Long-term decrease in intraocular pressure in survivors of Ebola virus disease in the PREVAIL III Study


PII: S2666-9145(22)00127-0
DOI: https://doi.org/10.1016/j.xops.2022.100238
Reference: XOPS 100238

To appear in: Ophthalmology Science

Received Date: 27 April 2022
Revised Date: 21 October 2022
Accepted Date: 21 October 2022


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Long-term decrease in intraocular pressure in survivors of Ebola virus disease in the PREVAIL III Study

Shwetha Mudalegundi, BS, BSPH; Robin D. Ross, MD, MPH; Jemma Larbelee, MD; Fred Amegashie, MD; Robert F. Dolo, BSN, BSc; S. Grace Prakalapakorn, MD, MPH; Vincent Ray, MD; Catherine Gargu, BSN, MPH; Yassah Sosu, BSN; Jennie Sackor, BSN; Precious Z. Cooper, BSN; Augustine Wallace; Ruth Nyain, BSC, MEd; Bryn Burkholder, MD; Collin Van Ryn, MS; Bionca Davis, MPH; Mosoka P. Fallah, PhD, MPH, MA; Cavan Reilly, PhD; Rachel J. Bishop, MD, MPH; Allen O. Eghrari, MD, MPH

*Co-Senior Authors

Author Affiliations:
1. Wilmer Eye Institute at Johns Hopkins, Baltimore, Maryland
2. Global Retina Institute, Scottsdale, Arizona
3. Redemption Hospital, Monrovia, Liberia
4. Liberia Noncommunicable Disease Alliance, Monrovia, Liberia
5. New Sight Eye Centre, Paynesville, Liberia
6. Department of Ophthalmology, Duke University, Durham, North Carolina
7. Department of Ophthalmology, California Pacific Medical Center, San Francisco
8. Partnership for Research on Vaccines and Infectious Diseases in Liberia, Monrovia, Liberia
9. Division of Biostatistics, University of Minnesota, Minneapolis
10. Africa Center for Disease, Addis Ababa, Ethiopia
11. National Eye Institute, National Institutes of Health, Bethesda, MD

Corresponding Authors: Allen O. Eghrari, MD, MPH and Rachel J. Bishop, MD, MPH

Financial Support: This study was supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH) and the Liberian Ministry of Health, and in part by NIH K12 EY015025-10 (AOE), NIH L30 EY024746 (AOE), Research to Prevent Blindness Special Scholar Award (AOE), the Tolsma Family (AOE) and the American Society of Cataract and Refractive Surgery Foundation Research Grant Award (AOE).

Disclosures: This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. PREVAIL is now Partnership for Research on Vaccines and Infectious Diseases in Liberia.

Conflict of Interest: The authors have no financial conflicts of interest to disclose.

Running Head: Intraocular Pressure in Survivors of Ebola Virus Disease

Address for Reprints: 1800 Orleans St, Woods 375, Baltimore, MD 21287
ABSTRACT

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 four years of follow-up and to identify associated risk factors.

Design: PREVAIL III is a five-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.

Subjects, Participants and Controls: 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 five consecutive visits.

Methods: IOP 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: IOP, 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 -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
optical coherence tomography 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 follow-up (-0.93 mmHg, 95% CI, -1.23 to -0.63) remained significant.

**Conclusions:** In this longitudinal cohort study, survivors of EVD experienced a sustained decrease in IOP relative to close contacts over a five-year period following EVD. The results highlight the importance of considering long-term sequelae of emerging infectious diseases within a population.
INTRODUCTION

*Zaire ebolavirus*¹ was responsible for the West African Ebola virus disease (EVD) epidemic, the largest epidemic of this disease to date, that started in 2014 and resulted in over 28,646 cases and 11,323 recorded deaths.² Subsequently, the more than 17,000 people who contracted the virus and survived demonstrated a wide range of post-infectious sequelae associated with EVD, including hearing loss, arthralgia, myalgia, neurological signs, abdominal pain, fatigue, anorexia, and ocular complications.³⁻¹³ 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.¹⁴

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 carried out through this partnership, PREVAIL III was a five-year, longitudinal cohort study of people who survived EVD and their close contacts.¹² It enrolled 3930 participants and included detailed ophthalmic evaluations.¹³

Approximately one year after infection, people who survived EVD had slightly lower intraocular pressure (IOP) relative to close contacts.¹³ 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 four additional years of follow-up, and we sought to identify factors associated with changes in IOP.
METHODS

This longitudinal cohort study includes survivors of EVD and their close contacts from the PREVAIL III eye sub-study. All participants received a detailed consent briefing and provided written informed consent. This manuscript followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.\textsuperscript{15} 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 three 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 sub-study, provided that the baseline eye exam was prior to July 1, 2016. This sub-study included a baseline and four annual follow-up ophthalmic exams. The median time from EVD symptom onset to enrollment was approximately 11 months.\textsuperscript{13}
Of the 3930 participants who enrolled at three sites across the country throughout the PREVAIL III enrollment period, 1427 participants enrolled at JFK Medical Center of which 1411 completed serological 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 four 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 Non-Clinical Animal Group (FANG) assay.\textsuperscript{16} Seropositivity was defined as having an Ebola virus glycoprotein IgG antibody titer of 548 U/mL or higher on the FANG assay.\textsuperscript{12,14,16} Close contacts also underwent testing for anti-Ebola virus antibodies to confirm a seronegative classification.

In the eye sub-study, all participants were examined by an ophthalmologist. Annual study evaluations included comprehensive ophthalmic examinations and ophthalmic imaging. IOP assessment was measured by rebound tonometry (iCare, Raleigh, NC) 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 fundoscopy were performed. In addition, optical coherence tomography (OCT) of the optic nerve and macula was performed for all participants older than four years with a Zeiss Cirrus 5000 OCT device (Carl Zeiss Meditec Inc, Dublin, CA). Standard-of-care treatment was initiated for any ophthalmic disorders identified.

Statistical Analysis
Statistical analyses were conducted using SAS (v9.3, SAS Institute Inc, Cary, NC) 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. 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 two-sided, and results are considered statistically significant if the P-values are less than 0.05. We include effect estimates as adjusted mean differences and 95% confidence intervals (CIs) when comparing rates of findings between groups.

To address 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 exam, 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.

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’s exact test). Overall, 537 (95%) survivors and 602 (93.5%) close contacts presented for at least one 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 four 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 four years of follow-up. There was no significant interaction between IOP and year (p=0.4), reflective of a sustained difference over the five-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 appears 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 appears in Table S2. 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). While 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.
compared to those who returned for follow-up. These data confirm 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 to 5.57).

We then sought to determine if these risk factors at baseline maintained their association throughout the duration of the study. Table S4 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 to 1.7).

To further determine whether these factors accounted for the difference in IOP in the follow-up period, we re-assessed 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). This data appears in Table S5. Consistent with the findings reported prior to 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 four 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 five years.

**DISCUSSION**

In this five-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 appear to be due to 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 appear 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.

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 (HIV). While 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 44mmHg. Such
inflammatory changes share some similarities with viral infections from herpes simplex and varicella-zoster,\textsuperscript{13} which may induce trabeculitis and contribute to transient IOP increases.

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. Serological testing of both survivor and control groups in this study for antibodies to Ebola virus strengthens the classifications into each group.

An additional strength of this study is the objective ascertainment of IOP. While some aspects of ophthalmic evaluation are based on subjective clinical judgment, we utilized a rebound tonometer for all IOP measurements that provides an automated numerical output. Compared to 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.

While it is unknown whether the findings reflect decreased production or increased outflow of aqueous humor, fluorophotometry studies of eyes of people with HIV offer one method to investigate this question, suggesting in HIV infection that such a decrease may be related to decreased production of aqueous humor.\textsuperscript{19} Animal models of EVD have identified viral antigens in ciliary body vasculature,\textsuperscript{20} offering one 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 (COVID-19) pandemic has created a renewed interest in long-term sequelae of emerging viral diseases, with data suggesting prolonged physiological impact and ongoing complications in survivors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. While our current understanding about post-COVID-19 syndromes relates to symptoms in the first one to two years after acute illness, 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 at least five years after infection. Broadly, these findings highlight the potential of long-term post-viral sequelae and the need to maintain and strengthen ongoing care for survivors of emerging infectious diseases.
REFERENCES


LEGEND

Figure 1. Flowchart illustrating enrollment in the Prevail III Eye Substudy from recruitment to last follow-up visit. Among the 3930 participants who enrolled in the study across three sites for baseline evaluation, 1411 participants enrolled at JFK Medical Center before April 1, 2016 and completed serological 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.

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

Table 1. Summary of intraocular pressure (IOP) in survivors of Ebola virus disease (EVD) and their close contacts over five years. All estimates are adjusted for age, gender and relationships among survivors and close contacts. Each year, people who survived EVD experienced significantly lower IOP relative to their close contacts.

Table 3. Risk factors for decreased intraocular pressure (IOP) among survivors of Ebola virus disease during the baseline ophthalmic examination. The finding of an afferent pupillary defect was associated with higher IOP. In contrast, the presence of vitreous cell on clinical examination and vitreous opacities identified through optical coherence tomography were associated with lower IOP. Data are presented as median and interquartile range, with mean difference and 95% confidence interval (CI). Estimates are adjusted for age and sex.
Table 1. Summary of intraocular pressure (IOP) in survivors of Ebola virus disease (EVD) and their close contacts over five years. 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.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>p-value for interaction</th>
</tr>
</thead>
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<tr>
<td>N multiply imputed observations</td>
<td>0</td>
<td>0</td>
<td>48</td>
<td>50</td>
<td>188</td>
<td>256</td>
</tr>
<tr>
<td>Mean Difference (95% CI)</td>
<td>-1.16 (-1.57, -0.74)</td>
<td>-0.93 (-1.34, -0.52)</td>
<td>-0.96 (-1.36, -0.56)</td>
<td>-0.72 (-1.16, -0.27)</td>
<td>-0.72 (-1.18, -0.27)</td>
<td>0.4</td>
</tr>
<tr>
<td>IOP (median, interquartile range)</td>
<td>12.4 (10.4-14.5)</td>
<td>13.5 (11.5-16.5)</td>
<td>12.8 (10.5-15.5)</td>
<td>14.5 (12.4-17.5)</td>
<td>12.8 (10.5-15.5)</td>
<td>14 (12.4-17.5)</td>
</tr>
</tbody>
</table>
Table 3. Risk factors for decreased intraocular pressure (IOP) among survivors of Ebola virus disease. 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 optical coherence tomography. Data are presented as median and interquartile range, with mean difference and 95% confidence interval (CI). Estimates are adjusted for age and sex.

<table>
<thead>
<tr>
<th>Factor</th>
<th>IOP for participants with factor (median, interquartile range)</th>
<th>IOP for participants without factor (median, interquartile range)</th>
<th>Effect estimate, adjusted for age and sex (mean difference)</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Examination Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Afferent pupillary defect</td>
<td>14.6 (9.1-17.4)</td>
<td>12.4 (10.4-14.5)</td>
<td>+3.57</td>
<td>(1.58, 5.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Keratic precipitates</td>
<td>12.1 (10.5-13.9)</td>
<td>12.4 (10.4-14.5)</td>
<td>-0.5</td>
<td>(-1.72, 0.71)</td>
<td>0.42</td>
</tr>
<tr>
<td>Synechiae</td>
<td>10.7 (9-13.9)</td>
<td>12.4 (10.5-14.5)</td>
<td>-1.12</td>
<td>(-2.56, 0.32)</td>
<td>0.13</td>
</tr>
<tr>
<td>Anterior chamber cells</td>
<td>11.6 (9.6-13)</td>
<td>12.4 (10.4-14.5)</td>
<td>-0.85</td>
<td>(-2.35, 0.65)</td>
<td>0.27</td>
</tr>
<tr>
<td>Vitreous cell</td>
<td>11 (9-12.8)</td>
<td>12.5 (10.5-14.7)</td>
<td>-1.61</td>
<td>(-2.69, -0.54)</td>
<td>0.003</td>
</tr>
<tr>
<td>Macular scar</td>
<td>12.7 (10.5-14.6)</td>
<td>12.4 (10.4-14.5)</td>
<td>+0.25</td>
<td>(-0.72, 1.22)</td>
<td>0.62</td>
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<tr>
<td>Peripheral retinal scar</td>
<td>12.5 (9.7-13.5)</td>
<td>12.4 (10.4-14.5)</td>
<td>-0.74</td>
<td>(-2.13, 0.64)</td>
<td>0.29</td>
</tr>
<tr>
<td>Cataract</td>
<td>12.8 (10.5-15)</td>
<td>12.4 (10.4-14.5)</td>
<td>+0.44</td>
<td>(-0.51, 1.39)</td>
<td>0.36</td>
</tr>
<tr>
<td>Optical Coherence Tomography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intraretinal fluid cysts</td>
<td>11.8 (10.5-12.8)</td>
<td>12.5 (10.4-14.5)</td>
<td>-0.42</td>
<td>(-1.83, 0.99)</td>
<td>0.56</td>
</tr>
<tr>
<td>Vitreous opacities</td>
<td>11.8 (10-14)</td>
<td>12.5 (10.5-14.7)</td>
<td>-0.68</td>
<td>(-1.34, -0.02)</td>
<td>0.045</td>
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<tr>
<td>Epiretinal membrane</td>
<td>11.8 (10.5-14)</td>
<td>12.8 (10.5-15)</td>
<td>-0.26</td>
<td>(-1.94, 1.43)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive Uveitis</td>
<td>12 (10.5-14.4)</td>
<td>12.4 (10.5-14.5)</td>
<td>-0.49</td>
<td>(-1.21, 0.24)</td>
<td>0.19</td>
</tr>
<tr>
<td>Active Uveitis</td>
<td>11.2 (9.5-12.8)</td>
<td>12.5 (10.5-14.5)</td>
<td>-1.21</td>
<td>(-2.5, 0.07)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
3930 participants enrolled in the PREVAIL III Eye Substudy across all sites in Liberia

- 661 Self-reported survivors enrolled at JFK Medical Center in Monrovia, Liberia before April 1, 2016
  - 659 completed baseline serologic testing
  - 587 Ebola virus-seropositive survivors
    - 565 seropositive survivors presented for baseline eye examination before July 1, 2016
    - 517 seropositive survivors presented for repeat eye examination at Year 1 follow-up
    - 377 seropositive survivors presented for repeat eye examination at Year 2 follow-up
    - 329 seropositive survivors presented for repeat eye examination at Year 3 follow-up
    - 383 seropositive survivors presented for repeat eye examination at Year 4 follow-up
  - 72 Ebola virus-seronegative survivors

- 766 Self-reported close contacts enrolled at JFK Medical Center in Monrovia, Liberia before April 1, 2016
  - 752 completed baseline serologic testing
  - 671 Ebola virus-seronegative close contacts
    - 644 seronegative close contacts presented for baseline eye examination before July 1, 2016
    - 594 seronegative close contacts presented for repeat eye examination at Year 1 follow-up
    - 388 seronegative close contacts presented for repeat eye examination at Year 2 follow-up
    - 397 seronegative close contacts presented for repeat eye examination at Year 3 follow-up
    - 407 seronegative close contacts presented for repeat eye examination at Year 4 follow-up
  - 81 Ebola virus-seropositive close contacts
Precis: In this five-year study, survivors of Ebola virus disease experience a sustained decrease in intraocular pressure relative to close contacts. This finding highlights the importance of considering long-term sequelae of emerging infectious diseases.