

# Clinical and Virological Characteristics of Ebola Virus Disease Patients Treated With Favipiravir (T-705)—Sierra Leone, 2014

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(See the Editorial Commentary by Kraft on pages 1295–6.)

**Background.** During 2014–2015, an outbreak of Ebola virus disease (EVD) swept across parts of West Africa. No approved antiviral drugs are available for Ebola treatment currently.

**Methods.** A retrospective clinical case series was performed for EVD patients in Sierra Leone–China Friendship Hospital. Patients with confirmed EVD were sequentially enrolled and treated with either World Health Organization (WHO)–recommended supportive therapy (control group) from 10 to 30 October, or treated with WHO-recommended therapy plus favipiravir (T-705) from 1 to 10 November 2014. Survival and virological characteristics were observed for 85 patients in the control group and 39 in the T-705 treatment group.

**Results.** The overall survival rate in the T-705 treatment group was higher than that of the control group (56.4% [22/39] vs 35.3% [30/85];  $P = .027$ ). Among the 35 patients who finished all designed endpoint observations, the survival rate in the T-705 treatment group (64.8% [11/17]) was higher than that of the control group (27.8% [5/18]). Furthermore, the average survival time of the treatment group ( $46.9 \pm 5.6$  days) was longer than that of the control group ( $28.9 \pm 4.7$  days). Most symptoms of patients in the treatment group improved significantly. Additionally, 52.9% of patients who received T-705 had a >100-fold viral load reduction, compared with only 16.7% of patients in the control group.

**Conclusions.** Treatment of EVD with T-705 was associated with prolonged survival and markedly reduced viral load, which makes a compelling case for further randomized controlled trials of T-705 for treating EVD.

**Keywords.** Ebola virus disease; favipiravir; treatment; clinical features; Sierra Leone.

In December 2013, the largest Ebola virus disease (EVD) outbreak in history began spreading through parts of West Africa [1]. As of 6 January 2016, a total of 28 637 cases, including 11 315 deaths, had been reported, of which 14 122 cases and 3955 deaths occurred in Sierra Leone [2]. This international public health emergency sparked debate about the potential for worldwide dissemination [3, 4]. Many candidate vaccines and antiviral drugs such as ZMapp, TKM-Ebola, and favipiravir (T-705) have been used to treat EVD patients during this current outbreak [5–7]. Among numerous medicines and therapies proposed, world

experts convened by the World Health Organization (WHO) have identified antivirals such as TKM-Ebola and T-705, which showed promise in nonhuman primate or mouse models, as potential treatments to be prioritized for EVD trials [8]. However, none have been systematically tested for effectiveness on EVD patients. T-705, developed by Toyama Chemical Co, Ltd, Japan, is an antiviral drug that selectively inhibits the RNA-dependent polymerase with broad antiviral activity [9]. A phase 3 clinical evaluation of T-705 for influenza therapy has been completed in both Japan and the United States [10] and was approved in Japan as an anti-influenza drug in 2014 [11]. The in vivo efficacy of T-705 for treatment of Crimean-Congo hemorrhagic fever has also been confirmed to exceed that of the current standard drug, ribavirin [12]. In 2014, T-705 was reported to be effective in treating Ebola virus (EBOV) infection in a mouse model, with rapid virus clearance preventing a lethal outcome for all infected mice [13, 14]. T-705 was also shown to suppress replication of Zaire EBOV in cell culture [14]. These findings suggest that T-705 shows potential as a treatment of EVD.

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In Sierra Leone, the first EVD case was confirmed on 25 May 2014 in Kenema Government Hospital, Kenema District, located in eastern Sierra Leone [15]. To support Sierra Leone in its containment of EVD, as well as to respond to the appeal of the United Nations and WHO to help West Africa control EVD, the China Mobile Laboratory Testing Team was dispatched on 16 September 2014 at the request of the Sierra Leone government [16]. The team, equipped with medical experts who specialize in laboratory testing, epidemiology, clinical medicine, and nursing, set up an Ebola treatment center (ETC) at the Sierra Leone–China Friendship (SLCF) Hospital in Jui Town, which is located 30 km southeast of Freetown. Owing to the exceptionally high mortality rate of the emerging EVD epidemic in Sierra Leone, and unavailable approved antiviral drugs for Ebola treatment, T-705 was administered to EVD patients hospitalized from 1 November till 10 November. The primary aim of this study is to retrospectively explore whether T-705 reduced EVD patient fatality rates in this circumstance and to estimate the effectiveness of T-705 on EVD in a clinical setting.

## METHODS

### Study Design and Patients

Suspected Ebola cases were isolated in the ETC, which was started on 1 October 2014. After initial screening by polymerase chain reaction (PCR), confirmed patients were sequentially enrolled. Patients admitted from 10 till 30 October 2014 were only treated with recommended schedules according to WHO guidelines [17] and from here onward will be referred to as the control group. Patients hospitalized from 1 till 10 November 2014 were treated with WHO-recommended schedules plus T-705 and from here onward will be referred to as the treatment group. By comparing the differences in the improvement of clinical symptoms, viral load reduction, and case fatality rate between these 2 groups, we evaluated the effectiveness of T-705.

### Therapy Regimens

In consideration of local medical conditions and biosafety practices at this hospital, the use of parenteral fluids was restricted. Supportive treatment was applied through oral administration according to the guidance for care of confirmed EVD patients issued by WHO [17]. In short, oral rehydration salts were administered for dehydration and hypovolemia; capsules or tablets of amoxicillin, azithromycin, tetracycline, or ciprofloxacin were used for antibacterial therapy and septic shock management; artesunate and amodiaquine were used for antimalarial treatment; furosemide was used in case of overload of fluids and diuretics; and diazepam for anxiety disorders and convulsions, loperamide for anti-diarrhea, loratadine for anaphylaxis, metoclopramide for antiemetic, morphine for analgesic, ondansetron for antiemetic, and vitamin supplementation were used for patients as appropriate.

The treatment group received an oral dose of T-705 (Lot 20140902), which was donated by Sichuan Zihao Shidai Pharmaceutical Co Ltd and approved by the Ministry of Health of the People's Liberation Army (2014JTP021), in addition to the WHO-recommended therapies mentioned above. As referenced in treating influenza, which was approved by the Japanese Ministry of Health, 800 mg of T-705 was taken twice in the first day (1600 mg total) and 2 doses of 600 mg on day 2, followed by at least 5 days of standard therapy, with treatment occurring for a total of 3–11 days or until discharge, transfer, or death. All patients in the treatment group received the same dose of T-705 regardless of age. T-705 was discontinued in patients who were doing well on the day of discharge or in patients being transferred to another facility.

### Procedures

When a suspected patient was sent to the SLCF hospital holding/treatment center, whole-blood samples were collected and processed by Ministry of Health and Sanitation (MOHS) staff, using emergency response guidelines jointly established by the MOHS and WHO. Clinical symptoms and epidemiological data were recorded simultaneously using standard case investigation forms. Samples were then transported to the China Mobile Laboratory located in the same hospital, where quantitative reverse-transcription PCR (qRT-PCR) testing was performed immediately, as previously described [18]. Confirmed patients were then administered therapies according to their grouping described above. All patients among the 2 groups received WHO-recommended therapy on hospital admission, before EBOV PCR results were reported. T-705 was started after confirmation of PCR diagnosis, which occurred within an approximately 1-day interval from hospital admission.

Clinical observations of cases upon admittance to the hospital, along with viral loads in the first sample collected prior to initiating treatment, were regarded as baseline measurements. Medical information and plasma samples were collected as a second data point after finishing WHO-recommended therapies or WHO therapies plus T-705, occurring 3–5 days after acute stage of infection or before being transferred to other ETCs. The clinical indexes of interest included the improvement of symptoms, viral load reduction, and an increase in survival rate posttreatment. All clinical indexes observed for hospitalized patients were recorded using case investigation forms and medical record forms. Using the comparison time point of 20 December 2014, definitive outcomes were acquired through telephone contact, medical records, and searches of the Viral Hemorrhagic Fever database conducted by the MOHS medical officer.

### Statistical Analysis

Descriptive statistics were calculated for all variables. Continuous variables were summarized as median (interquartile range), mean  $\pm$  SD, and range as appropriate; and categorical variables were summarized as frequencies and proportions. The cycle

threshold value was used to estimate the absolute concentration of RNA, which is representative of the original viral load and was normalized using adjusted concentrations of the standard reference.

To estimate the differences between groups, Student *t* test,  $\chi^2$  test, or Fisher exact test was used where appropriate. Patient actuarial survival was determined by Kaplan–Meier analysis.

### Ethical Considerations

This work was conducted as part of the surveillance and public health response to contain EVD outbreak in Sierra Leone, with all activities coordinated by the MOHS. Because there are no effective drugs for EVD that are readily available for public consumption, T-705 is thought to be the most promising anti-Ebola virus drug, considering its safety has already been confirmed in Japan [11]. The therapy administered by the Chinese medical team was authorized by the Sierra Leone government and approved by SLCF Hospital, agreed upon through the Memorandum of Understanding “Concerning Sending a Chinese Laboratory Team to Carry Out Laboratory Test and Treatment for Ebola Virus Disease,” signed by the government of the People’s Republic of China and the government of the Republic of Sierra Leone. The ethics committees of the No. 307 Hospital and the No. 302 Hospital, Beijing, China, approved study and therapy regimens. All patients provided oral or written informed consent before any study-specific procedures were performed.

## RESULTS

### Patients

During the study period, a total of 267 patients were suspected to have EVD, of whom 124 tested positive for EBOV by means of qRT-PCR. Eighty-five of 124 patients received control group

therapy as described previously. The remaining 39 infected patients received T-705 treatment therapy (Figure 1) successively. Age, sex, baseline viral load, and time between onset of symptoms and admission showed no significant difference between the 2 groups. The therapy group experienced a higher frequency of clinical symptoms than the control group (Table 1). Due to limited beds and patient demands to receive intravenous therapy, a total of 67 patients in the control group and 22 patients in the treatment group were transferred out of the ETC within 2 days after qRT-PCR diagnosis. Thus, designed endpoints were observed in only 17 patients in the T-705 treatment group and 18 patients in the control group (Figure 1). In the control and T-705 treatment group, 44.4% (8/18) and 35.2% (6/17) patients, respectively, were female. The median patient age (IQR) was 22.0 (18–31) years (control group) and 30.0 (24–38) years (treatment group). In the control and T-705 treatment groups, the median time from onset of symptoms to date of hospital admission was 6.0 days (3–6) and 8.0 days (4–8), respectively. The median value of viral load before drug administration showed no significant difference between the 2 groups (Table 1). All patients completed at least 80% of the standard schedule of T-705 doses.

### Effectiveness of T-705 Against EVD Patients

The survival rate of the 39 patients, including 22 who transferred elsewhere in the treatment group, was higher than that of the 85 patients, including the 67 transferred elsewhere in the control group (56.4% vs 35.3%; *P* = .027; Figure 1). There was no significant difference (*P* = .211) in the final survival rate for the transferred patients who received 1–2 days of therapy between the control group (25/67) and treatment group (11/22). Among the 35 patients who completed the study, 11 patients survived in the treatment group, whereas only 5

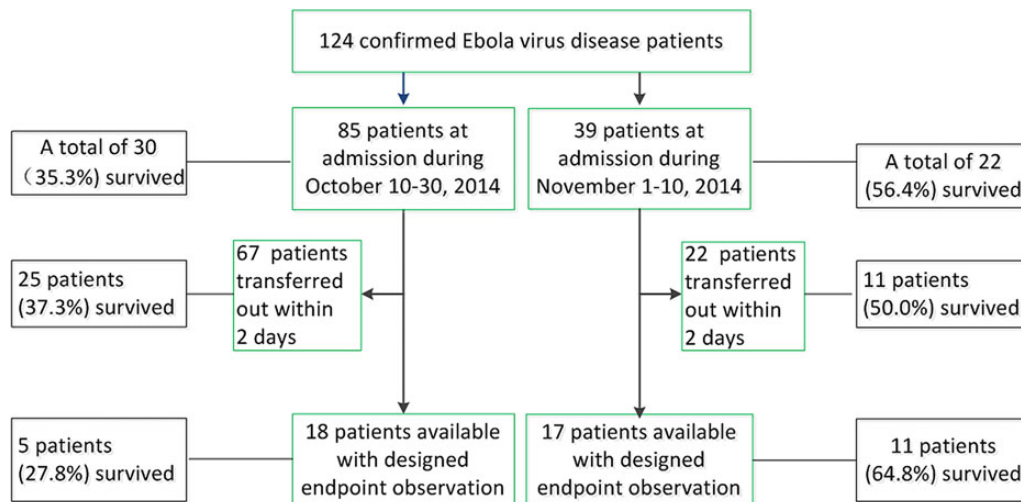


Figure 1. Trial profile and enrolled confirmed cases of Ebola virus disease for each analysis in this study.

**Table 1. Demographic and Baseline Clinical Characteristics of Participants With Confirmed Ebola Virus Disease, Sierra Leone–China Friendship Hospital, 10 October–10 November 2014**

Characteristic	No. (%) of Patients With Confirmed Ebola Virus Disease					
	Included Patients at Start of Therapy <sup>a</sup>			Patients With Available Designed Endpoint		
	Control Group (n = 85)	T-705 Group (n = 39)	P Value	Control Group (n = 18)	T-705 Group (n = 17)	P Value
<b>Sex</b>						
Female	42	28 (71.8)	.818	8 (44.4)	6 (35.3)	.581
Age, y, median (IQR)	27.0 (19–35)	30 (17–39)	.447	22.0 (18–31)	30.0 (24–38)	.062
Period from onset to drug use, d, median (IQR)	6.0 (4–7)	7.0 (4–8)	.150	6.0 (3–6)	8.0 (4–8)	.118
<b>Symptoms<sup>b</sup></b>						
Anorexia	72 (84.7)	37 (94.9)	.089	11 (61.1)	16 (94.1)	.020
Abdominal pain	55 (64.7)	33 (84.6)	.018	9 (50.0)	14 (82.4)	.044
Chest pain	49 (57.6)	30 (76.9)	.029	6 (33.3)	12 (70.6)	.028
Joint pain	58 (68.2)	32 (82.1)	.081	9 (50.0)	15 (88.2)	.015
Headache	57 (67.1)	34 (87.2)	.014	11 (61.1)	14 (82.4)	.155
Cough	44 (51.8)	28 (71.8)	.027	6 (33.3)	9 (52.9)	.204
Conjunctivitis	26 (30.6)	19 (48.7)	.041	2 (11.1)	5 (29.4)	.199
Hiccups	25 (29.4)	17 (43.6)	.090	2 (11.1)	8 (47.1)	.024
Pain behind eyes	17 (20.0)	14 (35.9)	.049	1 (5.6)	8 (47.1)	.001
Difficulty breathing	42 (49.4)	29 (74.4)	.007	7 (38.9)	11 (64.7)	.117
Difficulty swallowing	33 (38.8)	25 (64.1)	.008	6 (33.3)	9 (52.9)	.204
Confused or disoriented	39 (45.9)	31 (79.5)	.001	6 (33.3)	14 (82.4)	.005
Viral load (cycle threshold), median (IQR)	25.2 (22.5–29.2)	25.7 (22.7–30.4)	.992	26.5 (24.1–31.9)	26.9 (23.5–33.7)	.624

Abbreviation: IQR, interquartile range.

<sup>a</sup> Onset time was not known for 7 patients in the control group and 3 patients in the T-705 group.

<sup>b</sup> The other symptoms (including fever, vomiting/nausea, diarrhea, fatigue, muscle pain, sore throat, jaundice, and skin rash) that were listed in the case investigation forms showed no significant differences between the 2 groups, respectively ( $P > .05$ ).

patients survived in the control group; this is a significant difference between the 2 groups (64.8% vs 27.8%;  $P = .044$ ). Based on follow-up information during the study phase, the average patient survival time in the treatment group was significantly

longer than that in the control group ( $46.9 \pm 5.6$  vs  $28.9 \pm 4.7$  days;  $P = .049$ ; Figure 2).

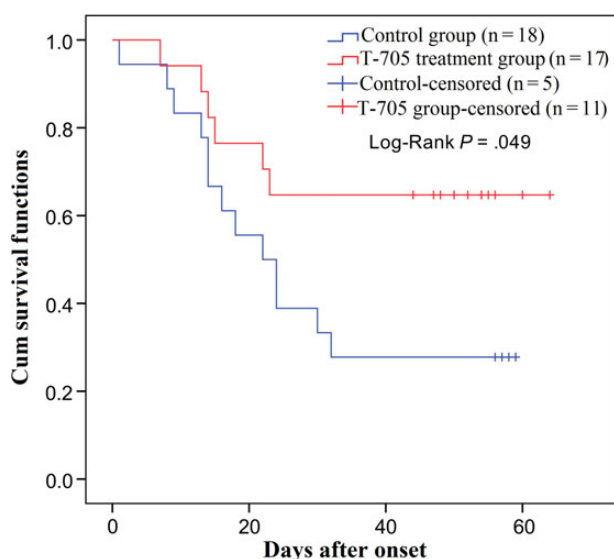
Additionally, after oral administration of T-705 for 5.1 days (range, 3–11 days), patient symptoms improved compared with the control group ( $P < .05$ ; Figure 3).

Viral loads were quantified for all 35 patients twice during their hospitalization. Patients in the treatment group had significantly more viral load reduction ( $P = .006$ ) than the control group (Figure 4A). In the treatment group, 52.9% (9/17) of patients and in the control group, 16.7% (3/18) of patients had a 100-fold reduction in viral load ( $P = .028$ ; Figure 4B).

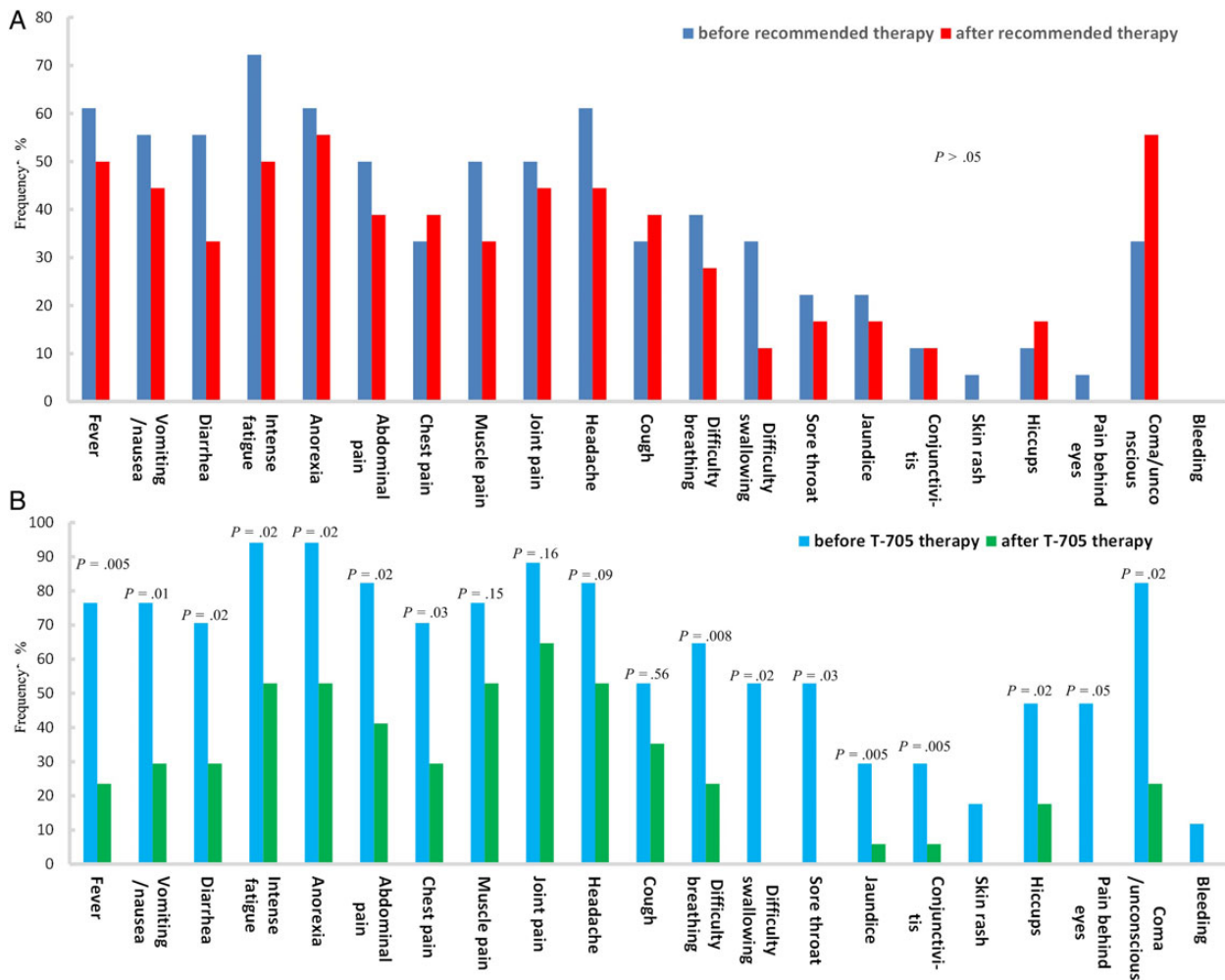
## DISCUSSION

Despite the limitations of an emergency experimental design, our preliminary results suggest that T-705 effectively reduced Ebola viral loads in patients, improved clinical symptoms, increased survival rate, and prolonged patient survival time.

A number of EVD therapeutic agents were used in accelerated human trials in EVD-endemic countries [19]. FX06 (small interfering RNAs) demonstrates possible utility in a rhesus monkey trial. ZMapp, TKM-Ebola, brincidofovir, and T-705 show promise in nonhuman primate and mouse models as potential treatments for EVD [8, 20]. Comparatively, the highly anticipated trials of TKM-Ebola were stopped early in Guinea and



**Figure 2.** Kaplan–Meier plot of patients' survival. Abbreviation: Cum, cumulative.



**Figure 3.** Baseline clinical characteristic and change after the treatment. *A*, Clinical change of patients in the control group. The dark-blue bars represent the frequency of observed symptom before drug administration. The red bars represent frequency of observed symptom after drug administration in the control group. *B*, Clinical change of patients in the T-705 treatment group. The sky-blue bars represent frequency of observed symptom before drug administration. The green bars represent frequency of observed symptom after drug administration in the T-705 treatment group.

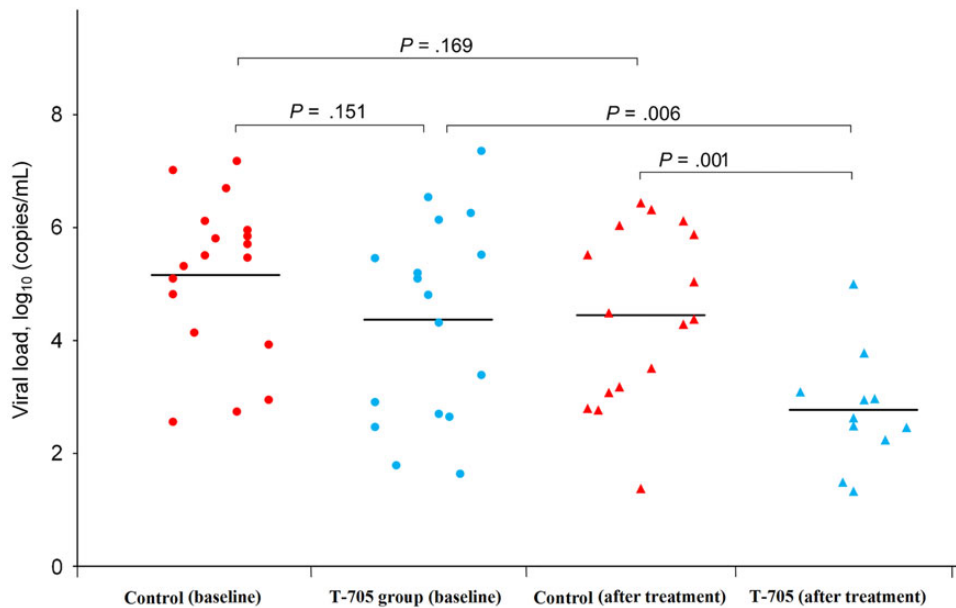
were reported without improvement for survival when administered to adult patients with severe EVD recently [21]. This is a setback for anti-Ebola drugs [22], with a long and difficult journey still ahead for the development of effective EVD treatments.

Recently, the similar before-after design, phase 2 multicenter noncomparative trial on T-705 in Guinea [23] showed that the treatment group case fatality rate was lower than the control group among patients with moderate viral load (RNA viral load  $\leq 7.7 \log_{10}$  genome copies/mL). Coincidentally, all 35 patients' viral loads were below this level. Our findings are consistent with this report and support further study of T-705 monotherapy efficacy in patients with medium to high viremia [23].

Nine of 17 patients given T-705 had a viral load reduction of at least 100-fold between study days 0 and 3–11, compared with 3 of the 18 patients in the control group. These findings are consistent with a previous study showing that treatment of EBOV-

infected mice with T-705 at 6–8 days postinfection can reduce the virus >100-fold within 2–4 days [12].

The proper dose regimen of T-705 for EVD patients is still being evaluated [24]. Recently, T-705 was used as a prophylactic treatment for Ebola contacts and children infected with Ebola in Guinea [25,26]. High-dose T-705 (6000 mg during the first day, followed by 1200 mg twice daily) combined with convalescent plasma from EVD survivors and ZMapp has already been used in 2 individual cases [5,6]. However, for safety, the route of medication and dosage of drugs are based on the drug recommendations from the Japan influenza clinical study (800 mg twice during the first day, followed by 600 mg twice daily), which still demonstrated improved clinical symptoms. It has been suggested that providing basic interventions early can improve the chances of EVD survival. As the use of parenteral fluids were restricted, orally taken T-705 contributed to clinical



	Control group (n = 18)	T-705 group (n = 17)	P value
Baseline viral RNA copies (Log transformation value)	5.5 (2.56–7.18)	4.8 (1.64–7.36)	.151
Viral RNA copies after therapy (Log transformation)	4.34 (0–6.4)	2.2 (0–5.0)	.001
Cases with negative result after therapy	2	6	.121
Cases with >100-fold reduction of viral load after therapy	3	9	.028

Note: viral RNA copies (Log transformation value) are presented as median (range)

**Figure 4.** Comparison of viral loads in 2 groups of patients before and after drug administration. The red and light-blue dots represent the log-transformed baseline viral loads in the patients from the control and T-705 treatment group, respectively. The red and light-blue triangles represent the log-transformed viral loads after treatment in the patients from the control and T-705 treatment group, respectively.

improvement for the EVD patients. Therefore, oral antiviral drugs such as T-705 are ideal agents in controlling and reducing the fatality rate during the EVD outbreak, as they do not require intravenous administration.

A limitation of our study is that it was a nonrandomized, non-double-blinded before-after design, and it was very difficult to manage EVD patients under such special circumstances. Second, as some patients demanded to receive intravenous therapy, 89 patients were transferred within 1–2 days. However, the final survival rate of transferred patients (37.3% and 50.0%; Figure 1) had no significant difference ( $P = .211$ ). Therefore, the intravenous therapy did not introduce any bias between the 2 treatment groups. Third, we were lacking the exact death date on many patients, so we could not analyze the difference in number of days survived for 67 and 22 transferred patients between these 2 groups. As there might be unnecessary risk to personnel,

in addition to patients transferring out of our study's ETC for fluid management, we were unable to test the viral load more than twice for the other 89 participants. These patients also did not receive the whole course of treatment. Fourth, the patients enrolled into the treatment group were older compared with the treatment group. Nevertheless, the case fatality rate among the young and middle-aged group (15–45 years) had no significant difference [18, 27]. Furthermore, the influence of time delay caused by waiting for qRT-PCR confirmation (approximately 24 hours) and the potential benefits of early administration of T-705 warrants investigation. Finally, we did not accept any new hospitalized patients from 11 to 14 November 2014, as our research group was rotated out for the next medical team. The fewer number of subjects in the T-705 group might influence our results. Thus, these findings should be interpreted with discretion, until further randomized,

double-blind, multicenter studies can be conducted to eliminate confounding effects. Despite these limitations, this study makes a compelling case for further investigations of T-705 for use in treating EVD.

## Notes

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