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MAJOR ARTICLE

Long-term Sequelae in Ebola Virus Disease Survivors Receiving Anti-Ebola Virus Therapies in the Democratic Republic of the Congo: A Prospective Cohort Study

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Background. The 2018–2020 Ebola outbreak in the Democratic Republic of the Congo marked the first major cohort of Ebola survivors treated with advanced therapeutics, including monoclonal antibodies (REGN-EB3, ansuvimab, ZMapp) and remdesivir. This study explored factors influencing long-term sequelae in survivors who received these specific therapies.

Methods. A prospective multicenter study enrolled 750 Ebola survivors from the 10th outbreak in the Democratic Republic of the Congo between April and October 2020. Participants were followed for 12 months to assess the recurrence of clinical sequelae according to Weibull and shared frailty models.

Results. Of 750 of Ebola survivors, 650 (86.7%) experienced post-Ebola sequalae. The median age of survivors was 32 years and 56.7% were female. Among them, 463 (61.7%) experienced neurologic sequelae, 373 (49.7%) musculoskeletal sequelae, and 288 (38.4%) general sequelae. Globally, these persisted for at least 38 months postdischarge, with slight decreases over time. At enrollment (median time to baseline visit, 330 days after discharge), neurologic sequelae were more frequent in the REGN-EB3 group (hazard ratio, 2.14; 95% CI, 1.28–3.57) as compared with the remdesivir group. Musculoskeletal sequelae were associated with age (1.02; 1.00–1.03), ZMapp treatment (3.17; 1.81–5.56), and acute-phase hemorrhagic symptoms (1.64; 1.14–2.36). Ocular sequelae were associated with age (1.04; 1.02–1.06). Female sex, older age, metabolic comorbidities, and REGN-EB3 therapy were associated with recurrent neurologic and musculoskeletal sequelae. Recurrent ocular sequelae were more frequent in adults (1.02; 1.01–1.03).

Conclusions. Despite improved survival with monoclonal antibody therapy, our findings highlight a high incidence of neurologic sequelae in the REGN-EB3 group and musculoskeletal sequelae in the ZMapp group as compared with the remdesivir group, as well as among older survivors, women, and those with comorbidities. These results underscore the need for targeting long-term care to effectively manage post-Ebola sequelae.

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[a]The Les Vainqueurs d'Ebola study group is listed in the Acknowledgments section and Supplementary Table 1.

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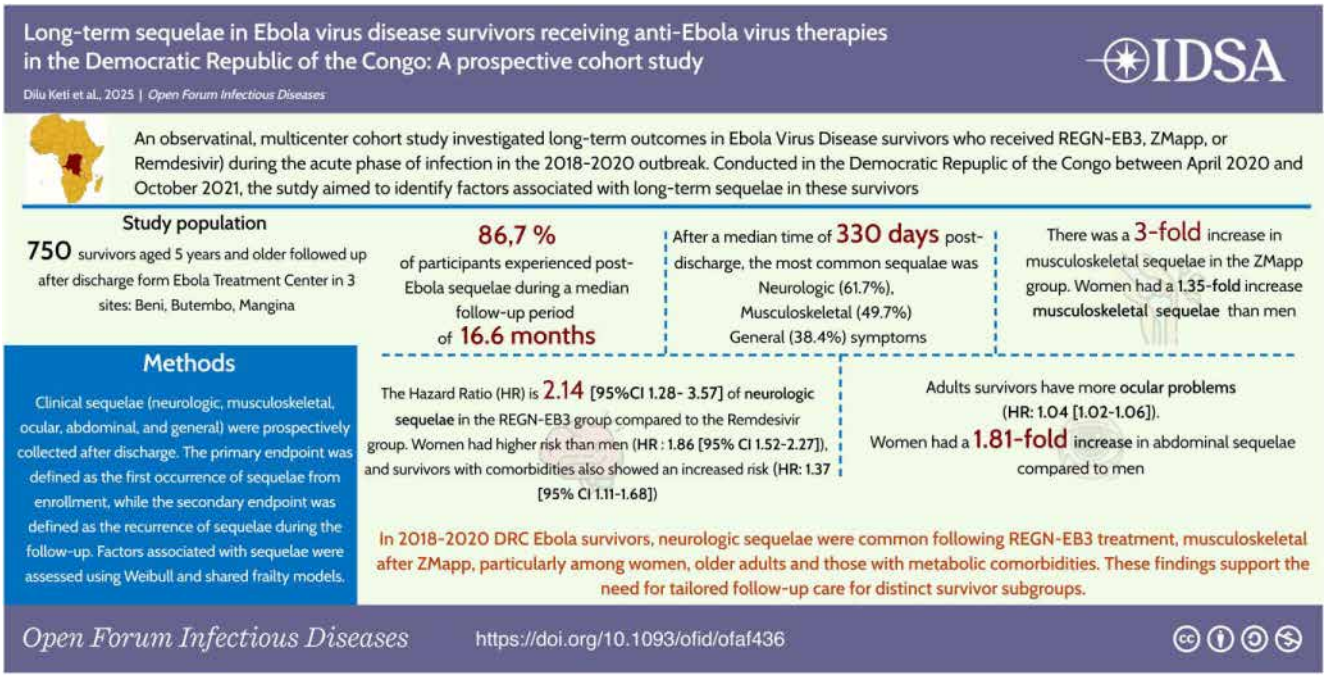
Graphical Abstract



This graphical abstract is also available at: https://tidbitapp.io/tidbits/long-term-sequelae-in-ebola-virus-disease-survivors-receiving-anti-ebola-virus-therapies-in-the-democratic-republic-of-congo-a-prospective-cohort-study?utm_campaign=tidbitlinkshare&utm_source=ITP

Keywords. Ebola virus disease; EVD sequelae; frailty model; monoclonal antibody treatment; Weibull model.

Ebola virus disease (EVD) is a severe viral disease caused by *Orthoebolavirus zairense* (EBOV), with case fatality rates ranging from 50% to 90% without optimized care or specific treatment [1]. The first EVD outbreak was reported in 1976 in Yambuku, Zaire, now the Democratic Republic of the Congo (DRC) [2]. The DRC, having experienced 15 of 42 epidemics in sub-Saharan Africa [3], remains particularly vulnerable. The 2018–2020 outbreak in the North Kivu and Ituri provinces was the country's largest and deadliest, with 3421 confirmed cases and 2299 deaths (67.2% case fatality rate) [4].

This outbreak marked the first time that EBOV affected an urban center in the DRC with significant movement of a population in a conflict-affected region, complicating the response efforts. Community distrust and attacks on facilities required coordinated efforts led by the Ministry of Health and international partners to enhance case detection, surveillance, and laboratory capacity. Inspired by the 2014–2016 West African outbreak, new strategies were implemented, including ring vaccination with ERVEBO (Merck) for >300 000 contacts and frontline workers [5] and investigational therapeutics in the acute-phase infection administered under the Monitored Emergency Use of Unregistered and Investigational Interventions or the randomized clinical trial Pamoja Tulinde Maisha (PALM RCT) [6]. Patients received monoclonal antibodies—ansuvimab (Ebanga) [7, 8], REGN-EB3 (Inmazeb) [9, 10], or ZMapp [11]—or the antiviral remdesivir (Veklury) [12]. Results from the PALM RCT [5] led to the US Food and Drug Administration's approval of Ebanga and Inmazeb as specific treatments for EVD [8, 13]. These efforts contributed to 1162 survivors [4], the highest number recorded in the DRC.

Despite clearance of the virus from the blood, survivors experience short- and long-term sequelae, including fatigue, arthralgia, headaches, abdominal pain, and vision impairment or ocular disorders [14–19]. Most prior studies on post-Ebola complications were cross-sectional, retrospective [15, 20, 21], or limited by small sample sizes [20, 22]. The largest study on long-term follow-up has been conducted in West Africa following the 2014–2016 outbreak of the disease, and it is the first cohort study to date [16, 17, 19]. In the DRC, available studies on survivors [23–28] involved <70 participants [27, 28]. So far, no studies have undertaken long-term follow-up or a large cohort of EVD survivors in the DRC.

Although new therapeutic agents improved survival, questions remain about their long-term impact. Research has reported late-onset ocular complications, such as uveitis [29, 30] and neurologic symptoms [31], even in survivors treated with monoclonal antibodies. Another study showed a rapid decline in antibody concentrations over time, particularly in recipients of ansuvimab [32].

Given these findings, there is a need to better understand how the treatment affects survivor outcomes. We designed the Les Vainqueurs d'Ebola study to investigate the clinical, immunologic, and virologic consequences of EVD and its therapies. Herein, we highlight factors influencing the development of

clinical sequelae among survivors treated with specific anti-Ebola therapies during the 2018–2020 EVD outbreak in the DRC.

METHODS

Study Design and Participants

Methods, including ethical compliance information, have been published and are briefly described here [32]. This prospective, multicenter, observational cohort study was conducted during the 2018–2020 EVD outbreak in the Ebola treatment centers (ETCs) of Beni, Butembo, and Mangina—the epicenters in the North Kivu and Ituri provinces, DRC. From 16 April 2020 to 18 October 2021, we prospectively followed EVD survivors, defined as patients who recovered from EBOV infection and had 2 consecutive negative results upon reverse transcription–polymerase chain reaction blood tests. Participants were enrolled in the study approximately 10 months after ETC discharge, regardless of whether they had received anti-Ebola drugs during the acute infection (Supplementary Figure 1).

Patient Consent Statement

As part of the national survivors' care program, called Programme National du Suivi des Personnes Guéries, survivors discharged from ETCs were enrolled over 6 months (Supplementary Figure 1). Enrollment was initially planned at ETCs on the day of discharge; however, due to contextual constraints, most individuals were enrolled several months later. Eligible participants were aged ≥5 years, willing to be followed for 12 months, and provided written informed consent (or their legal guardians did if age <18 years). The study was approved by the Kinshasa School of Public Health ethics committee (ESP/CE/287/2019) and the institutional review board of the French National Institute of Health and Medical Research (Avis 20-661), the latter of which sponsored the study with funding from the Research and Action Targeting Emerging Infectious Diseases Consortium and the European and Developing Countries Clinical Trials Partnership (grant RIA2018EF). The study is registered in ClinicalTrials.gov (NCT04409405).

Follow-up Procedures

Participants were followed for 12 months. Regular clinical assessments were conducted at baseline and approximately 1, 3, 6, and 12 months (Supplementary Figure 1). At each visit, trained clinicians recorded demographics (age, sex, study site), as well as ongoing or new symptoms and their onset dates. They were guided by a closed list of symptoms to be systematically searched, as well as *ICD-10* codes, supplemented by an open question recording other clinical events over the recall period. Dates of onset were best approached by local events calendars. Metabolic comorbidities and details from the acute phase of EVD, such as admission date, symptoms onset, discharge date, and treatment used (ansuvimab, REGN-EB3, ZMapp, or remdesivir) were collected when available (the assignment of molecules was part of the PALM RCT carried out 8 months prior to this study; Supplementary Figure 1). Regular monitoring visits and cross-site discussions with the medical staff were organized during the study to ensure data quality.

Definitions and End Point

We considered symptoms during the acute phase of EVD as a proxy for disease severity. These symptoms were categorized by organ system and included joint pain and myalgia; nausea, vomiting, diarrhea, and abdominal pain (abdominal); melena, purpura, gingival bleeding, hematemesis, and conjunctival hemorrhage (hemorrhagic); fever, fatigue, and anorexia (general); as well as dizziness, seizures, loss of consciousness, and coma (neurologic). Metabolic comorbidities were defined as the presence of 1 or more of the following: diabetes, hypertension, and overweight or obesity.

Based on the literature [19, 33], post-EVD clinical symptoms were grouped as follows: neurologic sequelae (headache, dizziness, motor/sensory disorders, numbness of hands or feet), musculoskeletal sequelae (joint pain, polyarthralgia, muscle pain, back pain), ocular sequelae (vision problems, eye pain, itchy eyes, photophobia), abdominal sequelae (abdominal/pelvic pain), and general sequelae (extreme fatigue, fever, anorexia). Herein, we present these groups. Recurrent sequelae were defined as repeated episodes of symptoms.

The primary end point was the time from ETC discharge to the first new episode of clinical sequelae, as reported at the baseline visit, and the secondary end point included the first and cumulative episodes of sequelae to the end of follow-up.

Statistical Analysis

Descriptive analyses were performed on all eligible participants. Continuous variables were summarized as median with IQR and categorical variables as counts and percentages. Differences between treatment arms were tested by a Kruskal-Wallis test for quantitative variables and Pearson χ^2 or Fisher exact test for qualitative variables. The prevalence of clinical sequelae was calculated by the proportion of survivors with at least 1 sequela at each visit. Incidence rates were estimated as events per person-years (PYs) at risk during follow-up. The mean cumulative function (MCF) graphically summarized the average number of sequelae events per person over time [34] and was used to compare event intensities across treatment and sex groups.

Since the primary objective was to explore the relationship between treatment options and the occurrence of sequelae, the analysis of end points was restricted to participants for whom complete data on acute-phase EVD treatment were available. Missing values were assessed for their impact on

results. All participants' data were included from ETC discharge until the end of the follow-up or last follow-up. For the primary end point, a time-to-first-event analysis was performed in a Weibull model instead of a Cox model due to nonproportional hazards. The time from ETC discharge to the first event at baseline was calculated, and model fit was assessed graphically. For the secondary end point, a time-to-recurrent-event analysis was performed in a shared frailty model with gamma-distributed random effects to account for within-subject dependence. The Andersen and Gill time scales for recurrent event data were applied [35, 36], with the best-fit model chosen by the minimum likelihood cross-validation criterion [35].

Separate models were computed for each sequela type, adjusting for age at time of enrollment, sex, comorbidities, and study site. The study site was included in the model to account for potential differences among sites regarding the time elapsed between ETC discharge and study recruitment. For the Weibull analysis, a site with insufficient event counts (<5 events per sequela type) was grouped with the geographically nearest site to preserve statistical validity and avoid data exclusion. Results were reported as hazard ratios with 95% CIs and *P* values, with statistical significance set at $P < .05$. Analyses were conducted in R software (version 4.3.3) with the *survival* and *frailtypack* packages [35].

Role of Funding Source

The authors had full access to the databases and were responsible for deciding to submit the manuscript. Funders had no role in study design, data collection, analysis, interpretation, writing, or publication decisions.

RESULTS

Participants and Characteristics

During the 10th Ebola outbreak, 1162 patients survived acute EVD. We selected survivors actively followed by the Programme National du Suivi des Personnes Guéries at the 3 selected study sites. During the inclusion period from 16 April to 12 October 2020, 787 survivors were included to participate in the Les Vainqueurs d'Ebola study. Of them, 37 were excluded for not meeting the eligibility criteria. A total of 750 participants were included in the present analysis, with 189 (25.2%) having missing data for the treatment variable (Figure 1). In total, 604 (80.5%) participants completed all scheduled visits (data not shown).

Baseline characteristics and follow-up information are displayed in Table 1. The median age of participants was 32 years (IQR, 24–45) and 425 (57%) were female. The median time between ETC discharge and study enrollment (baseline visit) was 330 days (262–423). Overall, the median length of follow-up time was 16.6 months (15.8–16.9). During the acute phase of EVD infection, 9.3% (70/750) received ZMapp, 11.5% (86/750) remdesivir, 26.7% (200/750) ansuvimab, and 27.3% (205/750) REGN-EB3. For 25.2% (189/750) of participants, the information regarding the treatment received during the acute phase was not retrievable in the medical records. Details of the clinical symptoms are presented in Supplementary Table 2. Survivors without treatment data showed no significant age or sex differences from those with complete data (Supplementary Table 3).

Prevalence and Incidence

Overall, 650 (86.7%) participants reported experiencing at least 1 clinical symptom. These participants were older than those who did not report symptoms ($P < .001$), with a median age of 33 years (IQR, 25–46) vs 25 years (17–35), and 387 (59.5%) were female. Table 2 shows the prevalence of post-Ebola sequelae over follow-up visits. Overall, the 3 most frequent post-Ebola sequelae were neurologic (463/750, 61.7%), musculoskeletal (373/750, 49.7%), and general (288/750, 38.4%). Abdominal and ocular sequelae were observed in approximately 33% of participants (248/750 and 254/750, respectively).

At 38 months after ETC discharge, neurologic and musculoskeletal sequelae showed a high incidence rate, which steadily declined from the first year (70.0 events per 100 PYs [95% CI, 61.7–79.1] and 59.7 per 100 PYs [52.1–68.1], respectively) to the end of the follow-up (43.9 per 100 PYs [27.8–60.0] and 36.3 per 100 PYs [21.8–56.7]). Ocular, abdominal, and general sequelae followed a similar trend, tending to plateau over time (Supplementary Table 4, Supplementary Figure 2).

Primary End Point

At the baseline visit—at a median 330 days (IQR, 262–423) after ETC discharge—49.5% (371/750) of participants had experienced at least 1 clinical sequela. Of them, 56.9% (211/371) had neurologic sequelae, 52.3% (194/371) musculoskeletal sequelae, and 24.5% (91/371) general sequelae. Ocular and abdominal sequelae were reported by 16.2% (60/371) and 16.4% (61/371) of participants, respectively.

Table 3 shows the factors associated with clinical outcomes reported at the baseline visit per the Weibull model. The risk of clinical sequelae 1 year postdischarge was similar for men and women. Neurologic sequelae were significantly more common in the REGN-EB3 group (adjusted hazard ratio, 2.14 [95% CI, 1.28–3.57]; $P = .004$) as compared with the remdesivir group. The following were positively associated with musculoskeletal sequelae: age (1.02 [1.00–1.03], $P = .004$), acute-phase hemorrhagic signs (1.64 [1.14–2.36], $P = .009$), and receiving ZMapp (3.17 [1.81–5.56], $P < .001$). Ocular sequelae were positively associated with age (1.04 [1.02–1.06], $P < .001$). Additionally, participants who experienced acute-phase hemorrhagic signs had fewer abdominal sequelae (0.49 [0.18–0.98], $P = .048$) and tended to have more general sequelae (1.57

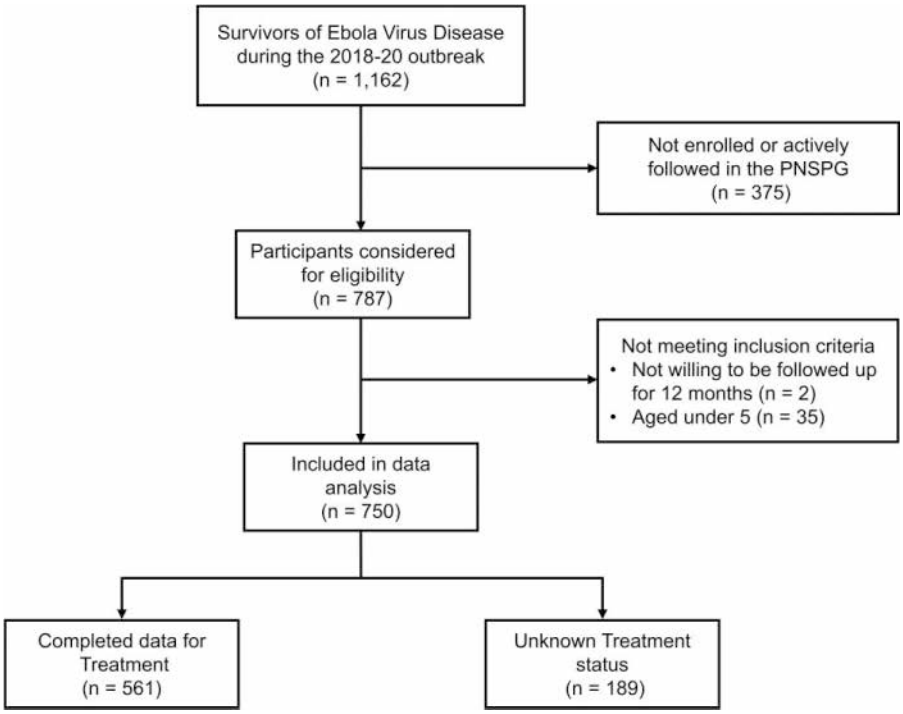


Figure 1. Study flowchart. PNSPG, Programme National de Suivi des Personnes Guéries de la maladie à virus Ebola.

[0.95–2.60], $P = .082$). We found that no factors were positively associated with abdominal sequelae at baseline. Comorbidities and hospitalization duration did not influence the presence of any sequelae at the baseline visit.

Secondary End Point

Figure 2*A* illustrates the MCF curves for recurrent post-Ebola sequelae. Over 38 months after discharge from the ETC, the MCF analysis revealed a high average of 1.93 (95% CI, 1.66–2.21) subsequent neurologic sequelae per survivor, followed by 1.66 (.95–2.38) ocular sequelae and 1.47 (1.15–1.79) musculoskeletal sequelae. The MCF curves for ocular, general, and abdominal complications were approximately linear, indicating a relatively constant rate of events over time. In contrast, the concave-down curves for neurologic and musculoskeletal sequelae suggest a decreasing rate of events over time.

The average number of neurologic and musculoskeletal events in all treatment arms was higher in women than in men. Additionally, men in the ZMapp group tended to experience more musculoskeletal events (Figure 2*B*).

Table 3 presents the factors associated with recurrent clinical sequelae over follow-up. We observed an association between recurrent neurologic sequelae and age (1.01 [1.00–1.02], $P = .003$), female sex (1.86 [1.52–2.27], $P < .0001$), REGN-EB3 (1.36 [1.03–1.80], $P = .030$), metabolic comorbidities (1.37 [1.11–1.68], $P = .003$), and headache in the acute phase (1.31 [1.01–1.70], $P = .042$). Recurrent musculoskeletal sequelae increased significantly with age (1.02 [1.02–1.03], $P < .0001$) and were higher in women (1.35 [1.08–1.69], $P = .008$) with comorbidities (1.30 [1.03–1.64], $P = .025$). Participants receiving ZMapp during the acute EVD phase tended to experience more frequent musculoskeletal sequelae (1.39 [0.96–2.00], $P = .082$). Recurrent ocular sequelae increased significantly with age (1.02 [1.01–1.03], $P < .001$). Women experienced recurrent abdominal sequelae more often than men (1.81 [1.32–2.47], $P < .001$). No factors were linked to recurrent general sequelae.

DISCUSSION

Our study investigated clinical sequelae in Ebola survivors treated with anti-Ebola therapies during the 2018–2020 EVD DRC outbreak. We evaluated the prevalence of post-EVD sequelae, the incidence of recurrent episodes over 12 months of follow-up, and contributing factors up to 38 months postdischarge. Consistent with previous research, survivors experienced various health conditions [14–17, 19, 20, 37], and half of them experienced at least 1 sequela within the first year, persisting in >80% at 38 months postdischarge. Neurologic, musculoskeletal, and general sequelae were the most common. Adult survivors were at higher risk for persistent neurologic, musculoskeletal, and ocular complications, while women had a 35%–86% increased risk of neurologic, musculoskeletal, and abdominal sequelae as compared with men. Ocular and general sequelae did not differ by sex. Our findings also highlight that metabolic comorbidities, as well as monoclonal antibodies, are

Table 1. Baseline and Follow-up Characteristics of Participants According to Anti-Ebola Therapies Received During the Acute Phase of EVD

Characteristic	All (N = 750)	Treatment Status Unknown (n = 189)	Anti-Ebola Drug During the Acute Phase				*P* Value[a]
			Remdesivir (n = 86)	Ansuvimab (n = 200)	REGN-EB3 (n = 205)	ZMapp (n = 70)	
Age at enrollment, y	32 (24–45)	32 (25–44)	33 (24–48)	32 (23–44)	32 (23–41)	32 (25–47)	.360
Age group: ≥18 y	681 (90.8)	174 (92.1)	78 (90.7)	181 (90.5)	182 (88.8)	66 (94.3)	.605
Sex: female	425 (56.7)	99 (52.4)	53 (61.6)	116 (58.0)	120 (58.5)	37 (52.9)	.742
Study site							.013
Beni	262 (34.9)	23 (12.2)	43 (50.0)	80 (40.0)	81 (39.5)	35 (50.0)	
Butembo	285 (38.0)	61 (32.3)	34 (39.5)	77 (38.5)	81 (39.5)	32 (45.7)	
Mangina	203 (27.1)	105 (55.5)	9 (10.5)	43 (21.5)	43 (21.0)	3 (4.3)	
Time between onset of symptoms and discharge, d	22 (17–27)	22 (18–28)	22 (17–28)	21 (16–25)	22 (19–28)	21 (17–25)	.015
Hospitalization duration, d	17 (14–22)	18 (13–23)	18 (15- 21)	17 (13–21)	18 (14–22)	17 (14–20)	.960
Time between discharge and recruitment, d	330 (262–423)	339 (300–397)	380 (294–472)	320 (239–426)	294 (217–398)	337 (288–388)	<.001
Length of follow-up, mo	16.6 (15.8–16.9)	16.6 (15.5–17.0)	16.6 (15.9–16.9)	16.6 (15.6–16.9)	16.6 (16.0–16.9)	16.6 (15.9–16.8)	.871
Experienced clinical sequelae over follow-up: yes	650 (86.7)	166 (87.8)	78 (90.7)	167 (83.5)	178 (86.8)	61 (87.1)	.420
Clinical symptoms of EVD acute phase							
General symptoms							
Fever	578 (77.1)	158 (83.5)	65 (75.6)	146 (73.0)	154 (75.1)	55 (78.5)	.823
Fatigue	488 (65.1)	128 (67.7)	60 (69.8)	127 (63.5)	128 (62.4)	45 (64.2)	.687
Anorexia	395 (52.7)	97 (51.3)	58 (67.4)	101 (50.5)	99 (48.2)	40 (57.1)	.018
Hemorrhage							
Conjunctive hemorrhage	90 (12.0)	22 (11.6)	15 (17.4)	20 (10.0)	26 (12.6)	7 (10.0)	.322
Melena	62 (8.3)	13 (6.9)	8 (9.3)	13 (6.5)	25 (12.1)	3 (4.3)	.107
Petechial eruption	13 (1.7)	4 (2.1)	2 (2.3)	2 (1.0)	4 (2.0)	1 (1.4)	.833
Gingival hemorrhage	24 (3.2)	9 (4.8)	5 (5.8)	4 (2.0)	5 (2.4)	1 (1.4)	.323
Hematemesis	43 (5.7)	10 (5.3)	6 (7.0)	7 (3.5)	16 (7.8)	4 (5.7)	.278
Purpura	10 (1.3)	2 (1.1)	0 (0)	2 (1.0)	4 (1.9)	2 (2.9)	.378
Abdominal symptoms							
Nausea	356 (47.5)	89 (47.1)	49 (56.7)	94 (47.0)	88 (42.9)	36 (51.4)	.153
Vomiting	465 (62.0)	128 (67.7)	55 (64.0)	109 (54.5)	125 (60.9)	48 (68.5)	.151
Diarrhea	448 (59.7)	120 (63.5)	55 (64.0)	102 (51.0)	123 (60.0)	48 (68.5)	.032
Abdominal pain	372 (49.6)	114 (60.3)	39 (45.3)	91 (45.5)	98 (47.8)	30 (42.9)	.901
Dysphagia	156 (20.8)	44 (23.3)	22 (25.6)	43 (21.5)	35 (17.0)	12 (17.1)	.332
Hiccup	13 (1.7)	6 (3.2)	0 (0)	3 (1.5)	4 (2.0)	0 (0)	.591
Myalgia	389 (51.9)	104 (55.0)	51 (59.3)	100 (50.0)	101 (49.2)	33 (47.1)	.376
Joint pains	37 (4.9)	8 (4.2)	4 (4.7)	13 (6.5)	11 (5.4)	1 (1.4)	.442
Dyspnea	78 (10.4)	15 (7.9)	10 (11.6)	15 (7.5)	27 (13.1)	11 (15.7)	.172
Neurologic disorders							
Headache	594 (79.2)	158 (83.6)	65 (75.6)	154 (77.0)	165 (80.5)	52 (74.3)	.643
Dizziness	25 (3.3)	7 (3.7)	2 (2.3)	6 (3.0)	8 (3.9)	2 (2.9)	.954
Seizure	2 (0.3)	1 (0.5)	1 (1.2)	0 (0)	0 (0)	0 (0)	.278
Memory loss	134 (17.8)	23 (12.1)	17 (19.7)	37 (18.5)	37 (18.0)	20 (28.5)	.261
Loss of consciousness	26 (3.5)	8 (4.2)	1 (1.2)	5 (2.5)	8 (3.9)	4 (5.7)	.369
Coma	5 (0.7)	1 (0.5)	0 (0)	1 (0.5)	3 (1.5)	0 (0)	.582
Comorbidities[b]	190 (25.3)	40 (21.1)	20 (23.2)	61 (30.5)	51 (24.8)	18 (25.7)	.498

Data are presented as No. (%) of participants or median (IQR).

Abbreviation: EVD, Ebola virus disease.

[a] *P* value based on Pearson χ^2 test, Fisher exact test, or Kruskal-Wallis rank sum test for the differences among treatment groups.

[b] Hypertension, obesity, overweight, diabetes.

associated with sequela occurrence, suggesting potential risks alongside their survival benefits.

When compared with West African studies, our cohort reported a lower prevalence of post-EVD sequelae [15–17]. Specifically, the baseline prevalence for headaches (26%), joint pain (14%), and ocular problems (8.1%) in our study was notably lower than that of the PREVAIL III study (47%, 47.6%, and 26.4%, respectively) [16]. This trend might reflect the effect of

Table 2. Prevalence of Post-Ebola Sequelae According to the Follow-up Visits

Clinical Sequelae[a]	Overall[b] (N = 750)	Treatment Status Unknown (n = 189)	Follow-up Visits				
			Baseline (n = 750)	First (n = 698)	Second (n = 720)	Third (n = 698)	Fourth (n = 644)
No clinical sequelae	100 (13.3)	23 (12.2)	379 (50.5)	307 (44.0)	372 (51.7)	431 (61.7)	365 (56.7)
Neurologic	463 (61.7)	119 (63.0)	211 (28.1)	170 (24.3)	163 (22.6)	139 (19.9)	141 (21.9)
Musculoskeletal	373 (49.7)	93 (49.2)	194 (25.9)	120 (17.2)	99 (13.7)	69 (9.9)	84 (13.0)
General	288 (38.4)	76 (40.2)	91 (12.1)	99 (14.2)	75 (10.4)	48 (6.9)	68 (10.5)
Abdominal	248 (33.0)	67 (35.4)	60 (8.0)	88 (12.6)	82 (11.4)	49 (7.0)	57 (8.9)
Ocular problems	254 (33.9)	67 (35.4)	61 (8.1)	105 (15.0)	68 (9.4)	56 (8.0)	77 (12.0)

Data are presented as No. (%) of participants.

[a]Participants could have >1 type of clinical sequelae.

[b]The column shows the total number of participants who experienced at least 1 episode of clinical sequelae during follow-up.

monoclonal antibody treatment on reducing post-EVD sequelae.

While prior studies described a rapid decline in sequelae [15, 16, 18], we observed a slower, steady decrease, with some symptoms remaining static over time, particularly ocular, general, and abdominal sequelae. The incidence rates of sequelae in our cohort were also higher when compared with other longitudinal studies [16, 18]. This may be due to the shorter intervals between follow-up visits, which could have led to improved detection of symptoms and faster recovery from recurrent episodes. Furthermore, additional research is needed to determine whether the rapid decline in antibody levels observed in treated survivors [26] is related to the progression of clinical sequelae, especially for joint and muscle pain.

Ocular sequelae, including vision problems, eye pain, and light sensitivity, gradually increased from 8% at baseline to 12% at the end of follow-up. This aligns with previous studies documenting EBOV persistence in ocular tissues and an increase in uveitis over time [17, 29]. The mechanisms behind ocular sequelae remain unclear, but as the eye is an immune-privileged site, EBOV persistence in ocular tissue or fluid may play a central role.

The results showed that preexisting metabolic conditions, such as hypertension, overweight or obesity, and diabetes, are strongly associated with the common recurrent sequelae (neurologic and musculoskeletal) in Ebola survivors, who had a 37% higher risk than those without these comorbidities. While these observations highlight a significant association, current evidence remains limited regarding the impact of metabolic comorbidities on long-term post-EVD outcomes, and whether EVD worsens preexisting conditions over time is still understudied. Understanding the potential interaction between chronic inflammation, such as that seen in diabetes, and the intensive chronic immune activation and inflammatory profile in Ebola survivors is essential [38]. Such insights could help identify high-risk subgroups among Ebola survivors and design specific strategies.

Our study identified an association between anti-Ebola therapies, particularly monoclonal antibodies, and the occurrence of sequelae. Survivors treated with REGN-EB3 had a 2-fold higher occurrence of neurologic disorders 1 year after ETC discharge, with a 36% greater risk of the recurrence of these sequelae as compared with those treated with remdesivir. Similarly, ZMapp recipients had a 3-fold higher occurrence of musculoskeletal complications within 1 year after ETC discharge. However, ansuvimab tended to decrease ocular sequelae during the early stages of recovery. No evidence of a relationship between these therapies and abdominal or general sequelae has been shown. As treatments against the Ebola virus continue to develop, especially monoclonal antibodies, the number of survivors is expected to increase. Yet, the proportion of patients who have received such treatment remains limited: since the 2018–2020 outbreak—the only outbreak in which such treatments have been widely used—just 35% of patients with EVD have had access to ansuvimab and REGN-EB3, leading to higher mortality than expected from these treatments [39, 40]. This low coverage prevents progress in research on the in-depth immune mechanisms that could mitigate long-term sequelae. To date, it remains unknown whether anti-Ebola therapies can reduce long-term sequelae in patients with EBOV. In a previous study, we found that survivors treated with ansuvimab experienced a more rapid decline in antibody concentrations over time when compared with an untreated survivor cohort [32]; however, whether this is linked to an increased risk of sequelae remains unclear. Furthermore, studies in animal models, particularly mice, have provided preliminary insights into assessment of the effects of EBOV-GP–targeted therapeutics on post-Ebola sequelae [41, 42]. Of note, ZMapp is a cocktail of 3 chimeric monoclonal antibodies (c13C6, c2G4, c4G7) with distinct activity profiles. c13C6 is a nonneutralizing antibody that strongly activates antibody-dependent neutrophil phagocytosis (ADNP) [43, 44]. Interestingly, in a study evaluating associations between antibody Fc–mediated functions and development of long-term sequelae in survivors of the

Table 3. Factors Associated With Post-Ebola Clinical Sequelae

	Neurologic Sequelae		Ocular Problems		Musculoskeletal Sequelae		Abdominal Sequelae		General Sequelae	
	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
Multivariate Weibull model[a]										
Age at enrollment, y	1.00 (.99–1.01)	.975	1.04 (1.02–1.06)	<.001	1.02 (1.00–1.03)	.004	0.99 (.96–1.00)	.197	1.00 (.99–1.02)	.700
Sex: female	1.13 (.81–1.57)	.464	0.91 (.48–1.72)	.784	1.30 (.91–1.87)	.149	1.25 (.66–2.37)	.490	1.10 (.661.82)	.715
Hospitalization duration, d	0.99 (.97–1.01)	.438	1.01 (.98–1.05)	.330	1.00 (.98–1.02)	.809	1.00 (.98–1.03)	.345	0.97 (.94–1.00)	.082
Anti-Ebola drugs										
Remdesivir	1	…	1	…	1	…	1	…	1	…
Ansuvimab	1.53 (.91–2.59)	.110	0.49 (.22–1.08)	.084	1.29 (.77–2.14)	.330	1.50 (.58–3.86)	.400	0.85 (.43–1.71)	.666
REGN-EB3	2.14 (1.28–3.57)	.004	0.68 (.32–1.48)	.344	1.25 (.74–2.12)	.398	1.45 (.55–3.83)	.446	1.34 (.69–2.59)	.383
ZMapp	1.72 (.92–3.24)	.088	0.43 (.14–1.34)	.156	3.17 (1.81–5.56)	<.001	1.47 (.46–4.70)	.512	0.73 (.29–1.86)	.522
Symptoms in the EVD acute phase[b]										
Abdominal symptoms	0.91 (.50–1.64)	.760	1.41 (.42–4.68)	.577	1.44 (.75–2.79)	.273	1.79 (.45–7.10)	.410	2.15 (.74–6.19)	.159
Myalgia	1.14 (.80–1.62)	.457	0.94 (.47–1.90)	.881	1.16 (.79–1.69)	.445	1.11 (.57–2.15)	.755	1.04 (.62–1.75)	.864
Hemorrhage	0.98 (.69–1.40)	.929	1.57 (.80–3.08)	.195	1.64 (1.14–2.36)	.009	0.42 (.18–.98)	.048	1.57 (.95–2.60)	.082
Headache	0.96 (.63–1.48)	.867	0.79 (.36–1.73)	.563	0.82 (.53–1.28)	.389	0.76 (.36–1.60)	.479	1.03 (.53–1.97)	.936
General symptoms	0.80 (.34–1.87)	.608	1.15 (.20–6.56)	.869	0.40 (.18–.90)	.028	0.73 (.12–4.27)	.727	0.97 (.24–3.95)	.972
Joints pains	0.62 (.34–1.14)	.126	0.57 (.17–1.91)	.363	0.84 (.45–1.56)	.577	0.84 (.29–2.45)	.756	0.70 (.25–2.00)	.516
Neurologic symptoms[c]	1.31 (.81–2.11)	.260	0.95 (.34–2.66)	.925	1.07 (.64–1.79)	.783	1.03 (.37–2.85)	.948	1.80 (.86–3.77)	.117
Comorbidities[d]	1.11 (.78–1.58)	.550	0.86 (.43–1.70)	.668	1.11 (.77–1.61)	.558	1.08 (.53–2.17)	.826	0.82 (.47–1.42)	.485
Multivariate frailty model[e]										
Age at enrollment, y	1.01 (1.00–1.02)	.003	1.02 (1.01–1.03)	<.001	1.02 (1.02–1.03)	<.0001	1.00(.99–1.01)	.943	1.01(1.00–1.01)	.338
Sex: female	1.86 (1.52–2.27)	<.0001	1.21 (.89–1.65)	.232	1.35 (1.08–1.69)	.008	1.81 (1.32–2.47)	<.001	1.15(.87–1.50)	.323
Hospitalization duration, d	1.05 (.96–1.15)	.304	1.07 (.93–1.24)	.331	1.04 (.93–1.15)	.493	1.07 (.93–1.21)	.327	0.96 (.84–1.09)	.494
Anti-Ebola drugs										
Remdesivir	1	…	1	…	1	…	1	…	1	…
Ansuvimab	1.15 (.87–1.52)	.337	0.84 (.54–1.29)	.423	0.97 (.71–1.32)	.840	1.11 (.72–1.72)	.623	0.91 (.62–1.34)	.640
REGN-EB3	1.36 (1.03–1.80)	.030	0.91 (.59–1.41)	.684	0.91 (.66–1.25)	.552	1.29 (.84–1.97)	.248	1.00 (.68–1.46)	.999
ZMapp	1.18 (.83–1.67)	.354	0.74 (.43–1.30)	.297	1.39 (.96–2.00)	.082	1.16 (.68–1.97)	.587	0.97 (.61–1.34)	.910
Symptoms in the EVD acute phase[b]										
Abdominal symptoms	1.07 (.79–1.44)	.664	1.11 (.69–1.78)	.660	1.24 (.89–1.75)	.208	1.31 (.79–2.16)	.289	1.44 (.92–2.24)	.109
Myalgia	1.07 (.87–1.32)	.511	1.14 (.81–1.59)	.455	1.08 (.85–1.38)	.508	1.21 (.88–1.66)	.248	1.13 (.84–1.51)	.423
Hemorrhage	1.10 (.88–1.38)	.412	1.24 (.87–1.78)	.238	1.26 (.97–1.64)	.080	0.92 (.65–1.30)	.630	1.29 (.95–1.75)	.108
Headache	1.31 (1.01–1.70)	.042	0.87 (.58–1.33)	.527	1.06 (.79–1.41)	.702	1.03 (.70–1.51)	.874	1.26 (.95–1.75)	.218
General symptoms	1.21 (.78–1.89)	.400	0.66 (.33–1.31)	.237	0.63 (.42–1.02)	.067	0.78 (.40–1.52)	.469	0.59 (.33–1.05)	.074
Joints pains	1.02 (.70–1.48)	.934	1.33 (.75–2.35)	.331	1.38 (.91–2.09)	.126	1.29 (.75–2.24)	.356	1.24 (.73–2.10)	.426
Neurologic symptoms[c]	1.20 (.88–1.63)	.251	1.01 (.61–1.68)	.971	1.12 (.78–1.60)	.534	0.89 (.54–1.47)	.654	1.33 (.85–2.07)	.213

Table 3. Continued

	Neurologic Sequelae		Ocular Problems		Musculoskeletal Sequelae		Abdominal Sequelae		General Sequelae	
	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
Comorbidities[d]	1.37 (1.11–1.68)	.003	1.22 (.87–1.70)	.255	1.30 (1.03–1.64)	.025	1.05 (.76–1.45)	.782	1.01 (.74–1.37)	.957

A separate multivariate model was performed for each sequela. Multivariate analysis included 561 survivors with documented treatment status, adjusted for age at enrollment, sex, and study site.

Abbreviations: aHR, adjusted hazard ratio; EVD, Ebola virus disease.

[a]Factors associated with post-Ebola clinical sequelae reported at baseline visit. For each covariate, the aHR with 95% CI based on the Weibull model is reported.

[b]Symptoms occurring in the EVD infection are presented as binary variables (yes or no) with the "no" category as the reference. Each symptom listed was included as a covariate in the model.

[c]Dizziness, seizure, loss of consciousness, coma, memory loss.

[d]Presence of any condition: hypertension, diabetes, overweight, obesity.

[e]Factors associated with recurrent clinical sequelae during the follow-up study. For each covariate, the aHR with 95% CI based on the frailty model is reported.

Bundibugyo Ebola virus outbreak, a trend for increased incidence of joint pain in survivors positive for ADNP was observed at 2 years postrecovery [45]. Overall, these findings support further investigation into the impact of combination therapies on the host response to mitigate persistent EVD sequelae.

Additionally, our results showed that the impact of monoclonal antibodies on clinical sequelae appeared more pronounced in women than men, suggesting a potential interaction between sex and treatment effects. Our study's increased risk of sequelae among adults and women aligns with findings from previous West African outbreaks [18, 19]. Women were particularly vulnerable to neurologic, musculoskeletal, and abdominal complications, while adult survivors had higher risks of neurologic, musculoskeletal, and ocular sequelae. In contrast, general sequelae, including fatigue, fever, and anorexia, did not differ significantly by age, sex, or treatment group. This finding contrasts with studies that linked general sequelae to older age and myalgia during acute illness [15, 18].

Acute EVD symptoms were significantly associated with sequelae, primarily during early recovery. For instance, survivors with bleeding during EVD were more likely to experience persistent joint and muscle pain. However, unlike previous reports [15, 19], our analysis did not find associations between acute-phase symptoms (eg, headaches, red eyes) and ocular complications. Additionally, we observed no relationship between the length of ETC stay and post-EVD complications, consistent with earlier findings [15, 16].

Our cohort's slower decline in sequelae suggests the need for prolonged follow-up and tailored care for survivors. Interestingly, the lower prevalence of sequelae observed in our cohort as compared with West African studies suggests a potential effect of anti-Ebola treatments received during the acute phase of the disease.

The Les Vainqueurs d'Ebola study's main strengths are its large prospectively followed cohort of EVD survivors in the DRC, advanced statistical methods to assess post-EVD outcomes, and implementation within a national care program during the outbreak. Our study is the first to evaluate the potential effects of anti-Ebola therapies on long-term clinical outcomes in the DRC. Routine monthly visits and systematic clinical assessments ensured detailed symptom monitoring and robust data collection.

However, this study has limitations. First, the absence of a control group makes it difficult to definitively attribute observed sequelae to specific factors, such as treatments or acute-phase symptoms. Additionally, concurrent viral infections could contribute to the findings, as they may present a range of nonspecific symptoms months after the initial infection similar to those observed in EVD, a phenomenon known as post-acute infection syndrome. Without a detailed comparative analysis with infection-specific biological markers, the effects

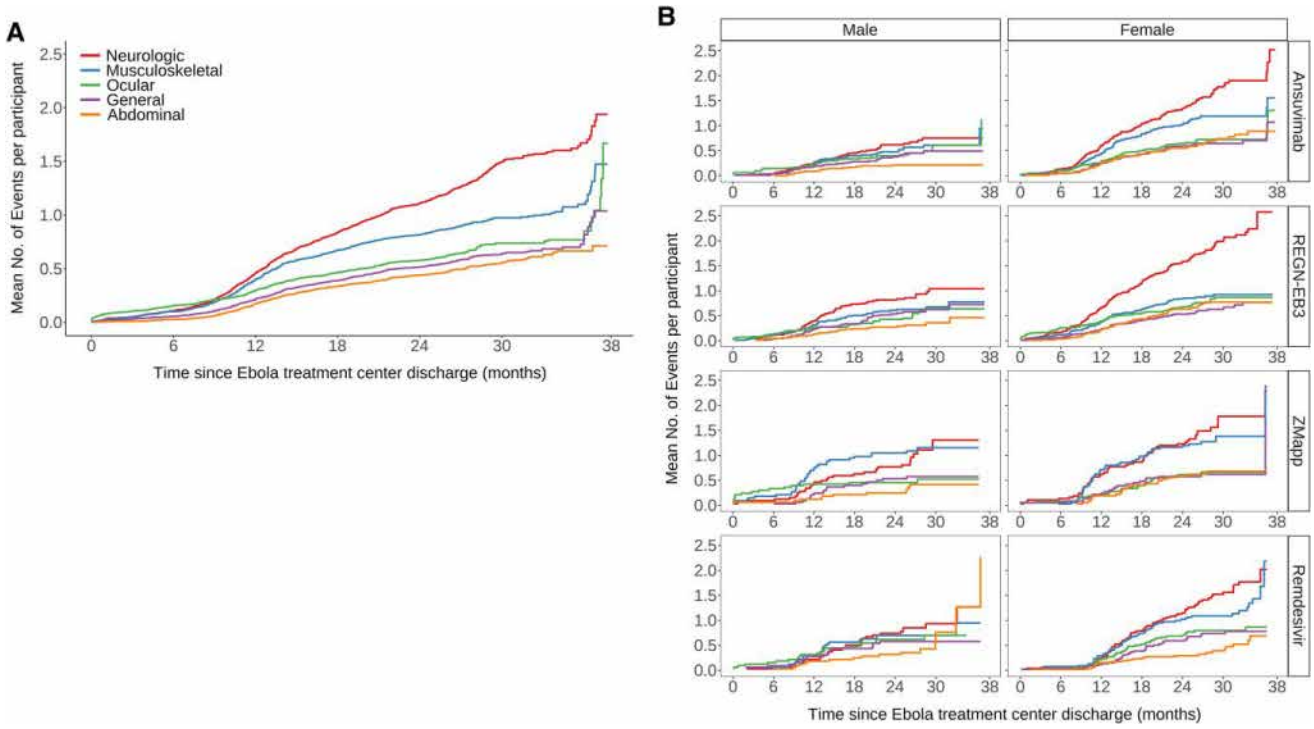


Figure 2. Mean cumulative function (MCF) for recurrent events for different clinical sequelae over follow-up time among Ebola survivors. This estimated the average number of recurrent events per patient up to 38 months after Ebola treatment center discharge. *A,* MCF stratified by clinical sequela for all 750 participants. Survivors averaged more neurologic and musculoskeletal sequelae over 38 months. These tended to decline over time. *B,* Comparison of MCF by sex and by anti-Ebola therapy among participants with completed treatment data. Women (right column) have a higher average number of events across all treatment groups as compared than men (left column). This trend was consistent with all therapies analyzed, with the largest disparities observed in the REGN-EB3 and ansuvimab groups.

of such infections on post-Ebola sequelae cannot be distinguished. Yet, postacute infection syndrome associated with other infections usually affects only a minority of exposed patients and varies in duration, unlike EVD, where sequelae are more frequent and persistent in most survivors. Second, while the absence of 375 survivors from the cohort may have introduced selection bias, their nonparticipation was likely random and unrelated to sequelae occurrence, as all survivors had been offered enrollment in the National Survivor Follow-up Program at discharge from ETCs, well before study recruitment. Third, unmeasured confounders may have influenced the observed associations. Our analysis focused on clinical outcomes without incorporating biological markers, such as EBOV persistence in body fluids or antibody levels, which have been linked to uveitis and sequela progression [20, 21, 32]. Additionally, we did not account for the potential impact of widespread use of the rVSV-ZEBOV vaccine during the outbreak, which may have affected survivor outcomes and treatment effects. Fourth, although survivors with and without treatment data were similar in age and sex, the high proportion of missing treatment data among symptomatic survivors may have led to an underestimation of the treatment's effect on sequelae. Last, delays between ETC discharge and the enrollment visit may have led to missed events, potentially resulting in an underestimation of certain outcomes. To address this, we used the counting process format (start-stop time) in all multivariate survival models, ensuring accurate handling of left truncation and avoiding bias in hazard estimates.

CONCLUSION

Our study highlights the substantial burden of post-Ebola sequalae, with the majority of survivors (86.7%) still experiencing complications up to 3 years after recovery. The most prevalent long-term outcomes, which decreased slowly over time, were headaches, dizziness, joint or muscle pain, and ocular complications. We identified age, sex, metabolic comorbidities, hemorrhage, and headache in EVD infection, as well as anti-Ebola monoclonal antibodies, as significant factors associated with EVD long-term sequelae. The severity and persistence of ocular complications highlight the need for regular eye examinations and specialized care as part of comprehensive follow-up. The rapid deployment of anti-Ebola therapies significantly improved survival during the 2018–2020 DRC outbreak. However, our findings established that these treatments, particularly REGN-EB3 and ZMapp, are associated with specific sequelae, especially in women with hypertension, diabetes, or obesity. Although ansuvimab could reduce ocular

complications, further research is needed to confirm this effect. These results reveal the challenge of balancing the lifesaving benefits of anti-Ebola therapies with their long-term consequences on survivors. Further research is required to understand the immunologic and clinical determinants of post-EVD outcomes in a comparative analysis. Developing targeted interventions in high-risk subgroups and refining therapeutic strategies will be critical to improving survivors' quality of life and addressing the long-term burden of EVD.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. A. D.-K., head of the Les Vainqueurs d'Ebola study in the DRC, analyzed the data, wrote the first draft of the manuscript, and critically reviewed the manuscript. T. T.-S. oversaw the follow-up activities and critically reviewed the manuscript. B. C. contributed to statistical analysis and critically reviewed the manuscript. A. N.-N. critically reviewed the manuscript. D. M.-B. supervised the fieldwork and follow-up activities and critically reviewed the manuscript. E. P.-K., data manager in the Les Vainqueurs d'Ebola study, supervised data collection and monitoring. R. K.-O., head of the Programme National du Suivi des Personnes Guéries activities in the DRC, supervised the follow-up activities. J. B.-P. and F. M.-M. supervised the data monitoring and follow-up activities. P. M.-K. supervised laboratory and field activities. A. A. contributed to the review of the manuscript. J.-F. E. contributed to statistical analysis and reviewed the manuscript. F. C. supervised, interpreted all results, and critically reviewed the manuscript. J.-J. M.-T. was a member of the steering committee and coordinator of Ebola response activities. E. D. and S. A.-M. were the coordinating investigators, conceived the study, interpreted all results, critically reviewed the manuscript, and approved the last version. A. D.-K., S. A.-M., and E. D. have access to all the data. All authors have reviewed the article, approved the final version, and signed the author disclosure form.

Data-sharing statement. We support data sharing of individual patient data. The patient data underlying the results reported in this article will be shared after deidentification (text, tables, figures, and appendix). Patient data will be available beginning 3 months and ending 1 year after publication. Supporting clinical documents, including the study protocol, statistical analysis plan, and the informed consent form, will be available immediately following publication for at least 1 year. Researchers who provide a scientifically sound proposal will be allowed access to the individual patient data. Proposals should be directed to Professor Eric Delaporte and Professor Steve Ahuka-Mundeke. These proposals will be reviewed and approved by the sponsor, investigator, and collaborators based on scientific merit. To gain access, data requesters will need to sign a data access agreement.

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