

ORIGINAL ARTICLE

A Test-and-Not-Treat Strategy for Onchocerciasis in *Loa loa*–Endemic Areas

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ABSTRACT

BACKGROUND

Implementation of an ivermectin-based community treatment strategy for the elimination of onchocerciasis or lymphatic filariasis has been delayed in Central Africa because of the occurrence of serious adverse events, including death, in persons with high levels of circulating *Loa loa* microfilariae. The LoaScope, a field-friendly diagnostic tool to quantify *L. loa* microfilariae in peripheral blood, enables rapid, point-of-care identification of persons at risk for serious adverse events.

METHODS

A test-and-not-treat strategy was used in the approach to ivermectin treatment in the Okola health district in Cameroon, where the distribution of ivermectin was halted in 1999 after the occurrence of fatal events related to *L. loa* infection. The LoaScope was used to identify persons with an *L. loa* microfilarial density greater than 20,000 microfilariae per milliliter of blood, who were considered to be at risk for serious adverse events, and exclude them from ivermectin distribution. Active surveillance for posttreatment adverse events was performed daily for 6 days.

RESULTS

From August through October 2015, a total of 16,259 of 22,842 persons 5 years of age or older (71.2% of the target population) were tested for *L. loa* microfilaremia. Among the participants who underwent testing, a total of 15,522 (95.5%) received ivermectin, 340 (2.1%) were excluded from ivermectin distribution because of an *L. loa* microfilarial density above the risk threshold, and 397 (2.4%) were excluded because of pregnancy or illness. No serious adverse events were observed. Non-serious adverse events were recorded in 934 participants, most of whom (67.5%) had no detectable *L. loa* microfilariae.

CONCLUSIONS

The LoaScope-based test-and-not-treat strategy enabled the reimplementa-tion of community-wide ivermectin distribution in a heretofore “off limits” health district in Cameroon and is a potentially practical approach to larger-scale ivermectin treatment for lymphatic filariasis and onchocerciasis in areas where *L. loa* infection is endemic. (Funded by the Bill and Melinda Gates Foundation and others.)

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MASS DRUG ADMINISTRATION WITH regimens containing ivermectin is the main strategy for the elimination of lymphatic filariasis and onchocerciasis. Although ivermectin is generally safe, the distribution of the drug has been associated with serious adverse events in central African countries. Since 1990, more than 500 cases of characteristic encephalopathy after ivermectin treatment,¹ including approximately 60 fatal cases, have occurred during mass drug administration and have been reported to the Mectizan Donation Program. These neurologic serious adverse events have occurred exclusively in persons with *Loa loa* microfilarial densities of greater than 30,000 microfilariae (mf) per milliliter of blood^{1,2} and are presumed to be related to eosinophil-mediated inflammation around dying microfilariae, microembolization with subsequent loss of vascular integrity in the central nervous system, or both.

Current World Health Organization guidelines allow the implementation of ivermectin-based mass drug administration in areas where onchocerciasis is mesoendemic or hyperendemic because the potential benefits of mass drug administration are thought to outweigh the risk of serious adverse events associated with ivermectin, although the guidelines stipulate that enhanced surveillance for adverse events is required.³ However, areas in which loiasis is endemic and onchocerciasis is hypoendemic are spread throughout Central Africa,⁴ and these parasitic diseases remain a serious problem. For these areas, a test-and-not-treat strategy has been proposed, in which persons with high *L. loa* microfilarial loads, who are at risk for serious adverse events, are excluded from ivermectin distribution and the remaining population (typically >95%) can be treated safely.

Successful implementation of the test-and-not-treat strategy requires a rapid, point-of-contact, field-friendly, and highly accurate method to quantify *L. loa* microfilariae. To this end, the LoaScope, a mobile-telephone-based videomicroscope (previously known as the CellScope Loa), was developed.⁵ With the use of a smartphone coupled to a simple optical device, the LoaScope automatically counts *L. loa* microfilariae in peripheral blood collected in disposable rectangular capillary tubes without the need for sample processing (Fig. S1 in the Supplementary Appendix, available with the full text of this article at

NEJM.org).⁵ To advance the elimination of *Onchocerca volvulus* and *L. loa* in countries in Central Africa in which onchocerciasis and loiasis are coendemic, the feasibility of this test-and-not-treat strategy was tested in the Okola health district in Cameroon, where the distribution of ivermectin was halted in 1999 after the occurrence of encephalopathy related to *L. loa* infection.

METHODS

STUDY SITE

The Okola health district (Fig. S2 in the Supplementary Appendix) includes 11 administrative health areas where mass drug administration was halted in 1999 by the Ministry of Public Health after 23 cases of encephalopathy occurred during the first treatment campaign. Mass drug administration resumed in 5 of the 11 areas in which onchocerciasis was deemed to be hyperendemic or mesoendemic (prevalence of onchocercal nodules among men, >20%). In 2013, the results of nodule surveys performed in the 6 excluded health areas showed prevalences of 6 to 40%, which is consistent with hypoendemic or mesoendemic onchocerciasis.⁶ *L. loa* infection is highly endemic in the entire Okola health district.^{7,8}

STUDY DESIGN

The test-and-not-treat strategy was implemented in 92 villages in the six health areas in which the population has been untreated since 1999. The location of the 92 villages and the timeline of the test-and-not-treat project are shown in Figures S2 and S3 in the Supplementary Appendix. Staff were trained to use the LoaScope with the aid of a video (Video 1, available at NEJM.org; a high-grade infection of 30,096 mf per milliliter of blood is shown in Video 2). All persons 5 years of age or older were invited to participate. The test-and-not-treat process consisted of the registration of persons 5 years of age or older who provided consent or assent (all participants provided written informed consent or assent [or parental consent in the case of minors] before blood sampling and again before treatment), quantification of *L. loa* microfilarial density with the LoaScope, provision of treatment with ivermectin (150 μ g per kilogram of body weight) to eligible persons, and surveillance for adverse events (see the Supplementary Appendix). Non-



A Quick Take is available at NEJM.org



Videos showing LoaScope training and testing are available at NEJM.org

pregnant participants who were excluded from ivermectin distribution because of high *L. loa* microfilariae counts were administered 400 mg of albendazole for intestinal deworming. Women who reported that they were pregnant did not receive treatment with ivermectin or albendazole but were offered iron and folic acid tablets. Ivermectin and albendazole were donated by Merck and GlaxoSmithKline, respectively, through the national program to eliminate onchocerciasis and lymphatic filariasis in Cameroon. KLA-Tencor provided in-kind donations related to the assembly of the LoaScope devices. Each participant was given a card (Fig. S4 in the Supplementary Appendix) that listed their *L. loa* microfilariae count, treatment received, and a contact telephone number for questions and for reporting of adverse events.

This study was authorized by the National Ethics Committee of Cameroon, and the protocol, available at NEJM.org, was approved by the Division of Operational Research at the Ministry of Health. All the authors vouch for the accuracy and completeness of the reported data and analyses and for the fidelity of the study to the protocol.

QUANTIFICATION OF *L. LOA* MICROFILARIAE AND EXPOSURE TO *O. VOLVULUS*

The LoaScope and its performance have been described previously.⁵ A cutoff *L. loa* microfilarial density of 26,000 mf per milliliter of blood was selected initially as the threshold below which ivermectin was administered; this threshold was chosen to attain a false positive rate below 1 in 1000 and a false negative rate below 1 in 10 million for the clinical threshold of 30,000 mf per milliliter,⁵ below which no neurologic serious adverse events were observed in previous studies.⁹⁻¹¹ Two weeks after initiation of the study, after 7065 participants had been assessed, a case of conjunctival hemorrhage, as described previously,¹² occurred in a participant who had an *L. loa* microfilarial density of 24,599 mf per milliliter, as assessed by LoaScope testing. For potential safety reasons, the risk threshold was decreased to 20,000 mf per milliliter for the remainder of the study.

Thick blood smears with a calibrated volume of 50 μ l were obtained as a backup for the blood samples that could not be analyzed with a LoaScope; the blood smears were used to identify and quantify *Mansonella perstans* microfilariae and

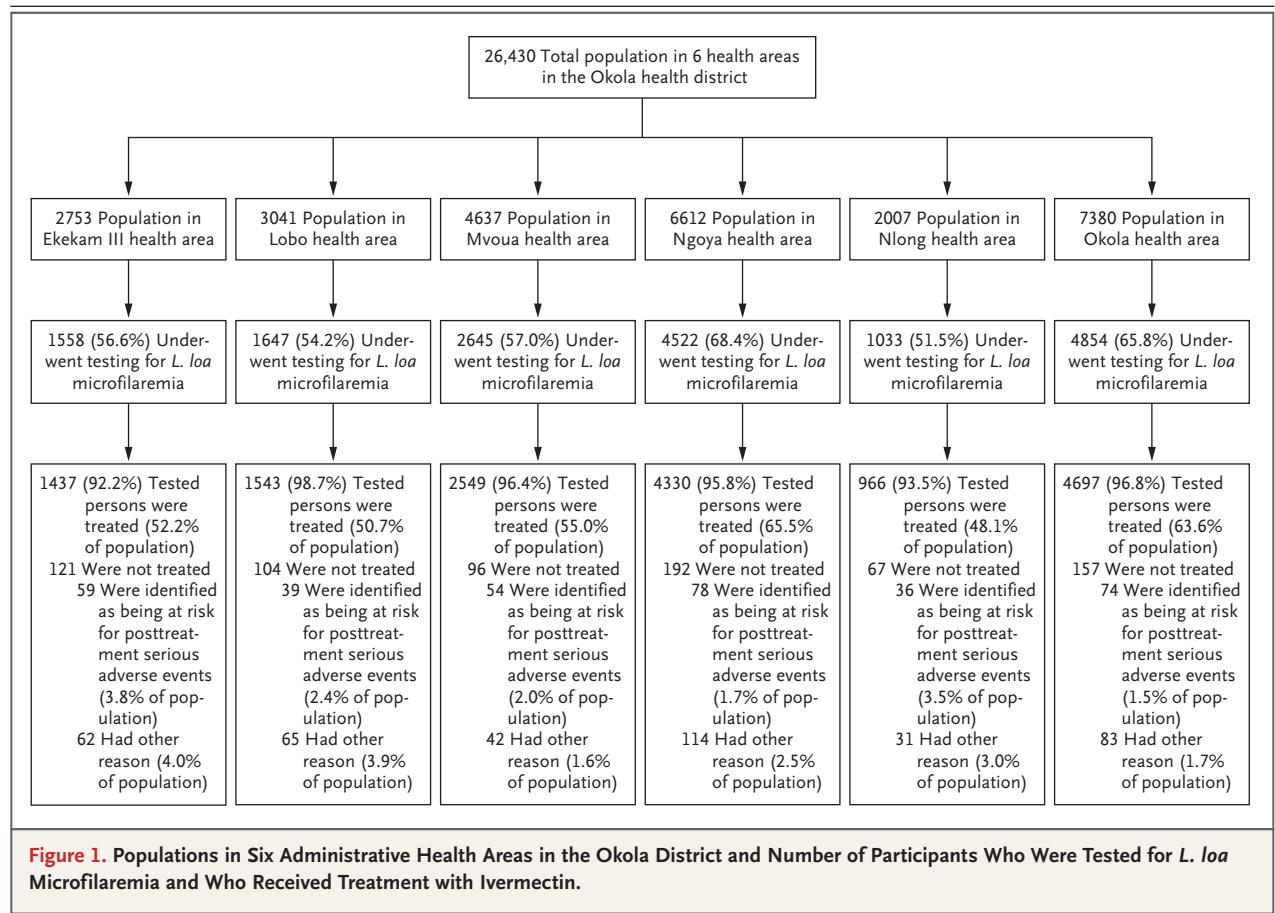
to corroborate the accuracy of the LoaScope. The blood smears were examined by two microscopists who were unaware of the LoaScope results. Dried blood spots were collected on filter paper and archived at a storage temperature of -80°C . To assess exposure to *O. volvulus*, the SD Bioline Onchocerciasis IgG4 Rapid Test (Standard Diagnostics) was used to determine the presence of anti-Ov16 IgG4 antibodies in 10- μ l eluates derived from each blood spot.^{13,14} The results were examined and recorded 24 hours after the eluates were dropped into the test sample well.

MONITORING OF POSTTREATMENT ADVERSE REACTIONS

Adverse events were monitored by two surveillance teams, each of which included a physician and a driver, with the assistance of selected community members and local nurses. The surveillance teams visited each village on days 1, 2, 3, and 6 after treatment, examined all participants who reported adverse events, and provided treatment for symptoms when clinically indicated. In addition, the teams toured the entire community by car to identify additional participants with posttreatment symptoms. All participants with a potential posttreatment adverse event underwent systematic evaluation, which was performed with the use of a standardized form (Fig. S5 in the Supplementary Appendix). A Karnofsky performance status score was assigned to each patient at the time of examination (scores range from 0 to 100, with higher scores indicating better functional status). A global adverse-event severity grade was assigned retrospectively to each person who presented with an adverse event; grade 1 indicated mild symptoms not requiring intervention; grade 2, moderate symptoms with local or noninvasive intervention indicated; grade 3, severe symptoms limiting self-care activities of daily living; grade 4, severe symptoms requiring hospitalization; and grade 5, death. Clinical management was based on reference guidelines.¹⁵

STATISTICAL ANALYSIS

Medians and interquartile ranges were used to indicate the central tendency and dispersion of the data. Multivariable logistic regression was used to examine associations between individual factors (sex, age, *L. Loa* microfilarial density [as assessed by LoaScope testing], presence of anti-



Ov16 IgG4 antibodies, and presence of *M. perstans* microfilariae [as assessed by thick blood smear microscopy] and the occurrence of adverse events. The logistic-regression coefficients were used to calculate population-attributable fractions.¹⁶ Thick blood smear microscopy was used as the reference standard in the assessment of the specificity and negative predictive value of LoaScope testing.

RESULTS

POPULATION CHARACTERISTICS

A total of 16,259 participants were examined during the test-and-not-treat process (Fig. 1). The median age of the examined populations in the various health areas ranged from 17 to 26 years. The sex distribution was relatively equal (48% male). The prevalence of onchocerciasis in the six health areas varied from 15.3 to 29.9%. The prevalence of *L. loa* microfilaremia varied from 15.3 to 22.8%, and the percentage of participants

with an *L. loa* microfilarial density greater than 20,000 mf per milliliter of blood, as assessed by LoaScope testing, ranged from 1.3% in the Ngoya health area to 2.4% in the Nlong and Ekekam III health areas (Table 1, and Table S2 in the Supplementary Appendix).

TEST-AND-NOT-TREAT PROCESS

The number of participants examined per village per day was typically between 50 and 100. The mean time from finger prick to the LoaScope result was 2 to 3 minutes. The LoaScope results were immediately available for 16,099 of 16,259 participants (99.0%) and were delayed for 160 participants (1.0%) because of technical problems that led to the use of thick blood smear microscopy to determine the microfilarial density. Ivermectin was administered in 15,522 participants (95.5%), all of whom had an *L. loa* microfilarial density below the risk threshold.

A total of 737 participants (4.5%) were excluded from ivermectin distribution: 340 (2.1%)

Table 1. Demographics, Prevalence of Onchocerciasis and *Loa loa* Microfilaremia, and Levels of *L. loa* Microfilarial Density among the Participants in Six Administrative Health Areas of the Okola Health District in Cameroon.

| Variable | Health Areas | | | | | | Total |
|---|--------------|------------|------------|------------|------------|------------|------------|
| | Ekekam III | Lobo | Mvoua | Ngoya | Nlong | Okola | |
| Census population — no. | 2753 | 3041 | 4637 | 6612 | 2007 | 7380 | 26,430 |
| Median age (interquartile range) — yr | 26 (13–49) | 23 (12–45) | 17 (10–43) | 17 (10–38) | 20 (12–50) | 18 (11–38) | 18 (11–42) |
| Male sex — % | 51 | 50 | 49 | 47 | 51 | 58 | 48 |
| Prevalence of onchocerciasis — %* | 18.8 | 29.9 | 20.2 | 15.3 | 23.8 | 27.0 | 22.4 |
| Prevalence of <i>L. loa</i> microfilaremia — %† | 22.8 | 21.3 | 18.9 | 15.3 | 20.3 | 16.1 | 17.8 |
| <i>L. loa</i> microfilarial density — microfilariae/ml of blood | | | | | | | |
| ≤8000 | 91.7 | 93.1 | 94.4 | 95.4 | 94.5 | 95.1 | 94.5 |
| 8001–20,000 | 5.9 | 5.3 | 3.7 | 3.3 | 3.1 | 3.5 | 3.9 |
| >20,000 | 2.4 | 1.6 | 1.9 | 1.3 | 2.4 | 1.4 | 1.6 |

* Prevalence of onchocerciasis was defined as the percentage of participants with a positive test result for anti-Ov16 IgG4 antibodies.

† Prevalence of *L. loa* microfilaremia was defined as the percentage of participants with at least one *L. loa* microfilaria in their thick blood smear.

were excluded because the *L. loa* microfilarial density was above the risk threshold, 228 (1.4%) were excluded because of poor health (signs or symptoms consistent with a serious acute or chronic concomitant illness) or inebriation, and 169 (1.0%) were excluded because they were pregnant or breast-feeding. The percentage of excluded participants per village varied from 0 to 15.1% (Fig. S6 in the Supplementary Appendix). All excluded participants (except pregnant women) received 400 mg of albendazole. The median treatment coverage in the six health areas was 55% of the total population (interquartile range among villages, 42.9 to 64.1) and 64% of the target population.

The prevalence of onchocerciasis was 22.0% among the participants who received ivermectin, 25.4% among the women who were excluded because of pregnancy or illness, and 33.5% among the participants with an *L. loa* microfilarial density above the risk threshold. Thus, participants potentially infected with *O. volvulus* who did not receive treatment with ivermectin because of *L. loa* microfilaremia represented 0.7% of the examined population.

FREQUENCY AND TYPES OF ADVERSE EVENTS

Among the 15,522 participants who received ivermectin, 934 (6.0%) presented for evaluation of posttreatment adverse events. The incidence of adverse events decreased slightly from 6.6%

(464 of 7065 participants) to 5.6% (470 of 8457 participants) ($P < 0.001$) after the risk threshold was lowered from 26,000 to 20,000 mf per milliliter of blood. A total of 2818 adverse events were recorded; dermatologic manifestations were the most common adverse events, followed by systemic and rheumatologic manifestations (Table 2). A total of 869 participants (93.0%) had a Karnofsky performance status score of 90, and 65 (7.0%) had a score of 80. Among the participants who presented with posttreatment adverse events, a global adverse-event severity grade of 1 was assigned to 88 (9.4%), a grade of 2 was assigned to 843 (90.3%), and a grade of 3 was assigned to 3 (0.3%). The 3 participants with grade 3 adverse events were female; were 6, 63, and 70 years old; and were bedridden during the first visit by the medical team owing to headache, myalgias and arthralgias, and abdominal pain, respectively. Two participants had no laboratory evidence of onchocerciasis or loiasis, and 1 had a positive IgG4 test result for the Ov16 antigen and had an *L. loa* microfilarial density of 21,560 mf per milliliter. No hospitalizations (grade 4 adverse events) or deaths (grade 5 adverse event) were reported. All adverse events resolved within 1 week after onset without further treatment or with basic supportive therapy (antihistamines, nonsteroidal antiinflammatory drugs, or acetaminophen).

Both *L. loa* microfilaremia and the presence

Table 2. Adverse Events Recorded during the 6-Day Posttreatment Surveillance Process.

| Adverse Event | Total No. of Events | Events in Participants with Detectable <i>L. loa</i> Microfilariae | Events in Participants with No Detectable <i>L. loa</i> Microfilariae | P Value |
|-------------------------------|---------------------|--|---|------------|
| | | number of events (%) | | |
| Pruritus | 564 | 188 (33) | 376 (67) | <0.001 |
| Asthenia | 389 | 171 (44) | 218 (56) | 0.002 |
| Headache | 326 | 149 (46) | 177 (54) | 0.14 |
| Rash | 274 | 52 (19) | 222 (81) | <0.001 |
| Back pain | 257 | 128 (50) | 129 (50) | 0.97 |
| Arthralgias | 235 | 124 (53) | 111 (47) | 0.39 |
| Edema | 125 | 21 (17) | 104 (83) | <0.001 |
| Myalgia | 115 | 51 (44) | 64 (56) | 0.20 |
| Vertigo | 106 | 48 (45) | 58 (55) | 0.35 |
| Anorexia | 89 | 42 (47) | 47 (53) | 0.57 |
| Abdominal pain | 67 | 19 (28) | 48 (72) | <0.001 |
| Blurred vision | 66 | 27 (41) | 39 (59) | 0.15 |
| Difficulty ambulating | 58 | 27 (47) | 31 (53) | 0.65 |
| Diarrhea | 46 | 18 (39) | 28 (61) | 0.14 |
| Difficulty in getting upright | 37 | 20 (54) | 17 (46) | 0.63 |
| Lymphadenopathy | 23 | 8 (35) | 15 (65) | 0.17 |
| Conjunctival hemorrhage | 20 | 14 (68) | 6 (32) | 0.14 |
| Conjunctival itching | 13 | 7 (54) | 6 (46) | 0.77 |
| Tinnitus | 6 | 4 (67) | 2 (33) | Not tested |
| Temporary hearing loss | 2 | 0 | 2 (100) | Not tested |
| Total | 2818 | 1118 (40) | 1702 (60) | <0.001 |

of anti-Ov16 IgG4 antibodies were assessed in 888 of the 934 participants who reported an adverse event, among whom 384 (43.2%) had neither *L. loa* microfilaremia nor anti-Ov16 IgG4 antibodies, 198 (22.3%) had only *L. loa* microfilaremia, 212 (23.9%) had only anti-Ov16 IgG4 antibodies, and 94 (10.6%) had both *L. loa* microfilaremia and anti-Ov16 IgG4 antibodies. Multivariable regression analysis showed that adverse events occurred significantly more frequently among older participants, female participants, and participants with either *L. loa* microfilaremia or anti-Ov16 IgG4 antibodies (Fig. 2). The risk of adverse events associated with the presence of anti-Ov16 IgG4 antibodies was similar to the risk associated with an *L. loa* microfilarial density of 1 to 8000 mf per milliliter of blood (odds ratios of 1.61 and 1.71, respectively) and was approximately half the risk associated with an *L. loa* microfilarial density of 8001 to 20,000 mf per

milliliter (odds ratio of 3.00). The risk of adverse events associated with both *L. loa* microfilaremia and the presence of anti-Ov16 IgG4 antibodies was similarly increased among participants with an *L. loa* microfilarial density of 1 to 8000 mf per milliliter (odds ratio of 2.47) and among participants with an *L. loa* microfilarial density of 8001 to 20,000 mf per milliliter (odds ratio of 2.57). Population-attributable fractions of adverse events were 8.0% for an *L. loa* microfilarial density of 1 to 8000 mf per milliliter, 8.3% for an *L. loa* microfilarial density of 8001 to 20,000 mf per milliliter, and 12.2% for the presence of anti-Ov16 IgG4 antibodies.

AGREEMENT BETWEEN LOASCOPE AND THICK BLOOD SMEAR MICROSCOPY

The distribution of *L. loa* microfilarial density in the population as assessed by LoaScope testing was similar to the distribution as assessed by

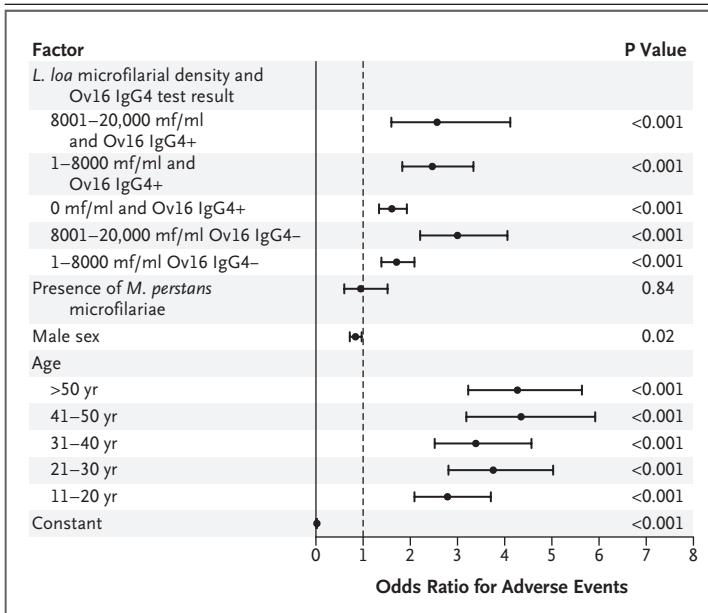


Figure 2. Odds Ratios of Adverse Events after Treatment with Ivermectin According to Individual Factors.

Multivariable logistic regression was used to examine associations between individual factors and the occurrence of adverse events. The dotted line (odds ratio of 1) represents an absence of association. Constant (odds ratio of 0.017) represents the odds ratio of adverse events when all covariates are set to zero. *L. loa* microfilarial density was measured as the number of *L. loa* microfilariae (mf) per milliliter of blood. Ov16 IgG4+ denotes a positive test result for IgG4 antibodies against the Ov16 antigen, and Ov16 IgG4– a negative test result for IgG4 antibodies against the Ov16 antigen. I bars indicate 95% confidence intervals.

microscopic examination of thick blood smears (Fig. 3). The specificity of LoaScope testing to provide a measurement of an *L. loa* microfilarial density below 20,000 mf per milliliter of blood in a person for whom thick blood smear microscopy indicated an *L. loa* microfilarial density below 20,000 mf per milliliter of blood was 99.7% (95% confidence interval [CI], 99.6 to 99.8), and the negative predictive value was 99.7% (95% CI, 99.6 to 99.7).

DISCUSSION

The extension of ivermectin-based mass drug administration to areas in which onchocerciasis is hypoendemic and loiasis is coendemic remains a large obstacle to the success of onchocerciasis elimination programs in Africa. In the current study, a LoaScope-based test-and-not-treat strategy was used to safely treat more than 15,000 persons with ivermectin in such an area. Despite

an initial reticence among the people in some villages to participate on account of the memory of serious adverse events (including deaths) that occurred in 1999, a total of 16,259 of the 22,842 persons 5 years of age or older recorded during the initial census (71.2%) participated in the test-and-not-treat campaign. This rate of participation suggests that test-and-not-treat is an acceptable strategy even in populations with a history of ivermectin-related serious adverse events. We believe that fear of serious adverse events, although not formally assessed, was probably the main reason for nonparticipation.

During the first mass drug administration campaign in the Okola health district in 1999, a total of 23 cases of neurologic serious adverse events, including 3 deaths, were recorded among the 6000 persons who received ivermectin before mass drug administration was stopped.¹⁷ The incidence of neurologic serious adverse events that occurred within 1 week after treatment with ivermectin was 38 per 10,000 persons, and the incidence of death resulting from adverse events that started within 1 week after treatment with ivermectin was 5 per 10,000 persons. Extrapolation of these data to the population enrolled in the current study shows that approximately 62 cases of neurologic serious adverse events and 8 deaths would have been anticipated.

Although 6.0% of the participants reported ivermectin-associated adverse events during the test-and-not-treat campaign, the percentage was lower than that typically observed after ivermectin-based mass drug administration for onchocerciasis in areas in which loiasis is not endemic (13.1% among persons in southeast Nigeria¹⁸; 12% and 20% in northern Cameroon in areas where onchocerciasis is mesoendemic and hyperendemic, respectively¹⁹; and 21.4% in eastern Sudan)²⁰ and much lower than the 26.3% recorded in a neighboring area of central Cameroon where *L. loa* infection is endemic.² The most likely explanation for this finding is that onchocerciasis is hypoendemic to mesoendemic in Okola.

LoaScope operators underwent a 1-hour training session 2 weeks before the field operations. This training sufficed for the entire study, and the teams noted the ease of use and reliability of the device despite daily use and demanding field conditions. Because *L. loa* microfilariae show a daytime periodicity,²¹ LoaScope examinations (and treatment) started at 10 a.m. and ended at

4 p.m. Despite this limitation, up to 162 persons were examined per village per day.

Given the low percentage of persons (2.4%) in the total population who were excluded from ivermectin distribution and the proposed implementation of the test-and-not-treat strategy in areas where onchocerciasis is hypoendemic and mesoendemic, the persons who were excluded are unlikely to be an epidemiologically significant reservoir of *O. volvulus* microfilariae at the community level. Nevertheless, some excluded persons are likely to be infected with *O. volvulus* and, for ethical reasons, should be treated with effective and safe drug regimens, particularly in the clinical setting of manifestations of onchocerciasis. Although a 4-to-6-week course of doxycycline, a regimen known to have macrofilaricidal activity against *O. volvulus*²² but not *L. loa*,²³ is impractical at the community level, this regimen could be used in this context. The identification of persons who were excluded from ivermectin distribution in the current study and the provision of doxycycline treatment for those persons are ongoing.

In summary, this test-and-not-treat strategy based on a scalable point-of-contact tool that allows for the rapid identification (and exclusion from ivermectin-based treatment) of persons at risk for serious adverse events related to *L. loa* infection has enabled district-level community treatment of onchocerciasis. Although this test-and-not-treat strategy was motivated by the need to tackle the problem of hypoendemic onchocerciasis in Central Africa, it could also be considered for other areas in which onchocerciasis and loiasis are coendemic. Many, but not all, areas in which onchocerciasis is mesoendemic or hyperendemic are already covered by community-directed treatment with ivermectin; a test-and-not-treat strategy would target persons who have not previously received ivermectin and persons who are routinely nonadherent to treatments.

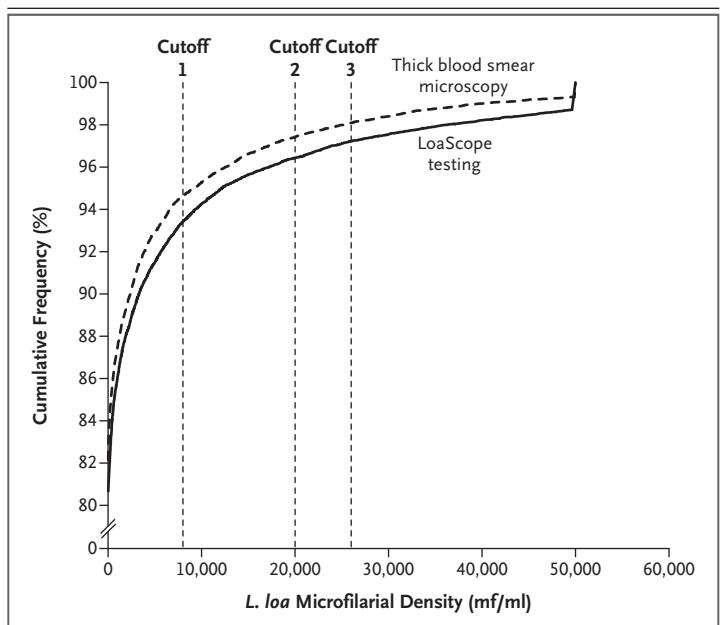


Figure 3. Cumulative Frequency Distribution of *L. loa* Microfilarial Density in the Tested Population.

Cutoff 1 (8000 mf per milliliter of blood) was used for information relevant to an increased likelihood of adverse events provided to each participant; all persons with an *L. loa* microfilarial density between cutoff 1 and cutoff 3 during the first 2 weeks of the study and at cutoff 2 after the first 2 weeks were told — before ivermectin treatment was proposed — that they might have a mild adverse event. For persons with an *L. loa* microfilarial density below cutoff 1, ivermectin treatment was just proposed, with no other specific message. Cutoff 2 and cutoff 3 were the risk thresholds that were used to exclude persons from ivermectin distribution. Two weeks after initiation of the study, the initial risk threshold of 26,000 mf per milliliter (cutoff 3) was lowered to 20,000 mf per milliliter (cutoff 2) after a case of conjunctival hemorrhage occurred in a participant who had an *L. loa* microfilarial density of 24,599 mf per milliliter, as assessed by LoaScope testing. The right tails of the distribution of *L. loa* microfilarial density were censored for counts above 50,000 mf per milliliter.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Center for Research on Filariasis and other Tropical Diseases (J.K., H.C.N.-D., R.G.-K., G.-R.N., P.N., J.B.T.-M.) and the Faculty of Medicine and Biomedical Sciences, University of Yaounde I (J.K.), Yaounde, and the Faculty of Health Sciences, Department of Microbiology and Parasitology, University of Buea, and Research Foundation for Tropical Diseases and Environment (REFOTDE), Buea (S.W.) — all in Cameroon; Institut de Recherche pour le Développement Unité Mixte Internationale 233-INSERM Unité 1175, Montpellier University, Montpellier, France (S.D.P., C.B.C., M.B.); the Department of Bioengineering and the Biophysics Program, University of California, Berkeley, Berkeley (M.H.B., M.V.D., D.A.F.); the Department of Pathobiology and Diagnostic Investigation, Michigan State University, East Lansing (C.D.M.); the Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands (W.A.S.); the Chan Zuckerberg Biohub, San Francisco (D.A.F.); and the Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD (A.D.K., T.B.N.).

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