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A Trial of a Triple-Drug Treatment for Lymphatic Filariasis

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ABSTRACT

BACKGROUND

The World Health Organization has targeted lymphatic filariasis for global elimination by 2020 with a strategy of mass drug administration. This trial tested whether a single dose of a three-drug regimen of ivermectin plus diethylcarbamazine plus albendazole results in a greater sustained clearance of microfilariae than a single dose of a two-drug regimen of diethylcarbamazine plus albendazole and is noninferior to the two-drug regimen administered once a year for 3 years.

METHODS

In a randomized, controlled trial involving adults from Papua New Guinea with *Wuchereria bancrofti* microfilaremia, we assigned 182 participants to receive a single dose of the three-drug regimen (60 participants), a single dose of the two-drug regimen (61 participants), or the two-drug regimen once a year for 3 years (61 participants). Clearance of microfilariae from the blood was measured at 12, 24, and 36 months after trial initiation.

RESULTS

The three-drug regimen cleared microfilaremia in 55 of 57 participants (96%) at 12 months, in 52 of 54 participants (96%) at 24 months, and in 55 of 57 participants (96%) at 36 months. A single dose of the two-drug regimen cleared microfilaremia in 18 of 56 participants (32%) at 12 months, in 31 of 55 participants (56%) at 24 months, and in 43 of 52 participants (83%) at 36 months ($P=0.02$ for the three-drug regimen vs. a single dose of the two-drug regimen at 36 months). The two-drug regimen administered once a year for 3 years cleared microfilaremia in 20 of 59 participants (34%) at 12 months, in 42 of 56 participants (75%) at 24 months, and in 51 of 52 participants (98%) at 36 months ($P=0.004$ for noninferiority of the three-drug regimen vs. the two-drug regimen administered once a year for 3 years at 36 months). Moderate adverse events were more common in the group that received the three-drug regimen than in the combined two-drug-regimen groups (27% vs. 5%, $P<0.001$). There were no serious adverse events.

CONCLUSIONS

The three-drug regimen induced clearance of microfilariae from the blood for 3 years in almost all participants who received the treatment and was superior to the two-drug regimen administered once and noninferior to the two-drug regimen administered once a year for 3 years. (Funded by the Bill and Melinda Gates Foundation; ClinicalTrials.gov number, NCT01975441.)

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LYMPHATIC FILARIASIS CAUSED BY MOSQUITO-borne nematode parasites is usually characterized by lymphedema of the arms and legs (“elephantiasis”), hydrocele, and long-term disability. The life cycle of the parasite requires the uptake of microfilariae by mosquitoes during a blood meal and further development of the microfilariae into infective larvae, which are transmitted by the mosquitoes to initiate new infections in humans.¹ *Wuchereria bancrofti* and, to a lesser extent, *Brugia* species have infected more than 100 million people in 52 countries, and another 856 million people are at risk.² The World Health Organization has targeted lymphatic filariasis for global elimination by 2020 with a strategy of mass drug administration³ that uses one of three antifilarial drug regimens: diethylcarbamazine plus albendazole in countries where onchocerciasis and loiasis are not coendemic, ivermectin plus albendazole in African countries where onchocerciasis is endemic, and albendazole alone in regions of Africa where loiasis and lymphatic filariasis are coendemic. Mass drug administration is intended to reduce the microfilarial reservoir in the human population to a level below that required to sustain transmission of the infection by mosquitoes. Because a single dose of these regimens does not sterilize or kill all adult filarial worms or reduce the number of microfilariae in the community to sufficiently low levels,^{4,7} many rounds of mass drug administration are required to interrupt transmission.⁸ Although this approach has successfully eliminated lymphatic filariasis in some countries, a treatment that is more effective for killing or sterilizing adult worms could greatly accelerate elimination efforts by reducing the number of doses and annual rounds of mass drug administration required to interrupt transmission.

We recently reported the results of a small pilot study that compared the pharmacokinetics and efficacy of a single dose of ivermectin plus diethylcarbamazine plus albendazole (three-drug regimen) with a single dose of diethylcarbamazine plus albendazole (two-drug regimen) for bancroftian filariasis in Papua New Guinea.⁹ The three-drug regimen resulted in 100% clearance of microfilariae from the blood at 12 and 24 months after treatment, as compared with 8% and 33% clearance, respectively, with the two-drug regimen at the same time points. This

result suggested that the three-drug regimen may have killed or permanently sterilized adult filarial worms. No severe or serious adverse events were observed among the participants in that study. In the current randomized, controlled trial, we aimed to evaluate the effects of the three-drug regimen administered once, as compared with the two-drug regimen administered once or once a year for 3 years, in a larger number of adults with *W. bancrofti* microfilaremia, who were residents of an area of Papua New Guinea where lymphatic filariasis is highly endemic and associated with high microfilarial burdens.⁴

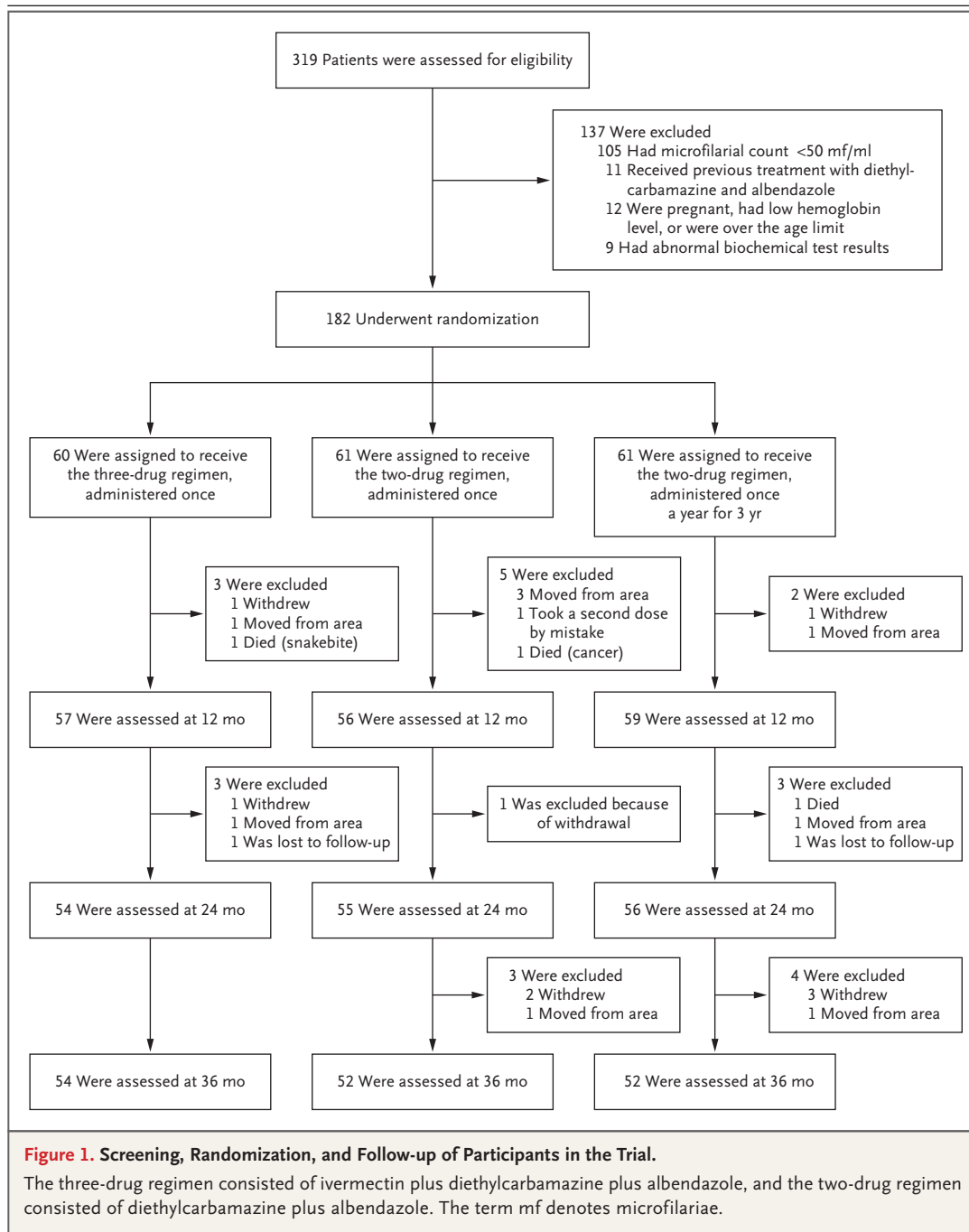
METHODS

TRIAL DESIGN AND PARTICIPANTS

We performed a randomized, controlled trial involving participants who were recruited from 12 villages in the Dreikikir District of East Sepik Province, Papua New Guinea. None of the participants had received previous treatment for lymphatic filariasis. Participants were eligible for inclusion if they had a microfilarial count higher than 50 microfilariae (mf) per milliliter of blood, were 18 to 65 years of age, had no recent history of illness, were not pregnant, had not received previous treatment with diethylcarbamazine or albendazole, had no clinically significant biochemical or hematologic abnormalities, and had no clinically significant proteinuria, hematuria, or glucosuria (Fig. 1). Institutional review boards at University Hospitals Cleveland Medical Center and the Papua New Guinea Institute of Medical Research and Medical Research Advisory Committee approved the trial. All participants provided written informed consent. Further details are provided in the protocol and statistical analysis plan, available with the full text of this article at NEJM.org.

RANDOMIZATION AND BLINDING

Using a computer-generated randomization table, we randomly assigned the participants, in a 1:1:1 ratio, to receive a two-drug regimen of 6 mg of diethylcarbamazine (Sanofi) per kilogram of body weight plus 400 mg of albendazole (GlaxoSmithKline) administered once at trial initiation, a two-drug regimen of 6 mg of diethylcarbamazine per kilogram plus 400 mg of albendazole administered at trial initiation and at 12 and 24 months, or a three-drug regimen of 200 μ g of ivermectin



(Stromectol, Merck) per kilogram plus 6 mg of diethylcarbamazine per kilogram plus 400 mg of albendazole administered once at trial initiation. Diethylcarbamazine and albendazole were provided by the Papua New Guinea National Department of Health. Ivermectin was purchased by the trial staff with grant funds.

A member of the trial staff was designated to

directly observe drug administration to ensure that all pills were swallowed. Microfilariae were counted by two independent readers who were specifically trained for preparing and reading slides of microfilariae samples and supervised by a lead reader (third author); the readers were unaware of the treatment-group assignments. Three slides were discordant for the presence or

absence of microfilariae, and 1 in 15 slides were discordant for microfilarial counts (>30% coefficient of variation). For discordant readings, a third count was performed by another reader. Independent readers were assigned to assess 10% of the slides as a measure of quality control. The trial staff who assessed adverse events in the participants while they were at the treatment center in the first 10 hours of follow-up may have been aware of the treatment-group assignments, but subsequent follow-up of the participants in their communities was performed in a blinded manner by different trial staff.

PROCEDURES

Screening and administration of the initial treatment were performed over a 10-hour period at the Dreikikir health center under the direct observation of the trial staff, and the participants were monitored over the next 2 days. A questionnaire regarding symptoms was administered, and vital signs were assessed before treatment and at yearly intervals after trial initiation. A symptom-directed physical examination was performed if moderate or severe adverse events were reported by a participant. New or worsening symptoms, changes in vital signs, and new abnormal findings on physical examination were considered by trial investigators to be drug-related events and were graded according to a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Microfilaremia was assessed by passing 2 ml of heparinized blood (collected by venipuncture between 9 p.m. and 1 a.m.) through polycarbonate filters with a pore size of 5 μm (1 ml of blood per filter, EMD Millipore). Filters were washed, placed on glass slides, dried, stained with Giemsa, and read with the use of microscopy to count microfilariae.¹⁰ Circulating filarial antigen levels, a biomarker of adult worm burden, were assessed with the use of semiquantitative filarial test strips (Alere).¹¹ Samples of plasma (75 μl each) that had been collected at baseline and 36 months after trial initiation were added to the filarial test strips for exactly 10 minutes, and the test strips were scored semiquantitatively: negative test strips with no visible test line were assigned a score of 0, test strips with a visible test line that was weaker than the control line were assigned a score of 1, test strips with a test line that was approximately equal in density

to the control line were assigned a score of 2, and test strips with a test line that was darker than the control line were assigned a score of 3.

OUTCOMES

The primary outcome was complete clearance of microfilaremia at 36 months after trial initiation. Secondary outcomes were complete clearance of microfilaremia at 12 and 24 months after trial initiation, a reduction in microfilarial counts, the percentage of participants who had complete clearance of circulating filarial antigen, and the percentage of participants who had a reduction in filarial antigen levels at 36 months.

STATISTICAL ANALYSIS

The first hypothesis with respect to the primary outcome was that a three-drug regimen of ivermectin plus diethylcarbamazine plus albendazole administered once at trial initiation would result in 75% microfilarial clearance at 36 months, as compared with 50% microfilarial clearance with a two-drug regimen of diethylcarbamazine plus albendazole administered once at trial initiation. The second hypothesis with respect to the primary outcome was that the three-drug regimen would be noninferior to the two-drug regimen administered once a year for 3 years at 36 months, with a noninferiority margin of 15 percentage points. We estimated that a sample of 46 participants in each treatment group would provide the trial with 80% power to test the first hypothesis at an alpha level of 0.05, and a sample of 54 participants in each treatment group would provide the trial with 80% power to test the second hypothesis at an alpha level of 0.05. Additional participants were recruited to account for potential dropouts. We performed an intention-to-treat analysis that included all participants from whom a sample was collected at 36 months.

Baseline characteristics and rates of microfilarial clearance according to treatment group, as well as between-group differences in microfilarial counts at 12, 24, and 36 months, were compared with the use of the chi-square test, and relative risks were calculated. With respect to the primary outcome, the three-drug regimen would be considered significantly superior to a single dose of the two-drug regimen at a P value lower than 0.025 and would be considered noninferior to the two-drug regimen administered once a year for 3 years at a P value for noninferiority of 0.025

or lower. With respect to the secondary outcome of complete clearance of microfilariae at 12 and 24 months after trial initiation (i.e., six between-group comparisons, with three performed at each of two time points), a *P* value of 0.008 (0.05/6=0.008) or lower was considered to indicate statistical significance in a post hoc analysis. To compare between-group differences in microfilarial counts across time, we used a negative binomial generalized estimating equation model (PROC GENMOD in SAS software, version 9.4; SAS Institute). The model included follow-up time points (12, 24, and 36 months), treatment (three-drug regimen administered once, two-drug regimen administered once, and two-drug regimen administered once a year for 3 years), and the interaction between treatment and time as fixed effects. The microfilarial count at baseline was included as a covariate. An unstructured correlation was used to account for correlation among repeated measurements. Wald chi-square tests were used to assess the significance of the effects of treatment, time, and the interaction between treatment and time. A significant interaction effect was further investigated with the use of pairwise comparisons between treatments within a given time period on the basis of Wald chi-square tests (Table S1A in the Supplementary Appendix, available at NEJM.org). *P* values of 0.006 or lower were considered to indicate statistical significance after adjustment for multiple comparisons (i.e., nine between-group comparisons, with three performed at each of three time points [0.05/9=0.006]; Table S1B in the Supplementary Appendix).

RESULTS

ENROLLMENT AND FOLLOW-UP

A total of 182 participants were enrolled between June 11 and December 13, 2014, and underwent randomization. Baseline demographic characteristics, microfilarial counts, and circulating filarial antigen levels were similar among the treatment groups (Table 1). Among 182 participants, 172 (95%) were evaluated at 12 months, 165 (91%) at 24 months, and 158 (87%) at 36 months after trial initiation. Reasons for exclusion are shown in Figure 1. Three participants died from unrelated causes, including snakebite (1 patient assigned to receive the three-drug regimen), liver cancer (1 participant assigned to receive a single dose of the two-drug regimen), and probable suicide

(1 patient assigned to receive the two-drug regimen once a year for 3 years).

EFFECTS OF TREATMENT ON MICROFILAREMIA

The three-drug regimen cleared microfilaremia in 55 participants (96%) at 12 months, in 52 (96%) at 24 months, and in 55 (96%) at 36 months after trial initiation. By contrast, a single dose of the two-drug regimen cleared microfilaremia in 18 participants (32%) at 12 months, in 31 (56%) at 24 months, and in 43 (83%) at 36 months. The three-drug regimen resulted in significantly greater microfilarial clearance at 36 months than a single dose of the two-drug regimen (*P*=0.02) (Table 2). The two-drug regimen administered once a year for 3 years cleared microfilaremia in 20 participants (34%) at 12 months, in 42 (75%) at 24 months, and in 51 (98%) at 36 months. Among the participants who received the three-drug regimen, microfilarial clearance at 36 months was noninferior to that with the two-drug regimen administered once a year for 3 years, with a -2 percentage-point difference (90% CI, -10 to 6) (one-sided *P* value for noninferiority, 0.004) (Table 2).

The microfilarial counts in the three treatment groups at each follow-up time point are provided in Figure 2A. One participant who received the three-drug regimen had a low level of persistence of microfilaremia at all follow-up time points. Another had a low level of persistence of microfilaremia at 12 and 24 months but had clearance at 36 months. One participant who received the three-drug regimen had clearance of microfilaremia at 12 and 24 months and had recurrence of microfilaremia at 36 months. This may have been due to reinfection, because very high filarial transmission was documented previously in his village.⁴

Model-adjusted mean microfilarial counts for each treatment group are provided in Figure 2B, and in Table S1B in the Supplementary Appendix. All the participants, regardless of treatment-group assignment, had a 90 to 99% reduction from baseline in the microfilarial count at 36 months. There were significant between-group differences in the model-adjusted mean microfilarial counts at all time points examined, except at 12 months for the comparison of the two groups that received the two-drug regimen (*P*=0.60) (Table S1C in the Supplementary Appendix).

Table 1. Characteristics of the Trial Participants at Baseline.*

Characteristic	Three-Drug Regimen Administered Once (N=60)	Two-Drug Regimen Administered Once (N=61)	Two-Drug Regimen Administered Once a Year for 3 Yr (N=61)
Age — yr			
Median	40	34	37
Range	19–60	18–62	18–61
Sex — no.			
Male	28	34	30
Female	32	27	31
Hemoglobin — g/dl	11.4±1.8	11.2±1.8	11.2±1.7
Weight — kg	50±6	51±5	52±7
Geometric mean microfilarial count — microfilariae/ml	699	744	596
Range	55–15,621	52–8290	61–9656
Filarial antigen test-strip score†	2.8±0.4	2.8±0.5	2.7±0.5

* Plus-minus values are means ±SD. The three-drug regimen consisted of ivermectin plus diethylcarbamazine plus albendazole, and the two-drug regimen consisted of diethylcarbamazine plus albendazole. There were no significant between-group differences at baseline.

† The test strips were used to assess circulating filarial antigen levels (a biomarker of adult worm burden) in plasma samples and were scored semiquantitatively: negative test strips with no visible test line were assigned a score of 0, test strips with a visible test line that was weaker than the control line were assigned a score of 1, test strips with a test line that was approximately equal in density to the control line were assigned a score of 2, and test strips with a test line that was darker than the control line were assigned a score of 3.

Among the 182 participants who underwent randomization, 22 (12%) were not evaluated at 36 months (Fig. 1). A sensitivity analysis was performed to evaluate the potential effect of the missing data on the primary outcome at 36 months. For this analysis, participants for whom data were missing were assumed to be positive for microfilariae. If that were the case, 54 of 60 participants (90%) who received the three-drug regimen and 43 of 61 participants (70%) who received a single dose of the two-drug regimen would have clearance of microfilariaemia at 36 months. The three-drug regimen was superior to a single dose of the two-drug regimen under this assumption ($P=0.01$ by the chi-square test; relative risk of incomplete clearance, 0.33; 95% confidence interval [CI], 0.14 to 0.79; $P=0.01$) — a finding that is consistent with the first hypothesis that the three-drug regimen is superior to a single dose of the two-drug regimen at 36 months after trial initiation. Using the same assumption, we determined that 51 of 61 participants (84%) who received the two-drug regimen once a year for 3 years would have clearance of microfilaria-

mia at 36 months — a clearance rate similar to that determined with the same assumption among the participants who received the three-drug regimen ($P=0.42$ by the chi-square test; relative risk of incomplete clearance, 0.61; 95% CI, 0.24 to 1.57; $P=0.31$).

EFFECTS OF TREATMENT ON CIRCULATING FILARIAL ANTIGEN

There were no significant between-group differences in levels of circulating filarial antigen at 36 months, as assessed with the use of semiquantitative filarial test strips. The mean (\pm SD) test-line scores were 2.21±0.93 among the participants who received the three-drug regimen, 2.25±0.88 among the participants who received a single dose of the two-drug regimen, and 2.25±0.90 among the participants who received the two-drug regimen once a year for 3 years ($P=0.94$ by analysis of variance). Two participants who received a single dose of the two-drug regimen were negative for circulating filarial antigen, as were three participants in each of the other treatment groups.

Table 2. Clearance of Microfilaremia after Treatment for Lymphatic Filariasis.*

Treatment Group and Outcome	Months after Initial Treatment		
	12	24	36
Three-Drug Regimen Administered Once			
Participants — no.	57	54	57
Participants with complete clearance of microfilariae			
No.	55	52	55
% (95% CI)	96 (87–100)	96 (87–100)	96 (88–100)
Two-Drug Regimen Administered Once			
Participants — no.	56	55	52
Participants with complete clearance of microfilariae			
No.	18	31	43
% (95% CI)	32 (20–46)	56 (42–70)	83 (70–92)
P value†	<0.001	<0.001	0.02
Relative risk of incomplete clearance (95% CI)‡	0.05 (0.01–0.20)	0.08 (0.02–0.34)	0.20 (0.05–0.90)
P value	<0.001	<0.001	0.04
Two-Drug Regimen Administered Once a Year for 3 Yr			
Participants — no.	59	56	52
Participants with complete clearance of microfilariae			
No.	20	42	51
% (95% CI)	34 (22–47)	75 (62–86)	98 (90–100)
P value§	<0.001	0.002	>0.99
Relative risk of incomplete clearance (95% CI)¶	0.05 (0.01–0.20)	0.15 (0.04–0.62)	1.80 (0.17–18.90)
P value	<0.001	0.009	0.87

* The 95% confidence intervals (CIs) were calculated with the use of the binomial exact method.

† P values are for comparisons between the group that received the three-drug regimen and the group that received a single dose of the two-drug regimen, as assessed by chi-square analysis.

‡ Relative risks are shown for the group that received the three-drug regimen, as compared with the group that received a single dose of the two-drug regimen.

§ P values are for comparisons between the group that received the three-drug regimen and the group that received the two-drug regimen once a year for 3 years, as assessed by chi-square analysis.

¶ Relative risks are shown for the group that received the three-drug regimen, as compared with the group that received the two-drug regimen once a year for 3 years.

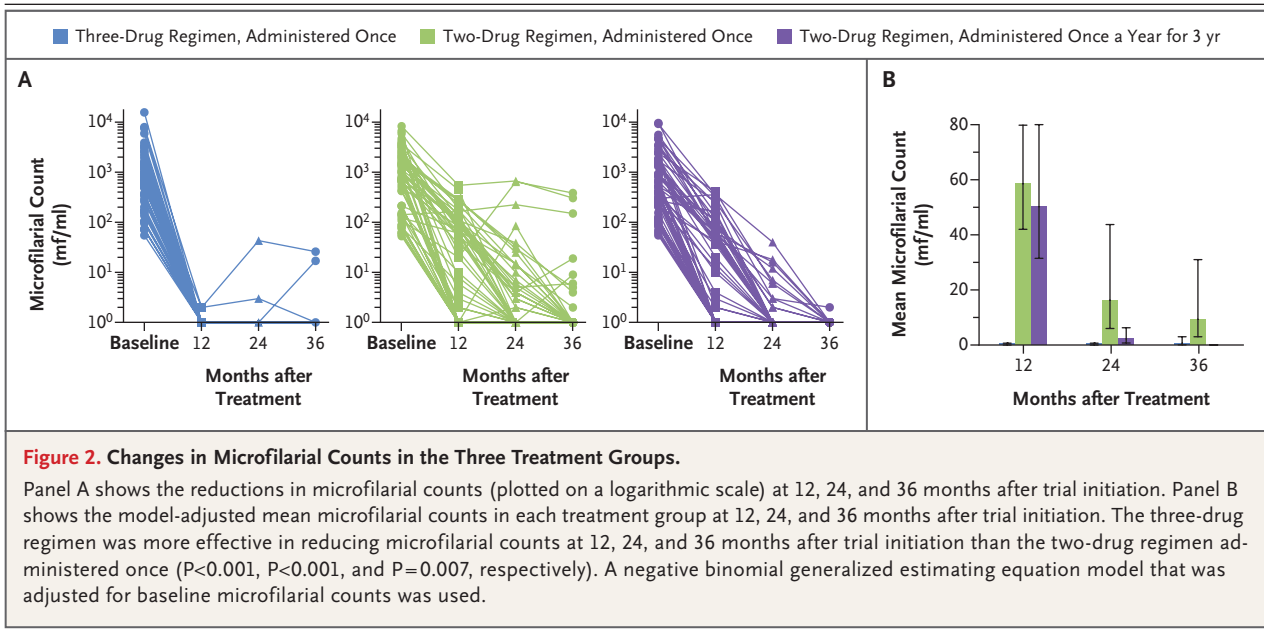
SAFETY

Among the participants who were assigned to receive the two-drug regimen once a year for 3 years, no adverse events occurred after the second dose was administered at 12 months. Consequently, only adverse events that were associated with the initial drug treatment are listed in Table 3, and the adverse-event data from the two groups that received the two-drug regimen were combined because the initial treatment was identical.

All participants were observed for adverse events for 10 hours after the initial treatment. A total of 73% of participants were assessed for

adverse events 24 to 36 hours after returning to their villages (Table 3). Adverse events occurred in five participants during the initial 10-hour observation period; three events were mild (headache, nausea, and fatigue in one participant each), one was moderate (temperature of 38.1°C and fatigue in one participant), and one was severe (described below). Other adverse events occurred later.

The severe adverse event (grade 3) occurred in a 42-year-old woman who had a baseline microfilarial count of 792 mf per milliliter. She had headache, nausea, and chills starting 6 hours



after the administration of the three-drug regimen. Physical examination revealed an auricular temperature of 41.1°C, orthostatic hypotension, and tachycardia. Her condition improved after she received oral treatment with fluids and acetaminophen, and she returned to her pretreatment state of health the next day. Objective findings of fever (defined as an auricular temperature $>37.5^{\circ}\text{C}$) and hemodynamic changes after initial treatment tended to be more common in the group that received the three-drug regimen than in the combined two-drug-regimen groups; however, these between-group differences were not significant (Table 3). The frequency of patient-reported adverse events was greater in the groups that received the three-drug regimen than in the combined two-drug-regimen groups. This difference was most pronounced among the participants who had adverse events of a severity higher than grade 1. The most common adverse events among the participants who had an adverse event of grade 2 or 3 were headache, fatigue, and nausea (Table 3). Higher baseline microfilarial counts were associated with a higher frequency and severity of adverse events. A logistic-regression model showed that the odds of a grade 2 adverse event increased by 19% for each increase in microfilarial count of 200 mf per milliliter (odds ratio, 1.19; 95% CI, 1.09 to 1.36; $P = 0.01$). This association was strongest among

the participants who had a microfilarial count higher than 500 mf per milliliter.

DISCUSSION

These results show that a single dose of a three-drug regimen of ivermectin plus diethylcarbamazine plus albendazole was more effective in clearing *W. bancrofti* microfilariae from the blood than a single dose of a two-drug regimen of diethylcarbamazine plus albendazole, which is the standard regimen used for mass drug administration for the elimination of lymphatic filariasis outside sub-Saharan Africa. The participants in this trial had not received previous treatment for lymphatic filariasis, and all had moderate to high microfilarial counts and filarial antigen levels at baseline. Clearance of microfilaremia was observed in almost all participants who received the three-drug regimen, and this effect persisted for at least 36 months. With respect to microfilarial clearance at 36 months, the three-drug regimen was superior to a single dose of the two-drug regimen and was noninferior to the two-drug regimen administered once a year for 3 years. The results observed after treatment with the two-drug regimen at 12 and 24 months were consistent with those reported in previous trials.^{9,12} Although microfilarial clearance did not occur in every participant who received the three-drug

regimen, the residual microfilarial counts in the few outliers were reduced to levels that were unlikely to support mosquito-borne transmission.^{13,14} Thus, the triple-drug treatment has the potential to contribute to the elimination of lymphatic filariasis.

Both the three-drug regimen and the two-drug regimen were shown to have partial macrofilaricidal effects on the basis of reductions in circulating filarial antigen levels at 36 months after trial initiation. These data are consistent with previous studies that documented partial macrofilaricidal effects of diethylcarbamazine plus albendazole,¹⁵⁻¹⁷ whereas ivermectin was shown to have little or no ability to kill adult worms.¹⁸ The addition of ivermectin to the regimen of diethylcarbamazine plus albendazole had only a marginal effect on reducing filarial antigen levels, but the triple-drug treatment appears to have been effective for sterilizing adult worms for a period of at least 3 years.

Our study has several limitations. First, the open-label assessment of adverse events could have introduced bias. Second, microfilaremia detected at follow-up could have been due to reinfection. We believe that reinfection is unlikely because of the high rates of bed-net use and ongoing mass drug administration for lymphatic filariasis in the communities where the participants resided. It is possible that ivermectin has an enhanced effect on adult worms damaged by exposure to diethylcarbamazine and albendazole.

Adverse events after the initial treatment were more frequent with the three-drug regimen than with the two-drug regimen. This finding is consistent with observations in a previous pilot study.⁹ Because adverse events are probably triggered by microfilarial death, it is not surprising that these were more common in people who received treatment with two potent microfilaricidal drugs (diethylcarbamazine and ivermectin). The single severe grade 3 adverse event was self-limited and similar to the occasional severe adverse events that were reported in previous studies of diethylcarbamazine plus ivermectin or even diethylcarbamazine alone.¹⁹ The frequency and severity of adverse events after treatment with ivermectin plus diethylcarbamazine plus albendazole are likely to be lower in communities included in mass drug-administration programs, where infection rates and blood microfilarial

Table 3. Adverse Events after Initial Treatment for Lymphatic Filariasis.

Variable	Three-Drug Regimen (N=41)	Two-Drug Regimen* (N=91)
	no. of participants with event (%)	
At least 1 adverse event	24 (59)	37 (41)
At least 2 adverse events	19 (46)†	24 (26)
Severe or serious adverse event	1 (2)	0
Fever‡	14 (34)	19 (21)
Hemodynamic changes§	5 (12)	4 (4)
Patient-reported grade 1 adverse event	22 (54)	36 (40)
Grade 2 or 3 adverse events¶	11 (27)	5 (5)
Fatigue	8 (20)	5 (5)
Headache	7 (17)	3 (3)
Nausea or vomiting or both	4 (10)	2 (2)
Itch or rash or both	2 (5)	0
Myalgia	5 (12)	3 (3)
Eye swelling	1 (2)	0
Scrotal pain or swelling or both	4 (10)	2 (2)
Dyspnea	2 (5)	0

* Data from the two groups that received the two-drug regimen (administered either once or once a year for 3 years) were combined.

† $P < 0.05$ for the comparison between groups, as calculated with the use of the chi-square test.

‡ Fever was defined as an auricular body temperature of at least 37.5°C. The highest temperature recorded after the initial treatment was 41.1°C.

§ Hemodynamic change was defined as a change in systolic blood pressure of 30 mm Hg or a change in diastolic blood pressure of 20 mm Hg from the baseline measurement. Reduced blood pressure occurred in three of the five participants with hemodynamic change in the group that received the three-drug regimen and in all four participants with hemodynamic change in the combined two-drug-regimen groups.

¶ With the exception of one participant, all the participants who had a grade 2 or 3 adverse event had more than one adverse event.

|| $P < 0.001$ for the comparison between groups, as calculated with the use of the chi-square test.

counts are typically lower than those in this trial.

Collectively, these findings indicate that the three-drug regimen produces sustained clearance of microfilaremia in almost all persons who receive the treatment. By contrast, treatment with the two-drug regimen administered either once or once a year for three years produces a slower reduction and clearance of microfilaremia. Incomplete or delayed clearance of microfilaremia can contribute to continued transmission.

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

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REFERENCES

1. Taylor MJ, Hoerauf A, Bockarie M. Lymphatic filariasis and onchocerciasis. *Lancet* 2010;376:1175-85.
2. World Health Organization. Global Programme to Eliminate Lymphatic Filariasis: progress report, 2016. *Wkly Epidemiol Rec* 2017;92:594-607.
3. Ramaiah KD, Ottesen EA. Progress and impact of 13 years of the Global Programme to Eliminate Lymphatic Filariasis on reducing the burden of filarial disease. *PLoS Negl Trop Dis* 2014;8(11):e3319.
4. Bockarie MJ, Tisch DJ, Kastens W, et al. Mass treatment to eliminate filariasis in Papua New Guinea. *N Engl J Med* 2002;347:1841-8.
5. Farid HA, Hammad RE, Hassan MM, Ramzy RM, El Setouhy M, Weil GJ. Effects of combined diethylcarbamazine and albendazole treatment of bancroftian filariasis on parasite uptake and development in *Culex pipiens* L. *Am J Trop Med Hyg* 2005;73:108-14.
6. Ismail MM, Jayakody RL, Weil GJ, et al. Long-term efficacy of single-dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. *Trans R Soc Trop Med Hyg* 2001;95:332-5.
7. Ismail MM, Jayakody RL, Weil GJ, et al. Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. *Trans R Soc Trop Med Hyg* 1998;92:94-7.
8. Michael E, Malecela-Lazaro MN, Kazura JW. Epidemiological modelling for monitoring and evaluation of lymphatic filariasis control. *Adv Parasitol* 2007;65:191-237.
9. Thomsen EK, Sanuku N, Baea M, et al. Efficacy, safety, and pharmacokinetics of coadministered diethylcarbamazine, albendazole, and ivermectin for treatment of bancroftian filariasis. *Clin Infect Dis* 2016;62:334-41.
10. Moulia-Pelat JP, Glaziou P, Nguyen LN, Chanteau S, Martin PM, Cartel JL. Long-term efficacy of single-dose treatment with 400 micrograms.kg-1 of ivermectin in bancroftian filariasis: results at one year. *Trop Med Parasitol* 1993;44:333-4.
11. Chesnais CB, Missamou F, Pion SD, et al. Semi-quantitative scoring of an immunochromatographic test for circulating filarial antigen. *Am J Trop Med Hyg* 2013;89:916-8.
12. Bockarie MJ, Tavul L, Ibam I, et al. Efficacy of single-dose diethylcarbamazine compared with diethylcarbamazine combined with albendazole against *Wuchereria bancrofti* infection in Papua New Guinea. *Am J Trop Med Hyg* 2007;76:62-6.
13. Snow LC, Bockarie MJ, Michael E. Transmission dynamics of lymphatic filariasis: vector-specific density dependence in the development of *Wuchereria bancrofti* infective larvae in mosquitoes. *Med Vet Entomol* 2006;20:261-72.
14. Erickson SM, Thomsen EK, Keven JB, et al. Mosquito-parasite interactions can shape filariasis transmission dynamics and impact elimination programs. *PLoS Negl Trop Dis* 2013;7(9):e2433.
15. Hussein O, El Setouhy M, Ahmed ES, et al. Duplex Doppler sonographic assessment of the effects of diethylcarbamazine and albendazole therapy on adult filarial worms and adjacent host tissues in Bancroftian filariasis. *Am J Trop Med Hyg* 2004;71:471-7.
16. Norões J, Dreyer G, Santos A, Mendes VG, Medeiros Z, Addiss D. Assessment of the efficacy of diethylcarbamazine on adult *Wuchereria bancrofti* in vivo. *Trans R Soc Trop Med Hyg* 1997;91:78-81.
17. Helmy H, Weil GJ, Ellethy AS, Ahmed ES, Setouhy ME, Ramzy RM. Bancroftian filariasis: effect of repeated treatment with diethylcarbamazine and albendazole on microfilaraemia, antigenaemia and antifilarial antibodies. *Trans R Soc Trop Med Hyg* 2006;100:656-62.
18. Geary TG. Ivermectin 20 years on: maturation of a wonder drug. *Trends Parasitol* 2005;21:530-2.
19. Horton J, Witt C, Ottesen EA, et al. An analysis of the safety of the single dose, two drug regimens used in programmes to eliminate lymphatic filariasis. *Parasitology* 2000;121:Suppl:S147-S160.

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