient reasons for defaulting HAT treatment monitoring visits would be useful.

There are other important limitations that affect the interpretation of the data. The study, being neither randomised nor controlled, does not allow for robust comparison between treatments or centres. It is also complicated by the fact that populations may have significantly varied between areas and over time, allowing important differences in baseline factors to exist. Data were often collected in difficult 'field' circumstances rather than research settings, thus affecting quality. However, randomised studies are extremely challenging to implement in these conditions. There thus exists an important need to monitor the 'effectiveness' of the limited range of stage 2 treatments for HAT.

The results of this descriptive analysis illustrate that melarsoprol is associated with poorer outcomes than eflornithine in most cases, suggesting that eflornithine could be promoted as first-line treatment for late-stage HAT gambiense infections. The remarkable stability of low failure probabilities in programmes that are near areas with known refractoriness indicates that refractoriness could be mapped and treatment strategies could be adapted accordingly. The

difficulties experienced in analysing the data owing to losses to follow-up point to the need for extensive investigation into the causes of losing patients to follow-up and a resulting strategy for their mitigation. The lack of information on HIV status and HAT infections necessitates a comprehensive exploration on the matter.[24]

To treat and control HAT better, less invasive diagnostic and staging methods are needed, especially as HAT is most prominent in resource-poor settings. Less staff-intensive therapies are also required, as both melarsoprol and eflornithine must be administered intravenously. Development of an efficacious, less toxic, more convenient treatment would greatly alleviate staff burden and influence more patients to seek treatment. A large, multicentre trial studying nifurtimox and eflornithine combination treatment (NECT) is currently ongoing.[25] NECT is shorter and requires only two daily eflornithine infusions and less total infusions than the conventional 14-day eflornithine treatment. In the near future this treatment may offer an alternative to the current monotherapies.

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