Trans R Soc Trop Med Hyg 2013; **107**: 176–182
doi:10.1093/trstmh/trs012 Advance Access publication 3 February 2013

ORIGINAL ARTICLE

Treatment practices in patients with suspected malaria in Provincial Hospital of Tete, Mozambique

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Received 16 March 2012; revised 24 September 2012; accepted 24 September 2012

Background: Nowadays, parasite-based diagnosis by microscopy or malaria rapid diagnostic tests (RDT) is universally promoted before malaria treatment. However, studies on adherence of primary caregivers to malaria test results have provided conflicting results.

Methods: The antimalarial and antibiotic prescription rates in patients with suspected malaria at Provincial Hospital of Tete, Mozambique, and the features associated with antibiotic prescription in non-severely ill parasite-negative patients were assessed.

Results: In March and April 2010, *Plasmodium falciparum* malaria was diagnosed by microscopy or RDT in 728 (27.2%) of 2672 patients tested. Almost all malaria patients were prescribed antimalarials and 20% were also given antibiotics. Of 1944 parasite-negative patients, 126 (6.5%) were prescribed antimalarials and 1213 (62.4%) antibiotics. Among non-severely ill parasite-negative patients with complete information (n = 1607), the antibiotic prescription rate was 68.8% and was more frequent with respiratory symptoms and leukocyte counts >10 000/μL (adjusted OR = 1.62, 95% CI 1.18–2.23 and adjusted OR = 2.12, 95% CI 1.66–2.71, respectively).

Conclusions: Adherence to malaria test results was good in this reference setting, but antibiotic prescription was relatively frequent in clinically stable non-malaria patients. Optimal management of parasite-negative patients must be further defined along with programmatic deployment of the parasite-based strategy.

Keywords: Malaria, Rapid diagnostic tests, Treatment practice, Microscopy, Antimalarials, Antibiotics

Introduction

In the last few years, management of malaria has radically changed with the large-scale deployment of malaria rapid diagnostic tests (RDT) in most endemic areas.[1] The accuracy and simplicity of such tests have recently led the WHO to promote parasite-based diagnosis of malaria (either by microscopy or RDT) before treatment, instead of the previous 'presumptive treatment' approach.[2] The current performance of most RDTs is such that they can replace microscopy, at least for the diagnosis of uncomplicated *Plasmodium falciparum* malaria,[3,4] and RDTs even outperform microscopy in some settings.[5,6] Compared with 'presumptive treatment', the parasite-based strategy for managing fever in malaria-endemic settings has proven to dramatically reduce malaria overdiagnosis and overtreatment,[7,8] to be safe and cost-effective[9–12] and to improve health outcomes.[13] The recent decline in malaria burden is another argument to advocate the parasite-based strategy,[14–16] but the universality of such an approach is still debated.[17,18]

However, recent studies have highlighted frequent reticence in health centres and rural hospitals to withhold malaria treatment in parasite-negative febrile patients[18–20] and the high frequency of antibiotic prescription in these patients.[7,18,21] Prescription behaviours have been less investigated in larger referral hospitals since the deployment of RDTs.

The purpose of this study was to assess the treatment practices of clinical officers in the emergency ward of Provincial Hospital of Tete (PHT), Mozambique, during the programmatic implementation of the parasite-based strategy (microscopy and/or RDT). A secondary objective was to identify clinical or first-line laboratory features associated with antibiotic prescription in non-malaria patients.

Methods

Study setting, design and population

The Province of Tete, located in central Mozambique, is an area with perennial transmission of malaria (mostly *P. falciparum*),

with peaks during the rainy season (February–April). The entomological inoculation rate was estimated at 38 infective bites/person/year for central Mozambique in 2004.[22] Treatment based on parasitological diagnosis has been promoted by the national malaria control programme since 2007, after the first artemisinin-based combination therapies were deployed in the country. The prevalence of HIV infection is high in the province (>10% of the adult population).

PHT serves as a reference hospital for the 1 700 000 inhabitants of the province. According to hospital statistics, approximately 50 000 patients present yearly with suspected malaria. In 2010 (the year of this study), RDTs were progressively implemented by the national malaria control programme in all provincial health facilities. In PHT during this transitional period, diagnosis of malaria still relied on microscopy for children aged ≤5 years. In older children and adults, a RDT was performed and, in the case of a positive result, a blood film was examined for confirmation and determination of parasite density. Of note, for pragmatic reasons, management could be based on a RDT alone when microscopy was not rapidly available for any reason (problems with electricity supply, night or weekend shifts, work overload).

This study on treatment practices was part of a larger laboratory research project conducted from January to April 2010 aimed at investigating the frequency of the prozone effect with different RDTs in *P. falciparum* malaria patients with high parasite density. The methodology and results of this laboratory study have been reported elsewhere.[23] Briefly, patients of any age with suspected malaria were prospectively enrolled in the emergency ward 24 h a day/7 days a week after providing informed consent. During this study, all children aged ≤5 years were assessed with a full blood count performed using an automated haematology analyser (KX-21N; Sysmex, Kobe, Japan) and Giemsa-stained blood film microscopy,[23] following national guidelines. All older children and adults were also tested by microscopy for study purposes, in addition to the routine full blood count and RDT specified by the national programme. Three RDT brands (Paracheck-Pf, Orchid Biomedical Systems, Goa, India; ICT Malaria Pf Cassette Test, ICT Diagnostics, Cape Town, Republic of South Africa; SD Malaria Antigen Pf FK50, Standard Diagnostics Inc., Hagal-Dong, Korea), all based on detection of histidine-rich protein-2, were used according to availability during the period of this laboratory study. In all patients with malaria, parasite density was quantified and hyperparasitaemic samples were submitted to an additional set of study RDTs.[23] All tests were performed under the daily supervision of the laboratory investigators (PG, AS and JS).

The present observational study on treatment practices was conducted prospectively in parallel to the laboratory study, but only in March and April 2010. Initial evaluation of enrolled patients and the prescribed treatment (antimalarial and/or antibiotic) were additionally registered for this purpose (see below).

Management of study participants

Almost all consecutive participants were initially assessed by clinical officers ('técnicos de medicina'; 3 years of medical school) as normally required in emergency wards of Mozambican reference hospitals. Clinical symptoms and signs of patients with suspected malaria were prospectively registered in pre-formatted individual report forms. A set of signs of disease severity (based on the WHO clinical criteria of severe malaria) was specifically listed as tick boxes on the forms, to be filled in during the initial evaluation. All enrolled patients were next submitted to the first-line laboratory tests (determination of haemoglobin level, leukocyte count with differentiation, platelet count) and blood film microscopy as required for the laboratory study. In addition, older children and adults were also tested with the available programme RDT according to national malaria control guidelines. Additional laboratory or radiological diagnostic evaluation was performed at the clinician's discretion and was not recorded for this study.

Laboratory results were attached to the individual forms and patients were sent back to the emergency clinicians as soon as they were available. For children aged ≤5 years, results of full blood count and supervised microscopy were usually obtained within 2–3 h after blood sampling. For older children/adults, haematological and RDT results were rapidly available. Emergency clinicians were then authorised to manage the patients according to the national protocols. Clinicians recorded whether patients were hospitalised or treated as outpatient in pre-formatted forms (boxes 'YES' and 'NO' to tick for each option) and whether they decided to prescribe antimalarial or/and antibiotic treatment (also by ticking 'YES' and 'NO' for each therapeutic option). It had been convened that the two 'NO' boxes ticked corresponded to 'prescription of symptomatic treatment only', that the 'YES' box ticked for antimalarial and the 'NO' box for antibiotic meant 'prescription of antimalarial treatment alone' (and conversely for 'prescription of antibiotic treatment alone') and that the two boxes 'YES' had to be ticked when both treatments were prescribed simultaneously. Of note, for older children and adults, in case supervised microscopy provided at a later stage any laboratory criteria of malaria severity (see below) or detected any false-negative RDT results, emergency clinicians were personally contacted by the laboratory supervisors to trace the patients and, if needed, to modify the treatment according to the newly available results.

Pre-study training was provided in January 2010 to all emergency clinicians in order to refresh and standardise clinical assessment of malaria symptoms and complications[24] and interpretation of laboratory criteria for malaria severity (parasite density ≥5% of red blood cells, presence of haemozoin in leukocytes or presence of schizonts). No specific refreshment course was provided regarding malaria treatment. During the study, the first-line treatment for uncomplicated *P. falciparum* cases was the fixed-drug combination artemether/lumefantrine; severe malaria, as defined by the 2000 WHO criteria,[24] was treated with i.v. quinine. Antibiotics most prescribed for outpatients were ampicillin, trimethoprim/sulfamethoxazole or chloramphenicol. Empirical antibiotic treatment for admitted patients mainly consisted of ampicillin combined with gentamicin or chloramphenicol. Fluoroquinolones and cephalosporins could be prescribed at the discretion of the supervising physicians.

Sample size, data management and statistical analysis

No specific assumption was made on the sample size since it was the first such study in the emergency ward of PHT in Mozambique. However, since approximately 5700 malaria suspects had to be included from January to April to investigate the

prozone effect in patients with high parasite density,[23] we decided to restrict this study on treatment practices to all consecutive participants enrolled in the last 2 months. We considered this a good compromise between the substantial additional workload for the clinicians and the representativeness of the data for prescribing practices.

As explained, emergency clinicians had to record the symptoms and signs of malaria suspects at initial presentation, systematically check for and report on signs of severity (by filling the pre-defined list), and specify the therapeutic decision when the haematological and microscopy or RDT results (according the local age-based protocol) were available. Accuracy of clinical data registration was controlled once a week for a subset of patients by the clinical supervisor through cross-checking with hospital files. Laboratory data registration was limited to the results of haematology, microscopy and RDT for this study and almost daily supervised by the laboratory investigators. Data recorded in the individual forms were then entered in Microsoft Access (Microsoft Corp., Redmond, WA, USA) and analysed with SPSS software v.19.0 (SPSS Inc., Chicago, IL, USA). Differences between proportions were tested for significance using the Pearson's χ^2 test. All tests were two-tailed and a p-value of <0.05 indicated statistical significance. For investigating the features associated with antibiotic prescription in non-malaria patients, we first excluded the patients presenting with any clinical sign of severity, since antibiotics are assumed to be justified in such cases. Presenting features studied by univariate analysis were age ($\leq$5 years vs older children/adults), gender, presence of respiratory symptoms, vomiting or diarrhoea, absence of focal symptom/sign of infection, and the rapidly available laboratory parameters with the following cut-off values: haemoglobin level $<$10 g/dL; leukocyte count $>$10 000/μL and platelet count $<$150 000/μL. Factors associated by univariate analysis with antibiotic prescription in non-severe non-malaria cases were then introduced in the multivariate model.

Ethical issues

Patients and children's parents or guardians were informed in Portuguese or in the local language (Nhungue) about the purposes of the main laboratory study and of the clinical nested study. Written informed consent was required prior to enrolment. The clinical study was observational and followed the national diagnostic and treatment malaria guidelines, with no additional risk than for standard of care.

Results

In March and April 2010, 2672 consecutive patients with suspected malaria were evaluated in the emergency ward. The male/female ratio was 0.95, 1110 (41.5%) were children aged $\leq$5 years (Table 1) and 574 patients (21.5%) were admitted to hospital. Of the included patients, 1142 (42.7%) were assessed by microscopy alone (mostly children $\leq$5 years), 1344 (50.3%) by RDT and microscopy and 186 (7.0%) by RDT alone.

A total of 728 patients (27.2%) were diagnosed with *P. falciparum* malaria, including 308 (27.0%) of the 1142 assessed by microscopy alone and 420 (27.5%) of the 1530 tested by RDT. Of note, among the 1344 patients evaluated by both the programme RDT and microscopy, 15 (1.1%) RDT results were falsely negative, including 12 because of low parasite density and 3 due to prozone.[23] The proportion of malaria cases was lower among children aged $\leq$5 years than among older children/adults (21.8% vs 31.1%; $p < 0.001$).

Baseline clinical and laboratory features of the evaluated patients are presented in Table 1. Data were incomplete for approximately 15% of the patients. Severe malaria was diagnosed at admission in 178 (24.5%) of the 728 malaria cases, including 92 (38.0%) of the 242 children $\leq$5 years and 86 (17.7%) of the 486 older children/adults. The distribution and frequency of severity criteria are provided in Table 1.

Compared with non-malaria cases, patients with malaria were more often referred from another health facility and presented more frequently with vomiting and less frequently with respiratory symptoms or diarrhoea. Anaemia (haemoglobin level $<$10 g/dL), severe anaemia (haemoglobin level $<$5 g/dL) and thrombocytopenia (platelet count $<$150 000/μL) were more often observed in malaria patients, while elevated leukocyte count ($>$10 000/μL) was less frequent. Patients with malaria presented more often with clinical signs of severity than non-malaria cases.

The frequency of prescription of antimalarials and/or antibiotics according to tests results is reported in Table 2. Of the parasite-positive patients, 87.1% were prescribed antimalarials, and data were missing for an additional 9.2%. Non-prescription of antimalarials (box 'NO' ticked in 27 cases) corresponded mostly to initial false-negative RDT results ($n = 15$ as already mentioned), errors in data recording or already completed antimalarial course ($n = 6$ for each). About 20% of patients with parasite-positive results received antibiotics concomitantly, most of them (55%) having been diagnosed with severe malaria. Information on antibiotic prescription was missing in 24.3% of parasite-positive patients, but in almost all cases the box 'YES' had been ticked for 'antimalarial'.

Regarding parasite-negative patients, 6.5% of them were prescribed antimalarials, with no significant difference according to the diagnostic method (Table 2). In contrast, 62.4% of the patients with parasite-negative results were given antibiotics, once again regardless of the type of diagnostic test. Information was not available for an additional 10.6% of the parasite-negative patients.

Antibiotics were given to 107 (81.7%) of 131 severely ill parasite-negative patients with complete prescription information. In non-severe parasite-negative patients with complete information ($n = 1607$), 1106 (68.8%) were given antibiotics and prescription rates were $>$60% whatever the presenting feature (Table 3). In this subgroup, antibiotic prescription was associated by univariate analysis with the presence of respiratory symptoms, the absence of focal symptom/sign of infection, haemoglobin concentration $>$10 g/dL and a leukocyte count $>$10 000/μL (Table 3). Both the presence of respiratory symptoms and a leukocyte count $>$10 000/μL remained associated with antibiotic prescription by multivariate analysis, with adjusted ORs of 1.62 (95% CI 1.18–2.23) and 2.12 (95% CI 1.66–2.71), respectively (Table 4).

Discussion

In Mozambique, as in many other malaria-endemic countries, WHO-recommended parasite-based malaria diagnosis and

Table 1. Baseline demographic, clinical and laboratory characteristics of the study population (n = 2672) by malaria diagnosis

	Total evaluated patients (n = 2672)	Malaria cases (n = 728)	Non-malaria cases (n = 1944)	p-value
Demographic data				
Male	1303 (48.8)	315 (43.3)	988 (50.8)	0.001
Children aged ≤5 years	1110 (41.5)	242 (33.2)	868 (44.7)	<0.001
Referral from another health facility	196/2310 (8.5)	82/501 (16.4)	114/1809 (6.3)	<0.001
Presenting symptoms				
Fever	2246/2373 (94.6)	499/515 (96.9)	1747/1858 (94.0)	0.01
Respiratory symptoms	834/2340 (35.6)	111/496 (22.4)	723/1844 (39.2)	<0.001
Vomiting	485/2340 (20.7)	124/501 (24.8)	361/1839 (19.6)	0.01
Diarrhoea	483/2350 (20.6)	77/504 (15.3)	406/1846 (22.0)	0.001
No focal symptom/sign	932/2362 (39.5)	213/509 (41.8)	719/1853 (38.8)	0.22
Laboratory testing				
Haemoglobin level <10 g/dL	864/2397 (36.0)	264/586 (45.1)	600/1811 (33.1)	<0.001
Leukocyte count >10 000/μL	971/2406 (40.4)	177/589 (30.1)	794/1817 (43.7)	<0.001
Platelet count <150 000/μL	512/2390 (21.4)	323/589 (54.8)	189/1801 (10.5)	<0.001
Severity parameters				
At least one clinical sign of severity	266/2672 (10.0)	127/728 (17.4)	139/1944 (7.2)	<0.001
Haemoglobin level <5 g/dL	69/2387 (2.9)	34/586 (5.8)	35/1801 (1.9)	<0.001

Data are number (%) or number/number with available data (%), unless otherwise indicated.
Distribution and frequency (n, %) of severity criteria in malaria patients (n = 728) were as follows (more than one criterion possible per patient): extreme weakness/prostration (103, 14.1%); parasite density ≥5% of red blood cells (50, 6.9%); severe anaemia (34, 4.7%); repeated generalised seizures (19, 2.6%); dyspnoea (15, 2.1%); coma (13, 1.8%); shock (8, 1.1%); jaundice (7, 1.0%) and spontaneous bleeding (2, 0.3%).

Table 2. Prescription behaviour (antimalarials and/or antibiotics) according to the rapid diagnostic test (RDT) and microscopy results

	RDT (n = 1530)		Microscopy (n = 1142)		Total (n = 2672)	
	Positive (n = 420)	Negative (n = 1110)	Positive (n = 308)	Negative (n = 834)	Positive (n = 728)	Negative (n = 1944)
Antimalarials						
Yes	368 (87.6)	72 (6.5)	266 (86.4)	54 (6.5)	634 (87.1)	126 (6.5)
No	19 (4.5)	926 (83.4)	8 (2.6)	684 (82.0)	27 (3.7)	1610 (82.8)
Unknown	33 (7.9)	112 (10.1)	34 (11.0)	96 (11.5)	67 (9.2)	208 (10.7)
Antibiotics						
Yes	95 (22.6)	695 (62.6)	70 (22.7)	518 (62.1)	165 (22.7)	1213 (62.4)
No	228 (54.3)	311 (28.0)	158 (51.3)	214 (25.7)	386 (53.0)	525 (27.0)
Unknown	97 (23.1)	104 (9.4)	80 (26.0)	102 (12.2)	177 (24.3)	206 (10.6)

Data are number (%).

treatment has been recently implemented by the national control programme. This study explored the adherence of clinical officers in a large urban reference hospital to current clinical guidelines. Antimalarials were prescribed in virtually all patients with parasitological confirmation and in a sizeable proportion of patients with a negative parasite result. Treatment practices were similar regardless of the malaria diagnostic method. In addition, antibiotics were often given to non-severely ill parasite-negative patients, whatever the clinical presentation. Antibiotic prescription was, however, more frequent with respiratory symptoms and leukocyte counts >10 000/μL.

Table 3. Clinical and laboratory presenting features associated in the univariate analysis with antibiotic prescriptions in non-severely ill parasite-negative patients (n = 1607 with complete prescription information)

Presenting feature	No. of antibiotic prescriptions/no. present features	No. of antibiotic prescriptions/no. absent features	p-value	OR (95% CI)
Children aged ≤5 years	490/729 (67.2)	616/878 (70.2)	0.21	1.15 (0.93–1.42)
Male	558/803 (69.5)	548/804 (68.2)	0.59	1.06 (0.86–1.31)
Respiratory symptoms	443/586 (75.6)	604/945 (63.9)	<0.001	1.75 (1.39–2.20)
Vomiting	198/304 (65.1)	848/1227 (69.1)	0.19	0.83 (0.64–1.09)
Diarrhoea	223/320 (69.7)	826/1214 (68.0)	0.59	1.08 (0.83–1.41)
No focal symptom/sign of infection	418/646 (64.7)	633/891 (71.0)	0.009	0.75 (0.60–0.93)
Haemoglobin level <10 g/dL	352/473 (74.4)	682/1013 (67.3)	0.006	1.41 (1.10–1.80)
Leukocyte count >10 000/μL	507/647 (78.4)	532/845 (63.0)	<0.001	2.13 (1.69–2.69)
Platelet count <150 000/μL	98/146 (67.1)	933/1334 (69.9)	0.51	0.88 (0.61–1.26)

Data are number (%) or number/number with available data (%), unless otherwise indicated.

Table 4. Presenting features associated in multivariate analysis with antibiotic prescription in non-severely ill parasite-negative patients

Presenting feature	p-value	Adjusted OR (95% CI)
Presence of respiratory symptoms	0.003	1.62 (1.18–2.23)
Absence of focal symptom/sign of infection	0.35	1.16 (0.85–1.57)
Haemoglobin level <10 g/dL	0.1	1.24 (0.96–1.61)
Leukocyte count >10 000/μL	<0.001	2.12 (1.66–2.71)

This study has important limitations. First, collected clinical data were kept as simple as possible since it was an additional effort for the hospital staff during routine activities in a crowded emergency ward; also, data recording was incomplete, but the proportion of missing values was acceptable compared with the large sample size and appeared to be randomly distributed. Second, the study was observational with no control group or historical series for comparison, preventing us from assessing the actual impact of the new strategy on antibiotic prescription patterns. Third, additional tests such as biochemistry, radiography or HIV testing were not performed systematically and results were not recorded, while other tests such as blood cultures were not available. Consequently, factors associated with, and adequacy of, antibiotic prescription could not be investigated in detail. Fourth, treatment practices were assessed in a study setting, with initial training, use of special forms and precise instructions—all aspects that did not reflect usual field conditions. Likewise, the findings may not be transposed to other types of health facilities, with different prescribers and smaller laboratory capacities. Finally, although initially planned, hospital follow-up data could not be properly registered and patient outcome could not be assessed.

The prevalence of malaria in ill patients presenting in the emergency department of PHT increased dramatically from January to April 2010 because the onset of the rainy season was unusually late. It reached 27% in the March/April period compared with 12% in the 4-month laboratory study.[23] Such abrupt seasonal variations in malaria-attributable fevers are well known in transitional malaria settings[25] and deserve special consideration in clinical decision-making. The impact of the pre-test probability of malaria on RDT predictive values may not be immediately appreciated by less educated health-care providers.[25] In addition, the rather high proportion of severe malaria observed across all age groups was probably due to the referral pattern for younger children, but might be related to the shift of malaria complications to older age in areas with declining transmission[26] and to the high underlying HIV prevalence in adults.[27]

Recent studies on prescribing behaviours in health centres and district hospitals using parasite-based diagnosis showed that adherence to positive test results is usually good.[18] However, the proportions of parasite-negative patients receiving any antimalarial varied extremely, from 4% in Tanzania[28] to 82.6% in Burkina Faso,[19] but exceeded 25% in almost all studies.[18] With 6.5% of antimalarial prescription in non-malaria cases (up to 17.2% in the worst case scenario with all missing data categorised as antimalarial treatment), this study ranked favourably. Reasons for such disparities between studies may depend on design (observational versus interventional), setting (peripheral versus referral health facilities) and professional level of drug prescribers.[29] In contrast to other studies,[11,20,30] the RDT design itself did not influence negatively clinicians' adherence compared with traditional microscopy.

A sizeable number of malaria patients were also given antibiotics, but this often appeared clinically justified since most of them presented with severe malaria, at high risk of concomitant bacteraemia.[31] Similarly, antibiotics are indicated in

severely ill patients with non-malaria febrile illness. However, about two-thirds of the parasite-negative patients with no clinical sign of severity were given antibiotics, and even more when respiratory symptoms were present. High rates of antibiotic prescription have often been reported in non-malaria patients.[18] This study was not designed to explore the appropriateness of antibiotic prescription and therefore no conclusion can be drawn on a potential overuse, although there is some evidence that antibiotic use has increased since the deployment of malaria rapid diagnostic testing.[7,21] The problem remains that clinical assessment of febrile conditions is notoriously insufficient to identify the subset of patients for whom antibiotics would be most beneficial, and no clinical prediction rule has been robustly validated in developing countries.[32,33] We observed here that emergency clinicians did take into account the result of leukocyte counts for initial decision-making, but this marker is far from being universally available, is little helpful in ruling in serious infections and has no value for ruling out severe conditions.[34] Other markers of inflammation such as C-reactive protein and procalcitonin provide better diagnostic values[34] but are not available in low-resource settings. Development of such 'bacterial' biomarkers under point-of-care format and with high negative likelihood ratios would be of invaluable help for first-line caregivers often left alone with the difficult decision to prescribe (or withhold) antibiotics in non-malaria febrile illnesses.[35,36]

In conclusion, this study demonstrated good adherence to malaria tests results in this reference setting, but also revealed that antibiotics were frequently prescribed in non-malaria patients who had no signs of severe illness. More studies are required to monitor the rates of antibiotic prescription in the increasing number of febrile patients not found with malaria and to further analyse the drivers for such prescriptions.

Authors' contributions: EB, PG and JJ conceived the study; EB, PG, ADW, AS, JS, CDDM and JJ designed the study protocol; ADW and CDDM supervised the clinical management; PG, AS and JS carried out the laboratory work; EB, PG, ADW and JJ analysed and interpreted the data; EB drafted the manuscript; PG, ADW, AS, JS, CDMM and JJ critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. EB is guarantor of the paper.

Acknowledgements: The authors thank Dr Jules Aimé Bonou Mahoudo and Dr Jesus Maria Baltazar for helping in patient care and data collection; and Dr Cedric Yansouni for critical review of the manuscript.

Funding: This work was conducted within a collaborative health project (Rede Integrada II) financed by the Flemish International Cooperation Agency.

Competing interests: None declared.

Ethical approval: This study was approved by the Institutional Review Board of the Institute of Tropical Medicine, Antwerp, and the Ethical Committee of Antwerp University (Belgium) as well as the National Bioethical Committee of the Ministry of Health (Mozambique).

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