ORIGINAL ARTICLE

Effect of Artesunate–Amodiaquine on Mortality Related to Ebola Virus Disease

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ABSTRACT

BACKGROUND

Malaria treatment is recommended for patients with suspected Ebola virus disease (EVD) in West Africa, whether systematically or based on confirmed malaria diagnosis. At the Ebola treatment center in Foya, Lofa County, Liberia, the supply of artemether–lumefantrine, a first-line antimalarial combination drug, ran out for a 12-day period in August 2014. During this time, patients received the combination drug artesunate–amodiaquine; amodiaquine is a compound with anti–Ebola virus activity in vitro. No other obvious change in the care of patients occurred during this period.

METHODS

We fit unadjusted and adjusted regression models to standardized patient-level data to estimate the risk ratio for death among patients with confirmed EVD who were prescribed artesunate–amodiaquine (artesunate–amodiaquine group), as compared with those who were prescribed artemether–lumefantrine (artemether–lumefantrine group) and those who were not prescribed any antimalarial drug (no-antimalarial group).

RESULTS

Between June 5 and October 24, 2014, a total of 382 patients with confirmed EVD were admitted to the Ebola treatment center in Foya. At admission, 194 patients were prescribed artemether–lumefantrine and 71 were prescribed artesunate–amodiaquine. The characteristics of the patients in the artesunate–amodiaquine group were similar to those in the artemether–lumefantrine group and those in the no-antimalarial group. A total of 125 of the 194 patients in the artemether–lumefantrine group (64.4%) died, as compared with 36 of the 71 patients in the artesunate–amodiaquine group (50.7%). In adjusted analyses, the artesunate–amodiaquine group had a 31% lower risk of death than the artemether–lumefantrine group (risk ratio, 0.69; 95% confidence interval, 0.54 to 0.89), with a stronger effect observed among patients without malaria.

CONCLUSIONS

Patients who were prescribed artesunate–amodiaquine had a lower risk of death from EVD than did patients who were prescribed artemether–lumefantrine. However, our analyses cannot exclude the possibility that artemether–lumefantrine is associated with an increased risk of death or that the use of artesunate–amodiaquine was associated with unmeasured patient characteristics that directly altered the risk of death.

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The outbreak of Ebola virus disease (EVD) in West Africa has led to more than 28,000 cases and has claimed more than 11,000 lives since the outbreak was first declared in March 2014, with most of the burden of disease observed in Guinea, Sierra Leone, and Liberia.[1] Few treatment practices or therapeutics are known to significantly reduce the risk of death. Recent in vitro assessments of drugs that have been approved by the U.S. Food and Drug Administration for anti-EVD activity have identified a number of candidates among compounds that are used to treat other diseases, including malaria.[2] However, little to no evidence exists on the clinical efficacy of any of these compounds against EVD.

Guidelines for the management of EVD recommend treatment for malaria in patients with suspected EVD, either for those patients in whom malaria has been confirmed by a positive laboratory or rapid diagnostic test or for all patients with suspected EVD regardless of malaria diagnosis.[3,4] The latter option (systematic treatment regardless of malaria confirmation) is often preferred in settings with a high malaria burden because of the prophylactic effect of malaria drugs, even in the absence of current infection. Some guidelines recommend an artemisinin-based combination of artemether and lumefantrine as the first choice of therapy because of concerns about potential liver-related toxic effects of amodiaquine in the primary alternative combination, artesunate–amodiaquine.[3]

In August 2014, the Ebola treatment center in Foya, Lofa County, Liberia, which was supported by Médecins sans Frontières, ran out of its supply of artemether–lumefantrine after a sudden spike in admissions to the center (Fig. 1). During a 12-day period, artesunate–amodiaquine was supposed to be prescribed systematically for all patients with suspected EVD who were admitted to the Ebola treatment center, with no other known systematic changes in care. Although this situation was unplanned, it provided the conditions to explore the possible differential effects of these two antimalarial therapies on

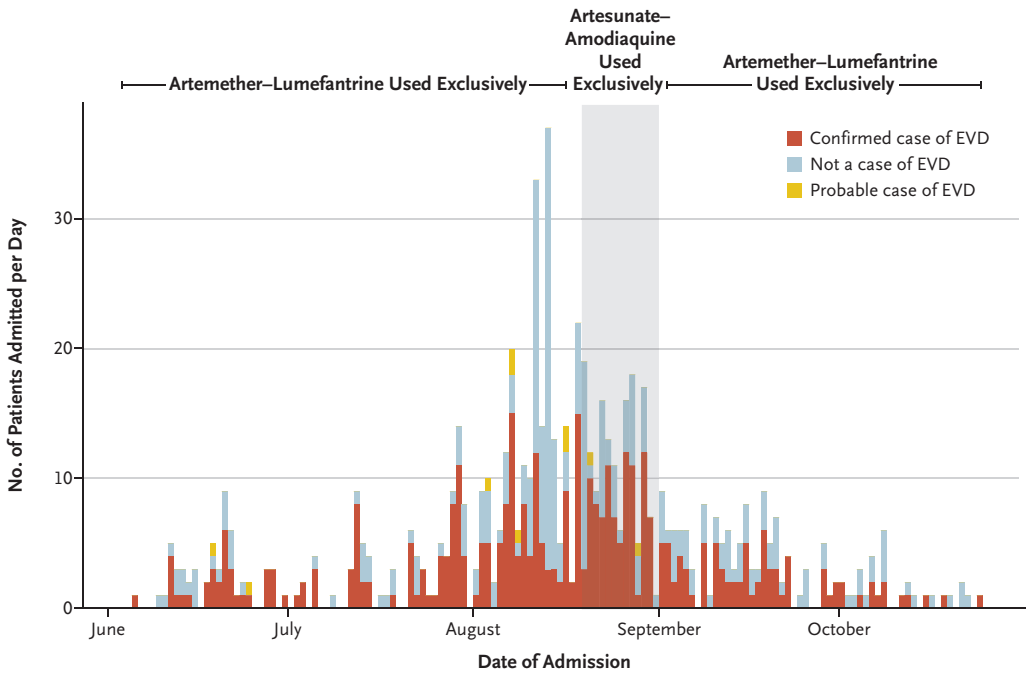

Figure 1. Patients Admitted to the Ebola Treatment Center in Foya, Liberia, June 5 to October 24, 2014.

The number of new cases admitted per day to the Ebola treatment center in Foya, Lofa County, Liberia, are shown, according to Ebola virus disease (EVD) status (confirmed EVD, probable EVD, or no EVD). The gray-shaded region represents the period during which artemether–lumefantrine was out of stock and artesunate–amodiaquine was the only antimalarial drug prescribed to patients.

survival among patients with confirmed EVD. Our interest in making these comparisons was driven by in vitro results that showed the efficacy of amodiaquine in inhibiting Ebola virus activity.[2] In the current study, we estimated the effectiveness of artesunate–amodiaquine, as compared with artemether–lumefantrine or no antimalarial treatment, in reducing mortality among patients with confirmed EVD who were admitted to the Ebola treatment center in Foya.

METHODS

STUDY SETTING

The first cases of EVD in Lofa County were reported in March 2014. The Ebola treatment center in Foya, which was initially a 10-bed isolation unit in a former refugee transit center, had no additional confirmed cases until a subsequent wave started in early June 2014. Bed and staff capacity increased as the number of patients increased; the bed capacity reached 100 beds in August 2014, at which time more than 100 new confirmed cases were being admitted each week.

According to protocol, all patients with suspected EVD who were admitted to the Ebola treatment center were supposed to be prescribed standard treatment consisting of prophylactic antibiotics and a 3-day course of the antimalarial combination therapy artemether–lumefantrine, with the dose determined according to the age of the patient.[3] Prepackaged standard treatment was supposed to be provided to each patient on admission and included a full course of antibiotics and antimalarial drugs. In addition, supportive treatment, including fluid replacement, was given according to the needs of the patients, although fluids were often provided only orally during the peak of the epidemic (see Fig. S5 in the Supplementary Appendix, available with the full text of this article at NEJM.org). However, on August 19, 2014, the supply of artemether–lumefantrine ran out, and during the subsequent 12-day "stock-out" period, patients who would have normally been prescribed artemether–lumefantrine were prescribed a 3-day course of another artemisinin-based combination, coformulated artesunate–amodiaquine, with the dose determined according to the age of the patient. No other systematic changes in patient care occurred during this period.

CLINICAL DATA

On admission, a venous blood sample was obtained from each patient for laboratory testing, including confirmation of EVD and malaria. The confirmation of EVD was based on the results of a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay (RealStar Filovirus Screen RT-PCR Kit 1.0, Altona Diagnostics). Patients with positive results on RT-PCR were considered to have confirmed EVD, and those with negative RT-PCR results after at least 72 hours from the onset of symptoms were considered to be negative for EVD. Patients classified as negative for EVD and those without available RT-PCR results were excluded from this analysis. Malaria was confirmed according to the results of a rapid antigen-detection test that detects the four primary species causing human malaria (BinaxNOW Malaria, Alere).

The laboratory confirmation of EVD and malaria was performed by the European Mobile Laboratory Consortium. Whole venous blood samples were shipped in accordance with the World Health Organization criteria for shipping and handling infectious substances[5] to Guéckédou, Guinea, the closest available laboratory, for laboratory confirmation during most of the study period, until September 12, 2014, when on-site laboratory services became available.

EPIDEMIOLOGIC SURVEILLANCE

The current analyses are based on individual patient-level data that were compiled by a staff epidemiologist from case-investigation forms, clinical files, and laboratory results from June 5 through October 24, 2014, for patients at the Ebola treatment center. Case-investigation forms were used by trained staff at the Ebola treatment center to record patient characteristics, including demographic and epidemiologic information, time of onset of symptoms, and clinical signs and symptoms at admission. Clinical files, which were kept in a low-risk zone of the center, were used to record each patient's prescribed treatments, with no indication of whether the drug was provided to and taken by the patient.

We used standard case definitions for suspected, probable, and confirmed cases of EVD that were established by the World Health Organization and Liberian Ministry of Health.[6] The time to admission was defined as the number of days between the onset of symptoms and admis-

sion to the Ebola treatment center. Viral load was expressed as a cycle-threshold value (i.e., the number of RT-PCR cycles needed to detect Ebola virus RNA). The total number of inpatients with suspected, probable, or confirmed EVD who were receiving care at the Ebola treatment center at the time a patient was admitted was used as a measure of workload at the facility.

STUDY OVERSIGHT

These analyses, which were performed in collaboration with the Liberian Ministry of Health, were based on retrospectively collected data without patient identifiers and were exempt from review by the ethical review board of the Médecins sans Frontières. All the authors vouch for the completeness and accuracy of the analyses presented.

STATISTICAL ANALYSIS

The distribution of key potential confounders in the relationship between antimalarial treatment and Ebola mortality was compared with the use of summary statistics, such as the mean or median for continuous variables and proportions for binary or categorical variables. To test for significant differences in distributions of the variables among the groups categorized by antimalarial prescription status, we used the Kruskal–Wallis test for continuous covariates and the chi-square or Fisher's exact test for categorical variables.[7,8] Two-sided P values less than 0.05 were considered to indicate statistical significance for all statistical tests. To explore the effect of malaria treatment on EVD-related mortality, we used Poisson regression models with robust error variance.[9] In adjusted analyses, we included risk factors for death from EVD that had been identified in previous studies or by an expert in the field[10-12] and compared their effects using alternative models according to Akaike's information criterion.[13] All adjusted analyses included only patients with complete data on the variables of interest, including clinical outcome, malaria treatment prescribed (including no prescription), and potential confounders. We also considered alternative models with different covariates and covering different time windows during the study period. The main analyses were performed with the use of the R statistical package (the R Foundation for Statistical Computing) and STATA statistical software, version 12 (StataCorp); source code for the main analyses is available on request.

RESULTS

PATIENTS

A total of 382 patients with confirmed EVD were admitted to the Ebola treatment center in Foya from June 5 through October 24, 2014; of these patients, 381 were included in our analysis and 1 patient was excluded because of missing outcome data. We categorized the patients according to their antimalarial drug prescription status into one of four groups: a group that included 194 of 288 patients (67.4%) with confirmed EVD who were hospitalized between June 6 and August 18, 2014, and after August 30, 2014, and who received artemether–lumefantrine as part of the recommended treatment for patients with suspected EVD[3] (artemether–lumefantrine group) (Fig. 1); a group that included 71 of 93 patients (76.3%) who received artesunate–amodiaquine from August 19 through 30, 2014, when artemether–lumefantrine was not available in the facility (artesunate–amodiaquine group); a group that included 63 of the 381 patients (16.5%) with confirmed EVD who did not receive antimalarial therapy, possibly because they tested negative for malaria or because of rationing of artemether–lumefantrine during the period of limited supply just before the stock ran out (no-antimalarial group); and a group that included 53 of the 381 patients (13.9%) with confirmed EVD for whom information on prescription of antimalarial treatment was missing (missing-data group; this group was assessed to understand patterns of missing data). The occurrence of missing prescription data was not associated with any clinical variables that we assessed, including EVD severity or discharge status; however, it was associated with increased case load at the Ebola treatment center and with being admitted early in the course of the epidemic (see Section 4 in the Supplementary Appendix).

Most of the patients (87.3%) with confirmed EVD were between 5 and 59 years of age, and 6.9% of the patients were younger than 5 years of age. The median PCR cycle-threshold value at admission was 19.4 (interquartile range, 17.1 to 22.8), and the median time between symptom onset and admission was 3.5 days (interquartile range, 2 to 6). Rapid tests for malaria were

positive in 19.3% of the patients. Overall, 32.6% of the patients received intravenous fluids, and the average proportion of patients receiving intravenous fluids increased over time, except for a sharp decline in early August when admissions to the Ebola treatment center increased substantially (see Fig. S5 in the Supplementary Appendix).

The characteristics of the patients in the artesunate–amodiaquine group were generally similar to those of patients in the artemether–lumefantrine group and the no-antimalarial group, except that patients in the artesunate–amodiaquine group had lower cycle-threshold values on admission, were prescribed antibiotics less often, and were admitted at times when the Ebola treatment center was busier (Table 1). The patients in the artesunate–amodiaquine group were less geographically clustered than were those in the artemether-lumefantrine group (3.9 cases per village vs. 4.6 cases per village).

MORTALITY

A total of 64.4% of the patients in the artemether–lumefantrine group died, as compared with 50.7% of the patients in the artesunate–amodiaquine group. In unadjusted analyses, the artesunate–amodiaquine group had a 21% lower risk of death than did those in the artemether–lumefantrine group (risk ratio, 0.79; 95% confidence interval [CI], 0.61 to 1.01). After adjustment for potential confounders (age, sex, cycle-threshold value, time from symptom onset to admission, malaria test result, receipt or no receipt of intravenous fluids, and number of inpatients at the Ebola treatment center on the day of patient admission), the artesunate–amodiaquine group had a 31% lower risk of death than did the artemether–lumefantrine group (risk ratio, 0.69; 95% CI, 0.54 to 0.89) (Table 2). Alternative adjusted models led to similar qualitative results (see Table S1 and Section 3 in the Supplementary Appendix).

The final model, which included 282 patients with complete data, was adjusted for demographic characteristics (age and sex), the time from symptom onset to admission, cycle-threshold value at admission, malaria rapid-test result, receipt or no receipt of intravenous fluids, and the estimated number of other patients being treated at the Ebola treatment center on the day a patient was admitted. In this model, as in the other models, we found a protective effect of artesunate–amodiaquine; in addition, we found that an age older than 60 years, a lower cycle-threshold value at admission, admission at a time during which there were more patients in the Ebola treatment center, and receipt of intravenous fluids were all associated with a significantly higher risk of death (Table 3).

In stratified analyses, among the 272 patients who tested negative for malaria, those who were prescribed artesunate–amodiaquine had a 36% lower risk of death than did those who were prescribed artemether–lumefantrine (risk ratio, 0.64; 95% CI, 0.49 to 0.85) (Table 4). However, among the 65 patients who tested positive for malaria, we found no protective effect of the prescription of artesunate–amodiaquine (risk ratio, 1.00; 95% CI, 0.54 to 1.85).

To account for the possibility that unmeasured trends during this dynamic epidemic could have confounded our estimates of the relationship between prescribed antimalarial treatment and mortality among patients with confirmed EVD, we assessed this effect during the period in which artesunate–amodiaquine was prescribed and also during the following three distinct time windows during which artemether–lumefantrine was prescribed: the week before and the week after the period during which artesunate–amodiaquine was prescribed (first window); the 10 days before the period during which artesunate–amodiaquine was prescribed (second window); and 10 days after the period during which artesunate–amodiaquine was prescribed (third window). Across all these subanalyses, our data still showed that artesunate–amodiaquine was associated with a significantly lower risk of death than was artemether–lumefantrine, with consistent (unadjusted) risk ratios of 0.66 during the first window, 0.64 during the second window, and 0.68 during the third window (see Section 3.5 in the Supplementary Appendix).

DISCUSSION

Our analyses of this natural experiment that was triggered by a stock-out of the standard antimalarial drugs at the Ebola treatment center in Foya showed that among patients with EVD, those who were prescribed artesunate–amodiaquine had a 31% lower risk of death than did those who were prescribed artemether–lumefantrine (risk ratio, 0.69; 95% CI, 0.0.54 to 0.89). The

Table 1. Characteristics of Patients with Confirmed Ebola Virus Disease Admitted to the Ebola Treatment Center in Foya, Liberia, According to Antimalarial Prescription Status.

Characteristic	Artemether–Lumefantrine (N=194)	Artesunate–Amodiaquine (N=71)	No Antimalarial Drug Prescription (N=63)	Missing Antimalarial Prescription Data (N=53)	P Value*
Age — no./total no. (%)					0.14
0–4 yr	12/193 (6.2)	3/71 (4.2)	5/63 (7.9)	6/51 (11.8)	
5–29 yr	94/193 (48.7)	43/71 (60.6)	29/63 (46.0)	20/51 (39.2)	
30–59 yr	80/193 (41.5)	18/71 (25.4)	25/63 (39.7)	21/51 (41.2)	
≥60 yr	7/193 (3.6)	7/71 (9.9)	4/63 (6.3)	4/51 (7.8)	
Female sex — no. (%)	96 (49.5)	33 (46.5)	37 (58.7)	31 (58.5)	0.34
Time from symptom onset to admission — days					0.79
Median	4	3	4	3	
Interquartile range	2–6	2–5	2–5	2–5	
Polymerase-chain-reaction cycle-threshold value at admission					0.05
Median	19.6	18.5	18.4	21.5	
Interquartile range	17.1–22.7	17.2–23.1	16.1–21.9	18.4–24.5	
Malaria test result — no. (%)					0.86
Positive	33 (17.0)	13 (18.3)	10 (15.9)	9 (17.0)	
Negative	148 (76.3)	47 (66.2)	44 (69.8)	33 (62.3)	
Missing data	13 (6.7)	11 (15.5)	9 (14.3)	11 (20.8)	
Intravenous fluids — no. (%)					0.87
Received	62 (32.0)	25 (35.2)	20 (31.7)	—	
Missing data	0	0	0	53 (100)	
Antibiotic prescribed — no. (%)					<0.001
Any	194 (100)	64 (90.0)	59 (93.7)	—	
Cephalosporine	188 (96.9)	53 (74.7)	53 (84.1)	—	
Penicillin	6 (3.1)	14 (19.7)	10 (15.9)	—	
Fluoroquinolone	5 (2.6)	0	6 (9.5)	—	
Nitroimidazole	10 (5.2)	0	10 (15.9)	—	
Missing data	0	0	0	53 (100)	
Mean no. of patients hospitalized in the Ebola treatment center at the admission date	54	102	50	72	<0.001
No. of cases per village	4.6	3.9	2.9	2.5	Not performed

* P values were derived from tests comparing the artemether–lumefantrine, artesunate–amodiaquine, and no-antimalarial groups.

biologic plausibility of our findings is based on in vitro experiments that showed the efficacy of amodiaquine in inhibiting Ebola virus activity.[2] Chloroquine, another 4-aminoquinolone compound, has shown mixed efficacy in in vivo studies.[2,14] In humans, the therapeutic dose of amodiaquine against malaria is 7.5 to 15.0 mg per kilogram of body weight,[15] and toxic effects (e.g., agranulocytosis and liver damage) have been reported only when amodiaquine was used for long-term prophylaxis.[16] Artesunate–amodiaquine has also been used in children with uncomplicated malaria, and to date, no obvious safety concerns have been identified.[17] Desethyl-

Table 2. Relative Risk of Death Among Patients with Confirmed Ebola Virus Disease, According to Antimalarial Prescription Status.

Antimalarial Prescription Status	Deaths	Unadjusted Risk Ratio (95% CI)	P Value	Adjusted Risk Ratio (95% CI)*	P Value
	no. of deaths/total no. of patients (%)				
Artemether–lumefantrine	125/194 (64.4)	Reference		Reference	
Artesunate–amodiaquine	36/71 (50.7)	0.79 (0.61–1.01)	0.06	0.69 (0.54–0.89)	0.004
No antimalarial drug prescription	41/63 (65.1)	1.01 (0.82–1.25)	0.92	0.85 (0.69–1.03)	0.11

* The final model was adjusted for antimalarial treatment prescribed, age, sex, log cycle-threshold value, time from self-reported symptom onset to admission, malaria test result, receipt or no receipt of intravenous fluids, and number of inpatients at the Ebola treatment center on the day of patient admission. Of the original 381 cases, 282 were included in the adjusted analyses; 99 cases were excluded because of missing data. However, multiple-imputations models were also used in additional analyses (see Section 4 in the Supplementary Appendix).

Table 3. Multivariate Analysis of Risk Factors for Death Among Patients with Confirmed Ebola Virus Disease.

Variable	No. of Patients	Adjusted Risk Ratio (95% CI)	P Value
Antimalarial prescription status			
Artemether–lumefantrine	173	Reference	
Artesunate–amodiaquine	57	0.69 (0.54–0.89)	0.004
No antimalarial drug prescription	52	0.85 (0.70–1.04)	0.11
Age			
0–4 yr	11	1.42 (0.94–2.14)	0.09
5–29 yr	141	Reference	
30–59 yr	115	1.11 (0.93–1.33)	0.24
≥60 yr	15	1.45 (1.14–1.84)	0.002
Female sex	147	1.06 (0.90–1.25)	0.47
Log cycle-threshold value at admission	292*	0.09 (0.05–0.14)†	<0.001
Days from symptom onset to admission	292*	0.97 (0.94–1.00)‡	0.09
Positive malaria test result	53	1.23 (0.53–2.86)	0.63
Receipt of intravenous fluids	95	1.29 (1.09–1.52)	0.002
No. of inpatients at the Ebola treatment center on the day of admission	292*	1.04 (1.01–1.06)§	0.002

* The value 292 represents the total number of observations.
† The adjusted relative risk is expressed as the risk per one-unit increase in log cycle-threshold value at admission.
‡ The adjusted relative risk is expressed as the risk per additional day from symptom onset to admission.
§ The adjusted relative risk is expressed as the risk per 10 additional patients.

amodiaquine, the active metabolite of amodiaquine, has a long half-life; in humans, the mean elimination half-life is 211 hours. The peak concentration of desethyl-amodiaquine is reached after the last dose of a standard 3-day course of treatment. It is possible that the effects of this antimalarial agent on the virus can be seen only at the time of peak concentration, which could explain the observed divergence in the survival curves of those prescribed artesunate–amodiaquine and those prescribed artemether–lumefantrine at approximately 5 days after admission (see Fig. S8 in the Supplementary Appendix).

Although we found that artesunate–amodiaquine was associated with a lower risk of death than was artemether–lumefantrine in the full study population, when we restricted the population to those with a positive malaria test, this association was attenuated. However, prescription of any antimalarial agent was associated

Table 4. Risk Ratio of Death among Patients with Confirmed Ebola Virus Disease, According to Malaria and Prescription Status.

Antimalarial Prescription Status	Deaths	Unadjusted Risk Ratio (95% CI)	P Value	Adjusted Risk Ratio (95% CI)*	P Value
	no. of deaths/total no. of patients (%)				
Patients positive for malaria					
Artemether–lumefantrine	18/33 (54.5)	Reference		Reference	
Artesunate–amodiaquine	7/13 (53.8)	0.99 (0.54–1.79)	0.96	1.00 (0.54–1.85)	0.98
No antimalarial drug prescription	9/10 (90.0)	1.65 (1.13–2.40)	0.009	1.22 (0.85–1.77)	0.28
Patients negative for malaria					
Artemether–lumefantrine	94/148 (63.5)	Reference		Reference	
Artesunate–amodiaquine	24/47 (51.1)	0.81 (0.59–1.09)	0.16	0.64 (0.49–0.85)	0.002
No antimalarial drug prescription	26/44 (59.1)	0.93 (0.70–1.22)	0.61	0.80 (0.63–1.01)	0.06

* The final model was adjusted for antimalarial prescription status, age, sex, log cycle-threshold value, time from self-reported symptom onset to admission, malaria test result, receipt or no receipt of intravenous fluids, and number of inpatients at the Ebola treatment center on the day of patient admission.

with a lower risk of death than the risk with no antimalarial agent (Table 4, and Section 3.4 in the Supplementary Appendix). The potential interaction between malaria status and type of antimalarial agent prescribed warrants further investigation.

As has been seen in previous studies of risk factors associated with death from EVD,[10,12] patients with a higher viral load at admission, as measured by PCR cycle-threshold value, and those who were older than 60 years of age had a higher risk of death. In addition, patients admitted during busy periods (i.e., days on which more patients were in the center) and patients who were prescribed parenteral treatment had a higher risk of death.

The stock-out of artemether–lumefantrine described in this article led to a natural experiment in which the exposure (i.e., the antimalarial treatment prescribed) was, in theory, unrelated to individual patient characteristics, which should reduce the confounding that limits inferences from observational studies. However, because the situation changed rapidly during this dynamic EVD epidemic, the characteristics of the patients who were admitted to the Ebola treatment center during the 12 days when artemether–lumefantrine was out of stock may have differed in undetected ways from those admitted at other times. To assess the potential effect of unobserved confounding factors, we analyzed several restricted time windows before and after the stock-out separately, and the findings remained consistent (see Section 3.5 in the Supplementary Appendix). Still, there could be other confounding factors that we were unable to measure and account for in our analyses.

This analysis has numerous limitations. The patient files contained information only about prescription of an antimalarial drug; no information was included on whether the patient completed the full course of the regimen. Because both drugs evaluated are taken orally, severely ill patients may not have been able to swallow the pills from either regimen. Because artesunate–amodiaquine causes gastrointestinal side effects more often than other artemisinin-based antimalarial drugs,[18] it is possible that patients who were prescribed artesunate–amodiaquine were less likely than patients who were prescribed artemether–lumefantrine to complete the full course. If this was the case, our results would underestimate the relative risk of death among patients in the artesunate–amodiaquine group. Among our study population, 63 patients were not prescribed antimalarial treatment for various possible reasons, including the rationing of artemether–lumefantrine that occurred in early August just before the stock-out. If these reasons were related to unmeasured patient characteristics that directly alter the risk of death, our results could be confounded.

Although artesunate–amodiaquine and artemether–lumefantrine are generally considered to

be safe drugs,[18] an alternative hypothesis is that artemether–lumefantrine increases the risk of death. This hypothesis is supported by our estimates of a protective, though nonsignificant, effect observed among patients who received no antimalarial prescription as compared with those who were prescribed artemether–lumefantrine (Table 2) and by the fact that this effect persisted in most adjusted sensitivity analyses (see Sections 3.3 and 3.4 in the Supplementary Appendix). However, the biologic plausibility of this hypothesis is uncertain.

Artemether–lumefantrine is contraindicated in patients with known hypokalemia or hypomagnesemia because it can increase the risk of QT-interval prolongation and lead to potentially fatal arrhythmias.[19] Diarrhea and vomiting are common in patients with EVD, and hypokalemia has been reported anecdotally.[10] One study in which the post-treatment electrocardiograms of children with uncomplicated malaria who received artemether–lumefantrine were compared with the post-treatment electrocardiograms of those who received artesunate–amodiaquine showed no significant difference in the QT-interval prolongation.[20] Artemether–lumefantrine is also contraindicated in patients who are receiving drugs associated with QT-interval prolongation,[19] including quinolone antibiotics. Five patients in the artemether–lumefantrine group were prescribed ciprofloxacin, although only one died (case fatality rate, 20%). None of the other drugs for which we have information are contraindicated in patients receiving artemether–lumefantrine. However, some case reports suggest that metoclopramide, an antiemetic agent that was commonly used in Foya, is associated with a range of cardiac effects,[21] although data on metoclopramide use were not recorded. Fatal arrhythmias associated with the use of artemether–lumefantrine might be expected to occur during the first days of administration; however, an excess of early deaths with artemether–lumefantrine did not occur in our study, as evidenced by the fact that the survival curves for the groups in our study started to diverge 5 days after admission (see Fig. S8 in the Supplementary Appendix).

The natural experiment described here provided an excellent opportunity to assess the potential effect of antimalarial regimens on mortality among patients with confirmed EVD. Although questions about the mechanism remain, the results suggest that artesunate–amodiaquine may be preferable to artemether–lumefantrine in patients with confirmed EVD. We urge health care providers in countries affected by EVD to try to confirm these findings, including analyses of the effect of mass drug administration of artesunate–amodiaquine on EVD transmission in Sierra Leone and Liberia.[22] Centers that used artemether–lumefantrine and have access to results of laboratory and cardiac monitoring of patients with EVD might be able to affirm or disprove the potential association between artemether–lumefantrine and fatal arrhythmias. More research is needed to independently test this apparent association, and if it is confirmed, to estimate the safest and most effective therapeutic dose against Ebola virus.

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