



# Long-Term Decrease in Intraocular Pressure in Survivors of Ebola Virus Disease in the Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL) III Study

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**Objective:** Survivors of Ebola virus disease (EVD) experience decreased intraocular pressure (IOP) relative to unaffected close contacts during the first year of convalescence. Whether this effect persists over time and its relationship to intraocular pathology are unclear. We sought to determine whether IOP remained lower in survivors of EVD over 4 years of follow-up and to identify associated risk factors.

**Design:** Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL) III is a 5-year, longitudinal cohort study of survivors of EVD and their close contacts and is a collaboration between the Liberian Ministry of Health and the United States National Institutes of Health.

**Participants:** Participants who enrolled in PREVAIL III at John F. Kennedy Medical Center in Liberia, West Africa from June 2015 to March 2016 who underwent comprehensive ophthalmic evaluation annually for 5 consecutive visits.

**Methods:** Intraocular pressure was measured at each visit by a handheld rebound tonometer using sterile tips. Comparisons are made between antibody-positive survivors and antibody-negative close contacts.

**Main Outcome Measures:** Intraocular pressure, measured in mmHg, at each study visit.

**Results:** Of 565 antibody-positive survivors and 644 antibody-negative close contacts enrolled in the study at baseline, the majority of participants returned annually, with 383 (67.8%) and 407 (63.2%) participants, respectively, presenting for the final study visit at a median of 60 months after symptom onset. A sustained, relative decrease in IOP was observed in survivors relative to close contacts, with mean difference of  $-0.72$  mmHg (95% confidence interval [CI]  $-1.18$  to  $-0.27$ ) at the final study visit. This difference remained constant throughout the study period ( $P = 0.4$  for interaction over time). Among survivors, physical examination findings of vitreous cell and OCT findings of vitreous opacities both demonstrated a significant association with decreased IOP at baseline ( $P < 0.05$  for both). After adjusting for such factors, the difference throughout the follow-up ( $-0.93$  mmHg, 95% CI,  $-1.23$  to  $-0.63$ ) remained significant.

**Conclusions:** Survivors of EVD experienced a sustained decrease in IOP relative to close contacts over a 5-year period after EVD. The results highlight the importance of considering long-term sequelae of emerging infectious diseases within a population.

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*Zaire ebolavirus*<sup>1</sup> was responsible for the West African Ebola virus disease (EVD) epidemic, the largest epidemic of this disease to date, which started in 2014 and resulted in over

28 646 cases and 11 323 recorded deaths.<sup>2</sup> Subsequently, the > 17 000 people who contracted the virus and survived demonstrated a wide range of postinfectious sequelae

associated with EVD, including hearing loss, arthralgia, myalgia, neurologic signs, abdominal pain, fatigue, anorexia, and ocular complications.<sup>3–13</sup> These eye findings carry particular relevance for understanding the potential long-term impact of viral infections, which can result in vision-threatening pathology in the eye.<sup>14</sup>

Large-scale or population-based research can assist in understanding the spectrum of clinical presentation, especially when understanding diseases with characteristics that present with low incidence. In Liberia, the Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL) was established by the Liberian Ministry of Health and the United States National Institute of Allergy and Infectious Diseases to explore questions around EVD, both its acute phase and convalescence. Among the series of studies conducted through this partnership, PREVAIL III was a 5-year, longitudinal cohort study of people who survived EVD and their close contacts.<sup>12</sup> It enrolled 3930 participants and included detailed ophthalmic evaluations.<sup>13</sup>

Approximately 1 year after infection, people who survived EVD had slightly lower intraocular pressure (IOP) relative to close contacts.<sup>13</sup> However, several questions remained. It was unclear how long this effect persisted and whether it diminished over time. Moreover, it was not known whether specific factors were associated with these IOP differences. In this study, we compared IOP between survivors of EVD and their close contacts across 4 additional years of follow-up, and we sought to identify the factors associated with changes in IOP.

## Methods

This longitudinal cohort study includes survivors of EVD and their close contacts from the PREVAIL III eye substudy. All participants received a detailed consent briefing and provided written informed consent. This manuscript followed the Strengthening of Reporting of Observational Studies in Epidemiology reporting guidelines.<sup>15</sup> The study was approved by the institutional review board and ethics committee at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and the Liberian National Research Ethics Board and adheres to the tenets of the Declaration of Helsinki.

## Participants

Survivors who were treated for EVD at an Ebola treatment unit were eligible and invited to enroll in the PREVAIL III study if their name was registered on the Ministry of Health listing of survivors. Household members, friends, and neighbors of survivors at the time of diagnosis or after recovery from EVD were classified as close contacts. Sexual partners of survivors after discharge from the treatment facility were also classified as close contacts. These close contacts were invited to serve as controls in analyses investigating sequelae of EVD. Among participants who enrolled in the PREVAIL III parent study across 3 sites in Liberia, those who enrolled at the John F. Kennedy Medical Center in Monrovia, Liberia from June 2015 to April 2016 were eligible to participate in a longitudinal eye substudy, provided that the baseline eye examination was before July 1, 2016. This substudy included a baseline and 4 annual follow-up ophthalmic examinations. The median time from EVD symptom onset to enrollment was ~11 months.<sup>13</sup>

Of the 3930 participants who enrolled at the 3 sites across the country throughout the PREVAIL III enrollment period, 1427 participants enrolled at the John F. Kennedy Medical Center, of which 1411 completed serologic testing. The 587 survivors who were Ebola virus seropositive and 671 close contacts who were Ebola virus seronegative were asked to present for eye examination, and return yearly for 4 additional visits. Participants who presented later or at distant sites were offered eye examinations as needed, and were not included in analyses. The participation from enrollment to final follow-up is depicted in [Figure 1](#).

## Study Design

In PREVAIL III, all survivors of EVD underwent serologic confirmation of prior infection by measurement of anti-Ebola virus antibodies using the Filovirus Nonclinical Animal Group assay.<sup>16</sup> Seropositivity was defined as having an Ebola virus glycoprotein immunoglobulin G antibody titer of 548 U/mL or higher on the Filovirus Nonclinical Animal Group assay.<sup>12,14,16</sup> Close contacts also underwent testing for anti-Ebola virus antibodies to confirm a seronegative classification.

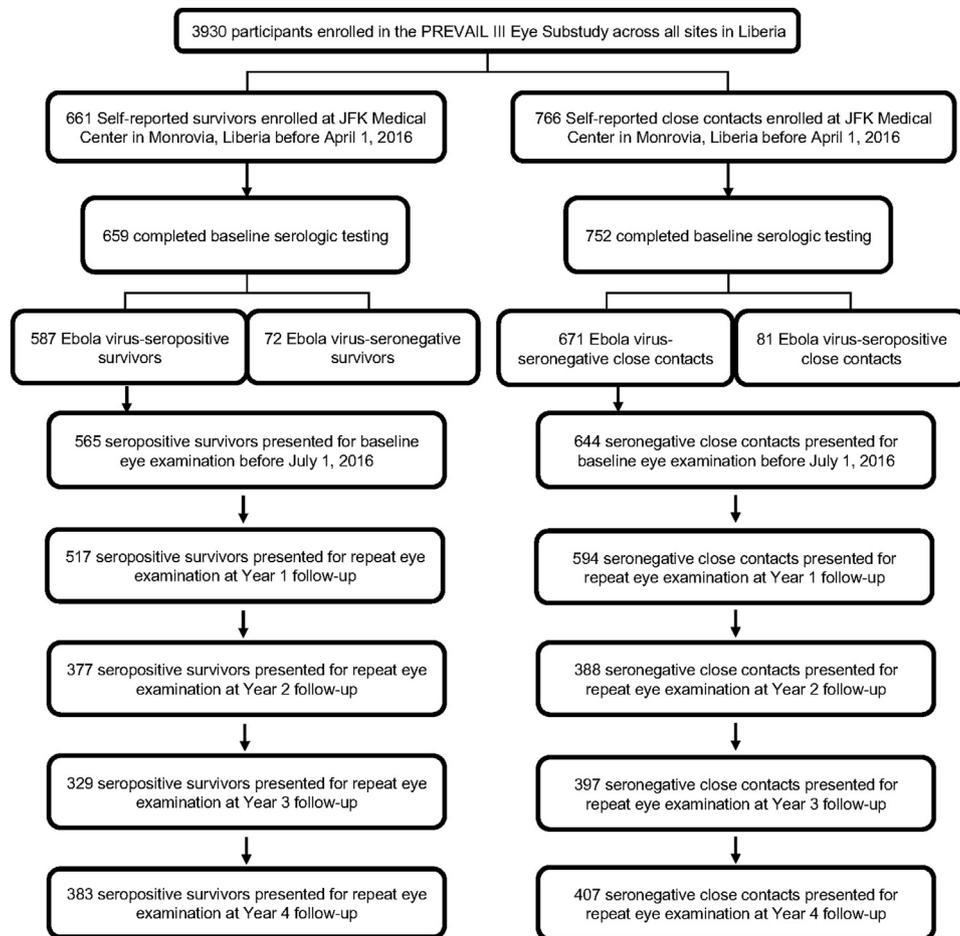
In the eye substudy, all participants were examined by an ophthalmologist (J.L., F.A., V.R., A.O.E., R.J.B., R.D.R., G.S.P., and B.B.). Annual study evaluations included comprehensive ophthalmic examinations and ophthalmic imaging. Intraocular pressure assessment was measured by rebound tonometry (iCare) using disposable probes. Visual acuity, refraction, pupil examination, ocular motility and alignment, slit-lamp biomicroscopic examination of the anterior segment, and dilated fundus examination with indirect funduscopy were performed. In addition, OCT of the optic nerve and macula was performed for all participants  $\geq 4$  years old with a Zeiss Cirrus 5000 OCT device (Carl Zeiss Meditec Inc). Standard-of-care treatment was initiated for any ophthalmic disorders identified.

## Statistical Analysis

Statistical analyses were conducted using the SAS (v9.3, SAS Institute Inc) and R (v3.2.3, R Project for Statistical Computing). Statistical comparisons were conducted between Ebola antibody-positive survivors and antibody-negative close contacts, between antibody-positive survivors with and without specific ocular physical examination findings, and across consecutive years among antibody-positive survivors. Data from participants whose serology did not correspond with their group classification were excluded from analysis, but such participants remained eligible to receive clinical evaluation and treatment during the course of the study.

Generalized estimating equations were used assuming an independence correlation structure.<sup>13</sup> Random effects were associated with groups of related survivors and close contacts, and models were adjusted for sex and age. All *P* values cited are 2-sided, and results are considered statistically significant if the *P* values are  $< 0.05$ . We include effect estimates as adjusted mean differences and 95% confidence intervals [CIs] when comparing rates of findings between groups.

To address the effects from variability in follow-up, missing IOP values were imputed using the mice package in R. A variety of baseline factors were used to predict missing IOP values, including age, sex, survivor status, presence of eye abnormalities at baseline examination, blood pressure, presence of anterior chamber cells, vitreous cells, vitreous opacities, afferent pupillary defect, retinal edema, synechiae, optic nerve swelling, macular scar, peripheral retinal scar, and uveitis. The imputation method did not account for within-subject correlation arising from repeated measurements.



**Figure 1.** Flowchart illustrating enrollment in the Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL III) Eye Substudy from the recruitment to the last follow-up visit. Among the 3930 participants who enrolled in the study across 3 sites for baseline evaluation, 1411 participants enrolled at John F. Kennedy (JFK) Medical Center before April 1, 2016 and completed serologic testing. The subset of 565 survivors and 644 close contacts whose classification was confirmed with serology and who also presented for baseline eye examination was asked to return yearly, and formed the longitudinal cohort.

## Results

At baseline, 565 serology-confirmed EVD survivors and 644 serology-confirmed close contact controls underwent ophthalmic evaluation. The majority of participants presented each year for follow-up, and by the final visit at year 4, 383 (67.8%) survivors and 407 (63.2%) controls presented for evaluation ( $P = 0.10$  for difference by Fisher exact test). Overall, 537 (95%) survivors and 602 (93.5%) close contacts presented for  $\geq 1$  of the follow-up visits. The participation from enrollment to final follow-up is depicted in [Figure 1](#).

Median IOP and mean differences between cohorts are shown in [Table 1](#). At baseline, IOP was statistically significantly lower in survivors (mean difference,  $-1.16$  mmHg; 95% CI,  $-1.57$  to  $-0.74$ ). Subsequently, over the next 4 years of the study, survivors demonstrated a statistically significantly lower IOP relative to close contacts. At year 4, there was a  $-0.72$  mmHg mean difference (95% CI,  $-1.18$  to  $-0.27$ ). The model without interaction terms estimates a mean difference in IOP

of  $-0.90$  mmHg (95% CI,  $-1.19$  to  $-0.60$ ) across 4 years of follow-up. There was no significant interaction between IOP and year ( $P = 0.4$ ), reflective of a sustained difference over the 5-year period.

[Figure 2](#) illustrates the distribution of IOP in each group at baseline and during each year of follow-up. In these histograms, no bimodal curve is present to suggest a single factor that may offset the mean, but rather, a single curve seems displaced lower in survivors of EVD relative to close contacts each year.

An analysis accounting for the potential bias from participants lost to follow-up is shown in [Table S2](#) (available at [www.ophtalmologyscience.org](http://www.ophtalmologyscience.org)). The comparison of IOP between participants who returned for follow-up and those who did not revealed a statistically significant interaction with survivor status ( $P < 0.05$ ). Although only 6.5% of close contacts did not present for follow-up at any point after the baseline ophthalmic evaluation, this group did demonstrate a statistically significantly lower baseline IOP than those who returned for follow-up. These data confirm

Table 1. Summary of IOP in Survivors of EVD and Their Close Contacts over 5 Years

N observed (95% CI)	Baseline		Year 1		Year 2		Year 3		Year 4		P Value for Interaction
	Survivors (N = 565)	Contacts (N = 644)	Survivors (N = 517)	Contacts (N = 594)	Survivors (N = 377)	Contacts (N = 388)	Survivors (N = 329)	Contacts (N = 397)	Survivors (N = 383)	Contacts (N = 407)	
Mean Difference	-1.16 (-1.57, -0.74)		-0.93 (-1.34, -0.52)		-0.96 (-1.36, -0.56)		-0.72 (-1.16, -0.27)		-0.72 (-1.18, -0.27)		0.4
IOP (median, interquartile range)	12.4 (10.4–14.5)	13.5 (11.5–16)	12.8 (10.5–15.5)	14.5 (12.4–17)	12.8 (10.5–15.5)	14 (12–16.5)	13.5 (11.5–16.5)	14.5 (12.5–17.4)	15 (12.4–17.5)	15.9 (13.5–18)	
N multiply imputed observations	0	0	48	50	188	256	236	247	182	237	

All estimates are adjusted for age, gender and relationships among survivors and close contacts. Each year survivors of EVD demonstrated a significantly lower IOP when compared with close contacts. Missing IOP values were multiply imputed using the mice package in R. CI = confidence interval; EVD = Ebola virus disease; IOP = intraocular pressure.

the benefit of the imputation used in the analyses. Table 3 assesses the risk factors associated with a change in IOP at baseline in survivors of EVD. The presence of vitreous cells on slit-lamp biomicroscopy (mean difference, -1.61 mmHg; 95% CI -2.69 to -0.54) and the presence of vitreous opacities on OCT (mean difference, -0.68 mmHg; 95% CI -1.34 to -0.02) were both associated with lower IOP. Median IOP was statistically significantly higher in participants with an afferent pupillary defect (mean difference, + 3.57 mmHg; 95% CI, 1.58–5.57).

We then sought to determine if these risk factors at baseline maintained their association throughout the duration of the study. Table S4 (available at [www.ophtalmologyscience.org](http://www.ophtalmologyscience.org)) demonstrates the associations between IOP and significant baseline risk factors among survivors from baseline to year 4 of follow-up. Afferent pupillary defect was significantly associated with a higher IOP in survivors at each year of follow-up. Presence of vitreous cell was associated with a significant decrease in IOP in survivors only at year 2 of follow-up (mean difference, -6.86 mmHg; 95% CI -12.3 to -1.42). Presence of vitreous opacities was associated with a significant change in IOP in survivors only at year 3 of follow-up (mean difference, + 0.87 mmHg; 95% CI 0.04–1.7).

To further determine whether these factors accounted for the difference in IOP in the follow-up period, we reassessed mean differences in IOP between survivors and close contacts, adjusting for these factors, as well as baseline factors (age, gender, and relationships between contacts and survivors). These data appear in Table S5 (available at [www.ophtalmologyscience.org](http://www.ophtalmologyscience.org)). Consistent with the findings reported before adjustment, IOP was significantly lower in survivors relative to close contacts (mean difference, -1.19 mmHg; 95% CI, -1.6 to -0.77) at baseline and remained lower over the next 4 years of the study. At year 4, there was a -0.75 mmHg mean difference (95% CI, -1.21 to -0.3). The model without interaction terms estimates a mean difference of -0.93 mmHg (95% CI, -1.23 to -0.63) across follow-up when adjusting for presence of baseline factors. There was no statistically significant interaction between IOP and year (P = 0.4), reflective of a sustained difference over 5 years.

## Discussion

In this 5-year, longitudinal cohort study of people who survived EVD and their close contacts, the data point to a sustained relative decrease in IOP among survivors. This difference, although mild, was sustained even after adjusting for risk factors related to Ebola-associated ocular pathology.

In assessing the distribution of IOP readings, the sustained IOP decrease among EVD survivors compared with controls does not seem to be because of a small proportion of individuals with extreme measurements, but rather a general shift in the curve toward decreased IOP. Given that the intraocular factors identified did not seem to completely account for the shift, the data allude to the possibility of a more systemic impact of the EVD process that contributes to a decrease in IOP.

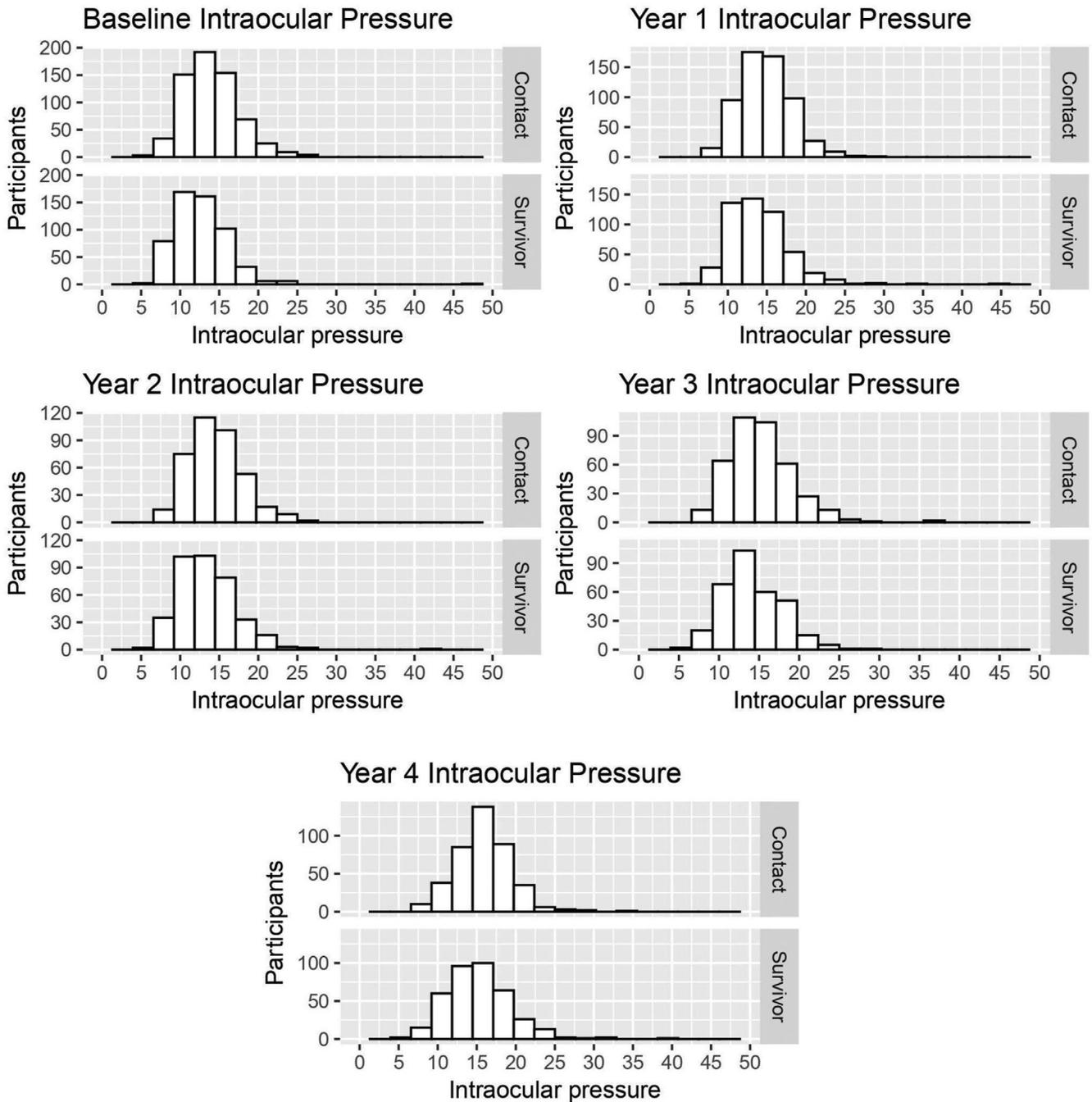


Figure 2. Histogram of intraocular pressure measurements in people who survived Ebola virus disease and their close contacts over the course of 5 years.

The plausibility of a long-term decrease in IOP in people infected by EVD is supported by a similar finding in people infected by human immunodeficiency virus.<sup>17</sup> Although the difference in IOP between groups in this study was small and does not suggest hypotony for most survivors, it demonstrates a long-term process taking place within the eye and adds Ebola virus to the compendium of known viruses causing changes in IOP over time.

Notably, this finding of decreased IOP is nuanced and in the setting of acute inflammation, IOP may initially increase in some EVD survivors. In a well-documented case of post-Ebola uveitis outside of this study, IOP temporarily increased to 44 mmHg.<sup>18</sup> Such inflammatory changes share some similarities with viral infections from herpes simplex and varicella-zoster,<sup>13</sup> which may induce trabeculitis and contribute to transient IOP increases.

Table 3. Risk Factors for Decreased IOP among Survivors of Ebola Virus Disease

Factor	IOP for Participants with Factor (Median, Interquartile Range)	IOP for Participants Without Factor (Median, Interquartile Range)	Effect Estimate, Adjusted for Age and Sex (Mean Difference)	95% Confidence Interval	P Value
Afferent pupillary defect	14.6 (9.1–17.4)	12.4 (10.4–14.5)	+3.57	(1.58, 5.57)	< 0.001
Keratic precipitates	12.1 (10.5–13.9)	12.4 (10.4–14.5)	–0.5	(–1.72, 0.71)	0.42
Synechia	10.7 (9–13.9)	12.4 (10.5–14.5)	–1.12	(–2.56, 0.32)	0.13
Anterior chamber cells	11.6 (9.6–13)	12.4 (10.4–14.5)	–0.85	(–2.35, 0.65)	0.27
Vitreous cell	11 (9–12.8)	12.5 (10.5–14.7)	–1.61	(–2.69, –0.54)	<b>0.003</b>
Macular scar	12.7 (10.5–14.6)	12.4 (10.4–14.5)	+0.25	(–0.72, 1.22)	0.62
Peripheral retinal scar	12.5 (9.7–13.5)	12.4 (10.4–14.5)	–0.74	(–2.13, 0.64)	0.29
Cataract	12.8 (10.5–15)	12.4 (10.4–14.5)	+0.44	(–0.51, 1.39)	0.36
OCT					
Intraretinal fluid cysts	11.8 (10.5–12.8)	12.5 (10.4–14.5)	–0.42	(–1.83, 0.99)	0.56
Vitreous opacities	11.8 (10–14)	12.5 (10.5–14.7)	–0.68	(–1.34, –0.02)	<b>0.045</b>
Epiretinal membrane	11.8 (10.5–14)	12.8 (10.5–15)	–0.26	(–1.94, 1.43)	0.77
Diagnoses					
Inactive Uveitis	12 (10.5–14.4)	12.4 (10.5–14.5)	–0.49	(–1.21, 0.24)	0.19
Active Uveitis	11.2 (9.5–12.8)	12.5 (10.5–14.5)	–1.21	(–2.5, 0.07)	0.07

Eyes with an afferent pupillary defect had a significantly higher median IOP. IOP measured during the baseline ophthalmic evaluation was relatively lower in participants with vitreous cell on clinical examination and vitreous opacities identified through OCT. Data are presented as median and interquartile range, with mean difference and 95% confidence interval. Estimates are adjusted for age and sex. Boldface indicates statistical significance.

IOP = intraocular pressure.

The data in this study confirm the need for a comparison/control group when interpreting longitudinal changes in clinical research studies. Between baseline measurements and year 4, for example, the IOP in both groups slowly increased. The reasons for such changes may be multifactorial and warrant further exploration. Without a comparison group, the data from survivors alone may have erroneously suggested that EVD infection results in an increase in IOP. Serologic testing for antibodies to Ebola virus of both survivor and control groups in this study strengthens the classifications into each group.

An additional strength of this study is the objective ascertainment of IOP. Although some aspects of ophthalmic evaluation are based on subjective clinical judgment, we used a rebound tonometer for all IOP measurements that provides an automated numeric output. Compared with applanation tonometry, we found rebound tonometry useful in a study involving multiple examiners to minimize variability and to allow for a sterile point of contact for the device, given our study of the effects of an infectious disease. One limitation of this study is its observational nature, which prevents us from attributing causality.

Although it is unknown whether the findings reflect decreased production or increased outflow of aqueous humor, fluorophotometry studies of eyes of people with human

immunodeficiency virus offer 1 method to investigate this question, suggesting in human immunodeficiency virus infection that such a decrease may be related to decreased production of aqueous humor.<sup>19</sup> Animal models of EVD have identified viral antigens in ciliary body vasculature,<sup>20</sup> offering 1 pathway through which IOP may be affected. Further research could explore whether issues around viral persistence, vascular permeability, or chronic inflammation may contribute to such changes in IOP.

Recently, the coronavirus disease 2019 pandemic has created a renewed interest in long-term sequelae of emerging viral diseases, with data suggesting prolonged physiologic impact and ongoing complications in survivors of severe acute respiratory syndrome coronavirus 2 infection.<sup>21</sup> Although our current understanding about post-coronavirus disease 2019 syndromes relates to symptoms in the first 1 to 2 years after acute illness,<sup>22</sup> the data here demonstrate the benefit of long-term studies after viral illness for several years.

Overall, this study demonstrated a significant decrease in IOP in EVD survivors relative to their close contacts, a change that persisted over  $\geq 5$  years after infection. Broadly, these findings highlight the potential of long-term postviral sequelae and the need to maintain and strengthen ongoing care for survivors of emerging infectious diseases.

## Footnotes and Disclosures

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#### Abbreviations and Acronyms:

**CI** = confidence interval; **EVD** = Ebola virus disease; **IOP** = intraocular pressure; **PREVAIL** = Partnership for Research on Vaccines and Infectious Diseases in Liberia.

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Ebola virus disease, global ophthalmology, intraocular pressure, Liberia, Ebola.

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