Clinical Infectious Diseases Advance Access published November 19, 2014

MAJOR ARTICLE

Efficacy and Safety of the Mosquitocidal Drug Ivermectin to Prevent Malaria Transmission After Treatment: A Double-Blind, Randomized, Clinical Trial

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Background. Artemisinin combination therapy effectively clears asexual malaria parasites and immature gametocytes but does not prevent posttreatment malaria transmission. Ivermectin (IVM) may reduce malaria transmission by killing mosquitoes that take blood meals from IVM-treated humans.

Methods. In this double-blind, placebo-controlled trial, 120 asymptomatic *Plasmodium falciparum* parasite carriers were randomized to receive artemether-lumefantrine (AL) plus placebo or AL plus a single or repeated dose (200 μg/kg) of ivermectin (AL-IVM1 and AL-IVM2, respectively). Mosquito membrane feeding was performed 1, 3, and 7 days after initiation of treatment to determine *Anopheles gambiae* and *Anopheles funestus* survival and infection rates.

Results. The AL-IVM combination was well tolerated. IVM resulted in a 4- to 7-fold increased mortality in mosquitoes feeding 1 day after IVM ($P < .001$). Day 7 IVM plasma levels were positively associated with body mass index ($r = 0.57$, $P < .001$) and were higher in female participants ($P = .003$), for whom *An. gambiae* mosquito mortality was increased until 7 days after a single dose of IVM (hazard rate ratio, 1.34 [95% confidence interval, 1.07–1.69]; $P = .012$). Although we found no evidence that IVM reduced *Plasmodium* infection rates among surviving mosquitoes, the mosquitocidal effect of AL-IVM1 and AL-IVM2 resulted in 27% and 35% reductions, respectively, in estimated malaria transmission potential during the first week after initiation of treatment.

Conclusions. We conclude that IVM can be safely given in combination with AL and can reduce the likelihood of malaria transmission by reducing the life span of feeding mosquitoes.

Clinical Trials Registration. NCT0160325.

Keywords. falciparum; gametocyte; transmission; survivorship; sporogony.

The transmission of *Plasmodium* from humans to mosquitoes depends on the presence of mature transmission stages, gametocytes. Once ingested, gametocytes may render mosquitoes infectious within 11–16 days after a blood meal [1]. Artemisinin combination therapy (ACT) forms the current first-line treatment for uncomplicated falciparum malaria. ACT rapidly clears asexual parasites and developing gametocytes but leaves mature *P. falciparum* gametocytes largely unaffected; a proportion of patients may transmit malaria after successful ACT treatment [2]. Strategies to prevent malaria transmission after ACT have received a sense of urgency with the emergence of artemisinin resistance in Southeast Asia [3, 4] and have

Received 13 June 2014; accepted 4 September 2014.

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Clinical Infectious Diseases®

DOI: 10.1093/cid/ciu797

mainly focused on supplementing ACT with gametocytocidal compounds [5–7]. An alternative approach to prevent post-treatment malaria transmission is to reduce the likelihood that mosquitoes that feed on gametocytemic human hosts survive long enough to become infectious to other humans. Ivermectin (IVM) reduces the life span of *Anopheles* mosquitoes that feed on humans who have taken IVM [8, 9] by activating glutamate-gated chloride channels in neuronal and neuromuscular tissues of invertebrates, thereby causing flaccid muscle paralysis [10]. IVM has an excellent safety profile in humans, allowing IVM to be used in mass drug administration campaigns to reduce the burden of onchocerciasis and lymphatic filariasis in Africa. IVM has never been tested in a clinical trial setting in malaria-infected individuals or in combination with ACT.

In this study, we report a randomized, double-blind, placebo-controlled clinical trial to determine the safety and impact of IVM, administered as single or repeated dose, in combination with artemether-lumefantrine (AL) in reducing the proportion of mosquitoes that survive sufficiently long to complete the sporogonic cycle of malaria.

METHODS

Study Design and Participants

This trial was conducted from January until March 2013 in Balonghin, Burkina Faso. Individuals aged 15–25 were eligible if found to be infected with *P. falciparum* by microscopy and otherwise healthy. Exclusion criteria were ≥20 000 malaria parasites/μL; severe malaria; fever (axillary temperature ≥37.5°C); hematological or biochemical abnormalities; body mass index (BMI) <16 or >32 kg/m^2; hemoglobin concentration <11 g/dL; use of IVM within the previous 3 months; *Loa loa* or other filariasis infection; travel history to *L. loa*–endemic areas; pregnancy or lactation; current tuberculosis or antiretroviral treatment; family history of congenital QTc interval prolongation or sudden death; use of drugs that influence cardiac function or prolong QTc interval; or electrolyte imbalance. Written informed consent was obtained. The trial was approved by the Interventions Research Ethics Committee of the London School of Hygiene and Tropical Medicine (reference number 6154), Comité d'Ethique pour la Recherche en Santé, Ministère de la Santé du Burkina Faso (reference number 2012-5-026), and Comité Technique d'Examen des Demandes d'Autorisation d'Essais Cliniques, Ministère de la Santé du Burkina Faso (reference number 50001020125EC00000).

Randomization and Masking

Included subjects (n = 120) were randomly assigned to 1 of 3 treatment arms and 1 of 2 membrane feeding schedules. A first set of 40 sealed envelopes contained cards indicating treatment with AL alone (AL, n = 20) or AL with a single dose of IVM (AL-IVM1, n = 20). After reviewing safety data, 80 additional participants were randomized to AL (n = 20), AL-IVM1 (n = 20), or AL with a repeated treatment dose of IVM (AL-IVM2, n = 40). Half of each treatment arm was allocated to membrane feeding on days 1 and 7, others to days 3 and 7.

Procedures

All subjects received 6 doses of 4 tablets of AL (Coartem [20 mg artemether and 120 mg lumefantrine], Novartis Pharma AG, Basel, Switzerland) at enrollment and after 8 hours (day 0), 24 and 36 hours (day 1), and 48 and 60 hours (day 2) (±90 minutes). In the AL arm, the first and fifth dose of AL were given together with placebo tablets (Albochin, Pharmachemie BV, Haarlem, the Netherlands); in the AL-IVM1 arm, the first dose of AL was given with IVM (Stromectol, Merck Sharp & Dohme BV, Haarlem, the Netherlands) and the fifth AL dose together with placebo. In the AL-IVM2 arm, both the first and fifth AL dose were given together with IVM. IVM was given as 3-mg tablets aiming for a dose of 200 μg/kg. All treatment was administered under direct supervision, with 1 sachet of Nestle NIDO powdered milk (containing 7.28 g of milkfat) dissolved in water to enhance bioavailability of AL [11].

Participants were examined clinically on days 1, 2, 3, and 7 after enrollment. Blood samples were taken for microscopy (days 0, 3, and 7), standard hematological and biochemical parameters (days 0 and 7), membrane feeding assays (days 1 and 7 or days 3 and 7), pharmacological assessment (days of membrane feeds), and gametocyte detection by Pfs25 messenger RNA quantitative nucleic acid sequence–based amplification (QT-NASBA; days 0, 3, and 7) [7].

Membrane feeding assays were conducted as described elsewhere [12] using 100–150 locally reared 4- to 5-day-old female *Anopheles gambiae* sensu stricto mosquitoes and 50–70 four- to 5-day-old *Anopheles funestus* mosquitoes. Because of mosquito husbandry limitations, experiments with *An. funestus* were done with a smaller number of mosquitoes and on days 1 and 3 only. Fully fed mosquitoes were kept on glucose for 10 days at 27°C–29°C to monitor daily mosquito mortality. *Anopheles gambiae* mosquitoes that survived until day 10, when residual DNA from the blood meal is highly unlikely [13, 14], were individually homogenized and processed for detection of *P. falciparum* oocysts or sporozoites by polymerase chain reaction (PCR) [14]. On day 7, lumefantrine plasma concentrations were determined for 20 randomly selected individuals per treatment arm [15]; on days 1, 3, and 7, IVM plasma concentrations were determined for all individuals participating in membrane feeding experiments using high-performance liquid chromatography with fluorescence detection and a sensitivity of 0.2 ng IVM/mL [16].

Outcome Measures

The study objective was to determine the safety and efficacy of IVM in combination with AL in reducing the proportion of

mosquitoes that survive long enough to complete the sporogonic cycle of *P. falciparum*. The primary efficacy endpoint was the survival of *An. gambiae* and *An. funestus* mosquitoes after taking a blood meal 1, 3, or 7 days after initiation of treatment. Plasma concentrations of AL and IVM after treatment and mosquito infection rates were secondary outcome measures. The associations of IVM plasma concentrations with sex and BMI were not initially defined in the study protocol.

Statistical Analysis

For the primary efficacy outcome, individual mosquito data were analyzed by Cox proportional hazard models with shared frailty to allow for the correlation between mosquito observations from the same donor. Cumulative mosquito mortality by day 10 after feeding was determined for each individual membrane feeding experiment, $\log_{10}$-transformed, and compared with the AL reference arm using *t* test. IVM (days 1, 3, 7) and lumefantrine plasma concentrations (day 7) were compared between groups using nonparametric Wilcoxon-rank sum test. Proportions were compared between arms by χ^2 test, associations between continuous variables were determined by Spearman correlation coefficients, and the association between sex and IVM plasma concentrations was determined by Wilcoxon rank-sum test.

The impact of IVM on transmission from patients during the first week after initiation of treatment was estimated using data from a clinical trial with detailed gametocyte quantification after AL [7], a meta-analysis of the association between gametocyte concentration and *An. gambiae* mosquito infection rates [17], and *An. gambiae* mosquito survivorship in relation to IVM concentration. Assuming that a similar number of mosquitoes would feed on individuals from treatment arms and on all days of follow-up, the impact of IVM at reducing the number of infectious mosquitoes can be calculated as

$$\frac{\sum_{i=0}^{7}(g_i p_i \mu_i^{\mathrm{AL}}) - \sum_{i=0}^{7}(g_i p_i \mu_i^{\mathrm{IVM}})}{\sum_{i=0}^{7}(g_i p_i \mu_i^{\mathrm{AL}})},$$

where g_i is the gametocyte prevalence at each day of follow up (i) after treatment, p_i is the proportion of mosquito infection in feeding assays with gametocyte levels at day i, and μ_i is the proportion of mosquito survival up to day 10.

Sample Size Calculation

This study was designed as a superiority trial, testing mosquito mortality in the 2 IVM arms against the AL comparator arm. The study sample size was based on 80–100 fully fed *An. gambiae* sensu stricto mosquitoes and ≤20% mortality in the control arm [12]. Including 20 individuals per time-point would allow us to detect an increase in mortality to ≥50% after 1 or 2 doses of IVM compared to the control arm ($k = 0.5$; $Z_\alpha/2 = 1.96$; $Z_\beta = 0.84$). For day 7, we expected the smallest difference in mortality and aimed for 40 experiments per treatment arm.

RESULTS

Trial Profile and Baseline Characteristics

Of 120 randomized individuals, 117 completed follow-up (Figure 1). Baseline asexual parasite densities ranged from 8 to 7063 parasites/μL (Table 1); all participants cleared their asexual parasites by day 3. Gametocyte prevalence by QT-NASBA declined from 91.9% (102/111) at baseline to 54.9% (62/113) by day 3 and 41.8% (43/103) by day 7 with no significant difference between treatment arms ($P \geq .81$).

Safety Results

Twenty-two adverse events (AEs) occurred; 10 AEs were ranked as mild and 12 as moderate in intensity (Table 2). None of the AEs were definitively associated with treatment and no serious AEs were seen. Platelet counts declined in 2 subjects during follow-up. In 1 subject of the AL group, platelets decreased from 327 000/μL at enrollment to 82 800/μL on day 7. This subject refused to return to the clinic for extra follow-up and was followed passively. In 1 subject in the AL-IVM1 group, platelets decreased from 191 000/μL at enrollment to 68 500/μL on day 7, and returned to 218 000/μL when measured 20 days later. There were no other clinically significant hematological and biochemical abnormalities.

Efficacy Results

The median number of fully fed *An. gambiae* mosquitoes was 94 per experiment (interquartile range [IQR], 92–96) and not different between treatment arms ($P = .15$), giving 22 818 mosquito observations from 233 experiments conducted on days 1, 3, and 7 posttreatment. The median number of fully fed *An. funestus* mosquitoes was 23 per experiment (IQR, 23–25) and not different between treatment arms ($P = .19$), giving 2469 mosquito observations from 102 experiments conducted on days 1 and 3. *Anopheles gambiae* mortality was significantly increased on day 1 after single-dose IVM (hazard rate ratio [HRR], 3.86 [95% confidence interval {CI}, 3.29–4.52]; $P < .001$), day 3 after single-dose IVM (HRR, 1.37 [95% CI, 1.14–1.65]; $P = .001$), day 3 after repeated-dose IVM (HRR, 4.07 [95% CI, 3.41–4.87]; $P < .001$), and day 7 after repeated-dose IVM (HRR, 1.30 [95% CI, 1.10–1.53]; $P = .002$), but not day 7 after single-dose IVM (HRR, 0.93 [95% CI, .79–1.11]; $P = .43$) (Figure 2*A*). Similarly, *An. funestus* mosquito mortality was significantly increased on day 1 after single-dose IVM (HRR, 7.12 [95% CI, 4.45–11.39]; $P < .001$), day 3 after single-dose IVM (HRR, 2.98 [95% CI, 1.62–5.48]; $P < .001$), and day 3 after repeated-dose IVM (HRR, 9.07 [95% CI, 5.06–16.25];

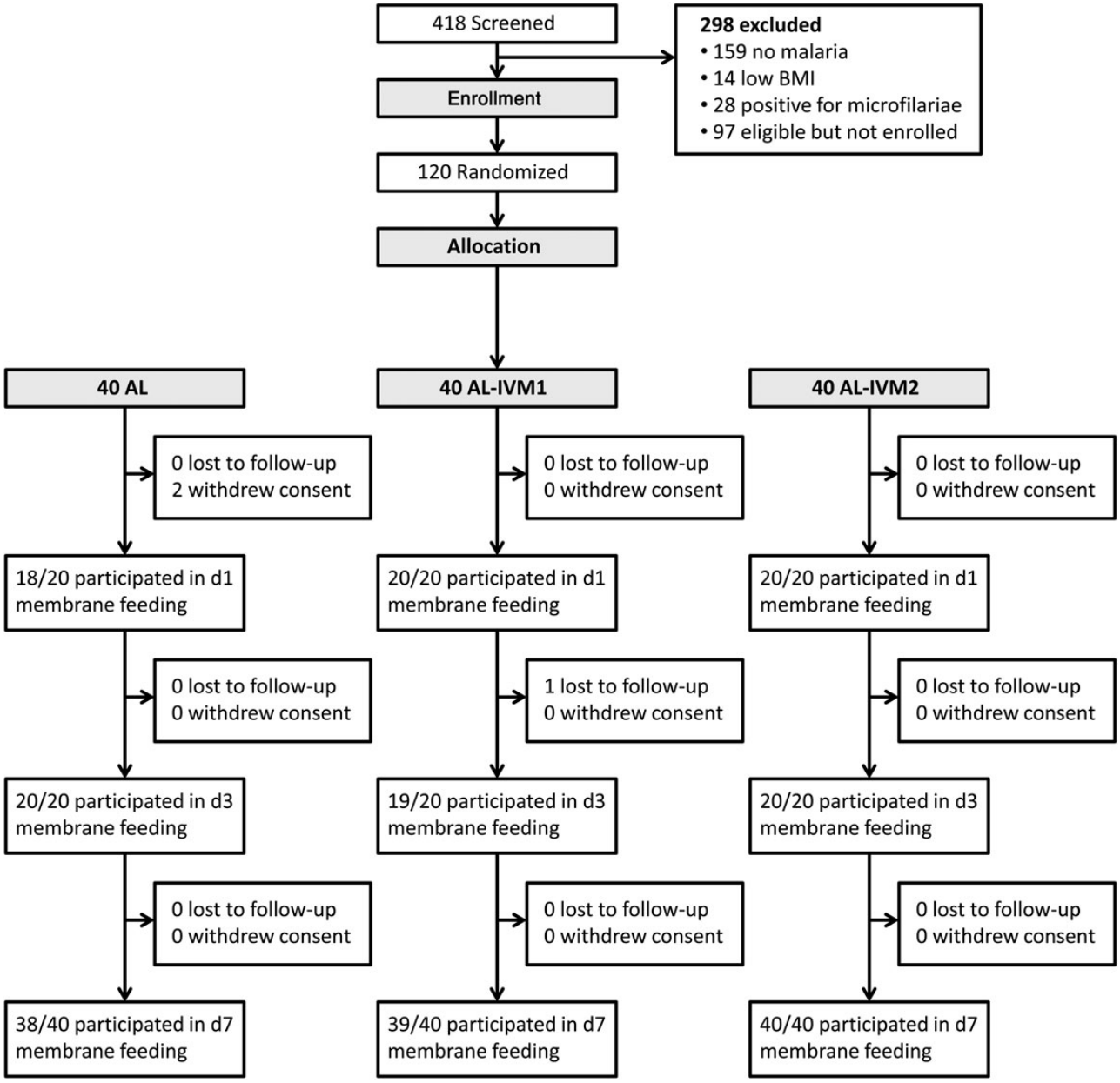

Figure 1. Trial profile. Membrane feeding participation rates are reported for *Anopheles gambiae*. Abbreviations: AL, artemether-lumefantrine; BMI, body mass index; IVM1, single-dose ivermectin; IVM2, repeated-dose ivermectin.

$P < .001$) (Figure 2*B*). Geometric mean cumulative *An. gambiae* mosquito mortality by day 10 after membrane feeding was 21.2% (95% CI, 18.5%–24.3%) in the AL arm; 59.1% (95% CI, 53.3%–65.6%; $P < .001$) on day 1 after single-dose IVM, 31.1% (95% CI, 26.5%–36.5%; $P = .001$) on day 3 after single-dose IVM; 66.2% (95% CI, 58.5%–74.9%; $P < .001$) on day 3 after repeated-dose IVM; 21.7% (95% CI, 18.5%–25.4%; $P = .82$) on day 7 after single-dose IVM; and 26.7% (95% CI, 23.2%–30.7%; $P = .013$) on day 7 after repeated-dose IVM. Geometric mean cumulative *An. funestus* mosquito mortality was 5.0% (95% CI, 3.2%–7.8%) in the AL arm; 40.0% (95% CI, 26.8%–59.8%; $P < .001$) on day 1 after single-dose IVM; 10.9% (95% CI, 5.4%–22.0%; $P = .033$) on day 3 after single-dose IVM, and 51.4% (95% CI, 37.7%–69.9%; $P < .001$) on day 3 after repeated-dose IVM.

Median lumefantrine concentration was 685 ng/mL (IQR, 474–894 ng/mL) in the AL arm, 634 ng/mL (IQR, 420–818 ng/mL) in the AL-IVM1 arm, and 449 ng/mL (IQR, 385–734 ng/mL) in the

Table 1. Baseline Characteristics of Enrolled Subjects

Characteristic	Treatment Group		
	AL (n = 40)	AL-IVM1 (n = 40)	AL-IVM2 (n = 40)
Age, y, median (IQR)	18.5 (16.0–21.3)	16.0 (15.0–20.0)	17.0 (16.0–18.5)
Sex, male, % (n/N)	65.0% (26/40)	45.0% (18/40)	70.0% (28/40)
Hemoglobin, g/dL, median (IQR)	13.3 (12.0–14.4)	13.2 (12.3–13.9)	12.9 (12.3–13.8)
Parasitemia by microscopy, parasites/μL, median (IQR)	109.5 (38.3–222.0)	87.0 (28.0–203.5)	134.0 (45.0–406.0)
Gametocyte prevalence by microscopy, % (n/N)	20.0 (8/40)	12.5 (5/40)	12.5 (5/40)
Gametocyte prevalence by QT-NASBA, % (n/N)	97.2% (35/36)	86.8% (33/38)	91.9% (34/37)

Abbreviations: AL, artemether-lumefantrine; IQR, interquartile range; IVM1, single-dose ivermectin; IVM2, repeated-dose ivermectin; QT-NASBA, quantitative nucleic acid sequence–based amplification.

AL-IVM2 arm ($P = .28$). IVM plasma concentrations declined quickly after the last dose of IVM (Figure 3*A*) and were significantly higher in female than in male participants when measured on day 3 after single-dose IVM ($P = .02$) and day 7 after single-dose ($P = .007$) or repeated-dose IVM ($P = .003$). IVM accumulates in fat tissue [18] and the proportion body fat is positively associated with BMI. BMI was associated with IVM plasma concentration on day 3 (IVM1: n = 18, $r = 0.64$, $P = .004$; IVM2: n = 20, $r = 0.19$, $P = .42$), and day 7 (IVM1: n = 37, $r = 0.73$, $P < .0001$; IVM2: n = 40, $r = 0.49$, $P = .001$; Figure 3*B*) but not on day 1. Female participants had a higher mean BMI than male participants (difference of means, 1.12 kg/m^2 [95% CI, .54–1.71 kg/m^2]; $P = .0002$). IVM plasma concentrations were strongly associated with cumulative mortality by day 10 after the blood meal for *An. gambiae* ($r = 0.75$, $P < .0001$; Figure 4) and *An. funestus* ($r = 0.48$, $P < .0001$). When stratified by sex, the lethal effect of IVM on *An. gambiae* was more pronounced and longer in women (Table 3). The number of *An. funestus* observations was 9-fold lower than for *An. gambiae* and considered too limited to allow robust sex-stratified analysis.

Individual *An. gambiae* mosquitoes from 68 membrane feeds performed on days 1 and 7 on Pfs25 QT-NASBA–confirmed gametocyte carriers were successfully analyzed by PCR. Remaining assays failed because of freeze–thaws of mosquito samples, giving noninterpretable results. In total, only 0.8% (13/1619) of the successfully assayed mosquitoes were *P. falciparum* positive: 0.7% (4/560) in the AL arm, 0.5% (3/556) in the AL-IVM1 arm, and 1.2% (6/503) in the AL-IVM2 arm. Supporting in vitro experiments found no apparent effect of sublethal IVM concentrations on *P. falciparum* development in *Anopheles stephensi* and *An. gambiae* mosquitoes (Supplementary Data 1).

We combined our longitudinal data on IVM concentrations (Figure 3), our data on the association between IVM concentration and *An. gambiae* mosquito survivorship (Figure 4), previously published data on gametocyte prevalence and density following treatment of symptomatic malaria patients [7], and a meta-analysis of the association between gametocyte density and mosquito infection rates [17] to estimate the potential impact of IVM on onward malaria transmission in the first week after initiation of treatment (Supplementary Data 2). Despite the incomplete and short-lived mosquitocidal effect of IVM, mosquito survivorship is significantly reduced in the first days after treatment when gametocyte concentrations are highest and onward transmission is most likely. Compared to the AL-only arm, we estimated that individuals in the AL-IVM1 and AL-IVM2 arms had a 27.2% and 35.4% reduction, respectively, in their contribution to transmission in the first week after initiation of treatment (Figure 5).

Table 2. Adverse Events of Any Severity in the Different Treatment Arms

Adverse Event	Treatment Group		
	AL (n = 38)	AL-IVM1 (n = 39)	AL-IVM2 (n = 40)
Abdominal pain		2	
Abscess on hand			1
Abscess on leg			1
Bronchitis	1		
Conjunctivitis		1	
Cough		1	1
Dental pain			1
Diarrhea		1	
Fever	1		
Headache	1	1	4
Orchitis		2	
Painful swelling of leg			1
Pharyngitis			1
Urinary tract infection			1

Abbreviations: AL, artemether-lumefantrine; IVM1, single-dose ivermectin; IVM2, repeated-dose ivermectin.

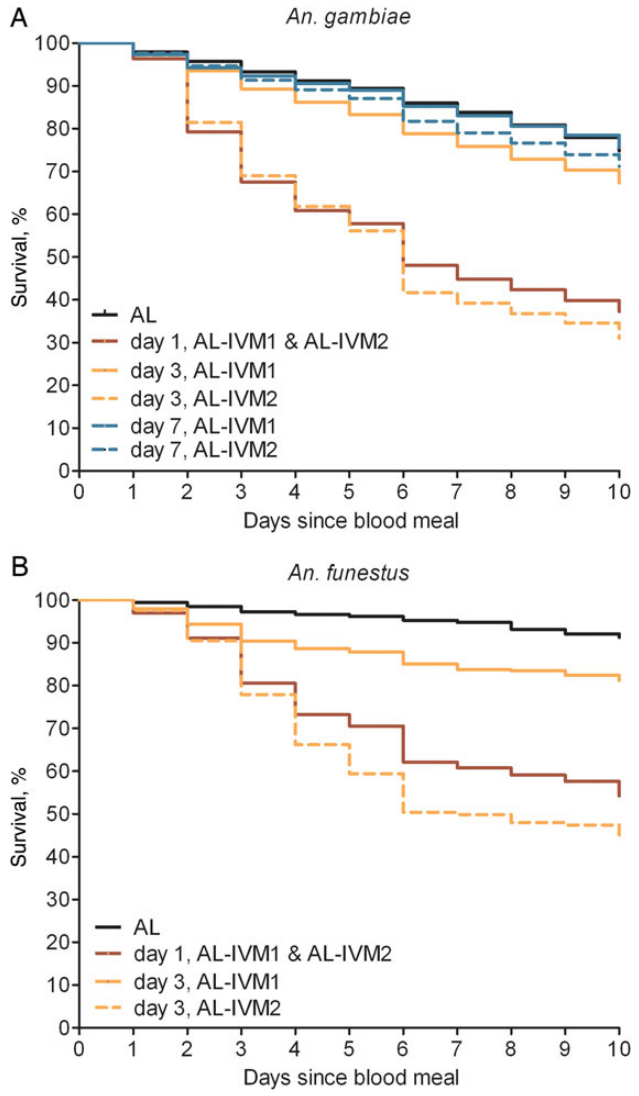

Figure 2. Mosquito survival rate in relation to treatment arm for *Anopheles gambiae* and *Anopheles funestus*. The proportion of *An. gambiae* (*A*) or *An. funestus* (*B*) that survive in 10 days following membrane feeding in various treatment arms at days 1, 3, and 7 was combined for artemether-lumefantrine (AL); day 1 was combined for AL with single-dose ivermectin (IVM1) and AL with repeated-dose ivermectin (IVM2) as this was before the second dose of ivermectin.

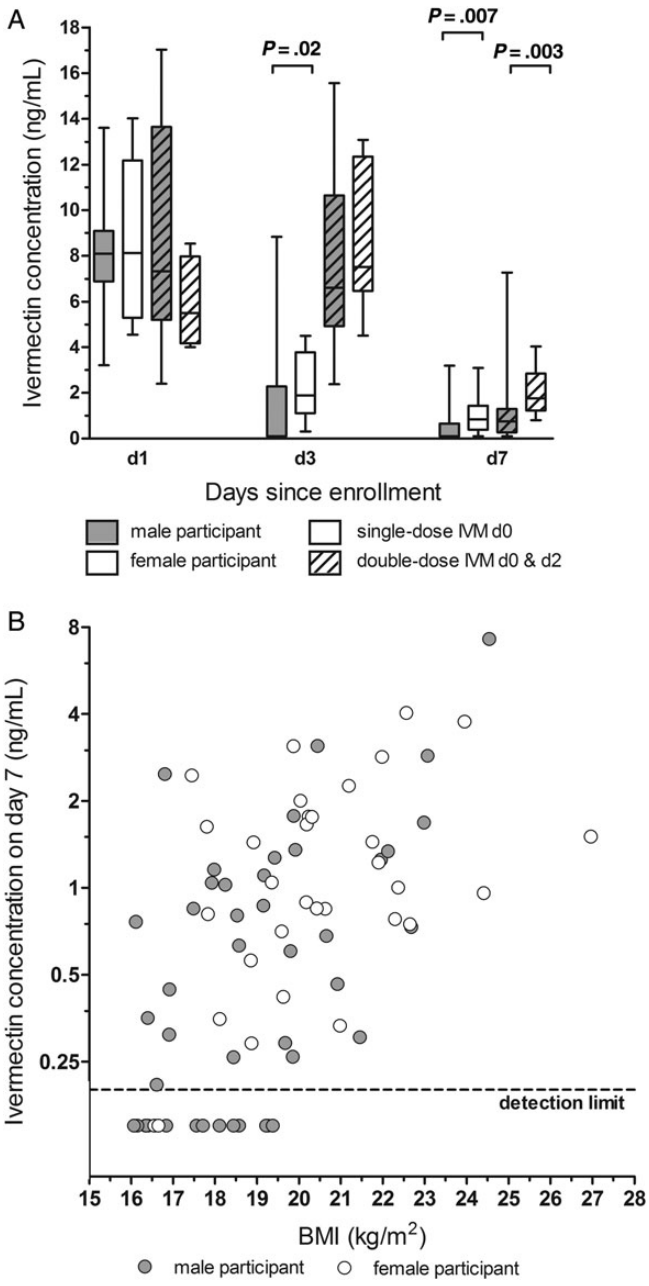

Figure 3. Ivermectin (IVM) plasma concentrations in relation to the sex of participants and body mass index (BMI). *A*, Sex-stratified ivermectin plasma concentration for the different treatment arms and time-points of follow-up. *B*, Association between BMI and day 7 ivermectin plasma concentrations for male (gray dots; n = 45; $r = 0.52$, $P = .0002$) and female (n = 32; $r = 0.37$, $P = .037$) participants. The limit of detection of the assay was 0.2 ng/mL (dashed line); plasma samples with undetectable IVM concentrations are given below the line.

DISCUSSION

In this study, the AL-IVM combination was safe and significantly reduced the survival of 2 major malaria vectors in sub-Saharan Africa, *An. gambiae* and *An. funestus*. The mosquitocidal effect of IVM was apparent 3–7 days after a single dose depending on volunteer sex, with a more pronounced effect when mosquitoes fed on blood from female participants.

The continued move toward malaria elimination has reinvigorated the search for strategies to prevent the spread of malaria, bolstered by a sense of urgency from the threat of artemisinin resistance [4]. Our findings confirm that IVM reduces the life span of different malaria vectors [19], including 2 dominant and important vectors in sub-Saharan Africa, *An. gambiae*

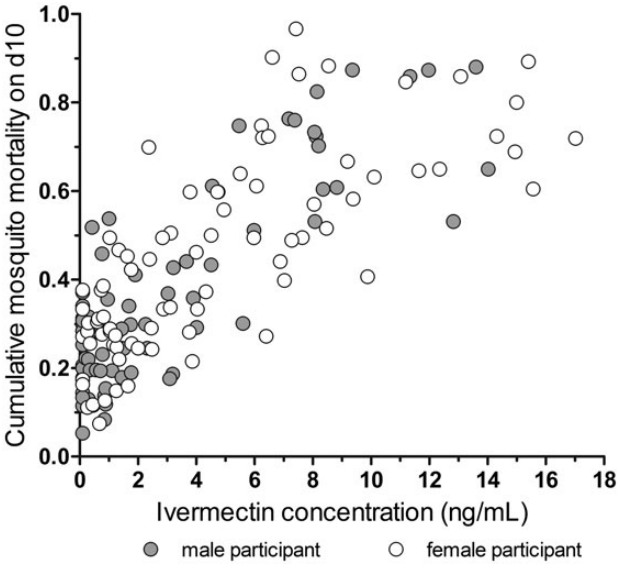

Figure 4. Ivermectin plasma concentrations in relation to cumulative mortality of *Anopheles gambiae*. The association between ivermectin plasma concentrations (all time-points combined) and cumulative *An. gambiae* mosquito mortality by day 10 (d10) after taking a blood meal. $r = 0.75$, $P < .0001$.

and *An. funestus*. Mosquito mortality was 4- to 7-fold increased in mosquitoes that took a blood meal 1 day after IVM. Mosquito mortality was associated with IVM plasma concentrations that decreased markedly during the week after IVM treatment [20]. The waning of the mosquitocidal effect of a single or repeated dose of IVM was slower for female participants, in line with a higher IVM bioavailability in females [21]. The accumulation of IVM in fat tissue [18] and the strong association between BMI and day 7 IVM plasma concentrations suggests that body fat may act as a slow-release reservoir that results in a longer effective half-life of IVM in female participants.

Our findings indicate that higher, repeated doses or sustained presence of drug may be needed for maximal effect. Although IVM is currently recommended as single dose of 200 μg/kg with an excellent safety profile [22], there have been reports where IVM was used repeatedly at higher concentrations [23, 24]. We confirmed the tolerability of repeated IVM dosing in a small group of malaria-infected individuals and found no evidence that coadministration of IVM affects the bioavailability of lumefantrine. The primary safety concern for IVM is encephalopathy in individuals heavily infected with microfilariae of *L. loa* [25] and precludes the use of IVM without prior screening for *L. loa* in endemic areas of Central and West Africa.

Even in individuals with the highest IVM plasma concentrations, the mosquitocidal effect of IVM was not complete and a proportion of mosquitoes survived until day 10. *Plasmodium falciparum* parasites were detected in a small proportion of these surviving mosquitoes. Although our findings do not rule out a sporontocidal effect of IVM, which would require a larger study that is powered for infectivity outcomes, it indicates that malaria transmission potential is not completely abrogated by the AL-IVM combination. If IVM has no impact on gametocytes or their infectivity, its transmission-blocking effect is restricted to its capacity to reduce malaria survivorship in the days immediately following treatment. We estimated that single and repeated doses of IVM may lead to 27% and 35% reductions in posttreatment malaria transmission from symptomatic malaria patients in the first week after treatment with an effective antimalarial. This effect reflects the contribution of an individual patient to malaria transmission and does not reflect population-level impacts that need to take into account effects of IVM on total vector density [8, 9, 26], reduced mosquito refeeding rates, and recovery following a blood meal containing sublethal doses of IVM [19] and may therefore be larger than reported here. Future studies should further quantify the importance of IVM accumulation in fat tissue for (the duration of)

Table 3. Hazard Rate Ratios for *Anopheles gambiae* Mortality on Different Days After Initiation of Treatment

	Male Participants		Female Participants	
Treatment	Hazard Rate Ratio	*P* Value	Hazard Rate Ratio	*P* Value
No ivermectin	1 (ref)		1 (ref)	
Day 1, IVM1 & IVM2	3.29 (2.67–4.07)	<.001	5.03 (4.00–6.31)	<.001
Day 3, IVM1	1.39 (1.04–1.85)	.025	1.67 (1.31–2.13)	<.001
Day 3, IVM2	3.54 (2.81–4.46)	<.001	5.23 (4.01–6.83)	<.001
Day 7, IVM1	0.70 (0.55–0.89)	.003	1.34 (1.07–1.69)	.012
Day 7, IVM2	1.14 (0.92–1.42)	.23	1.61 (1.25–2.08)	<.001

Hazard rate ratios were determined relative to the artemether-lumefantrine placebo arm and adjusted for the correlation between observations from the same individual.

Abbreviations: IVM1, single-dose ivermectin; IVM2, repeated-dose ivermectin; ref, reference.

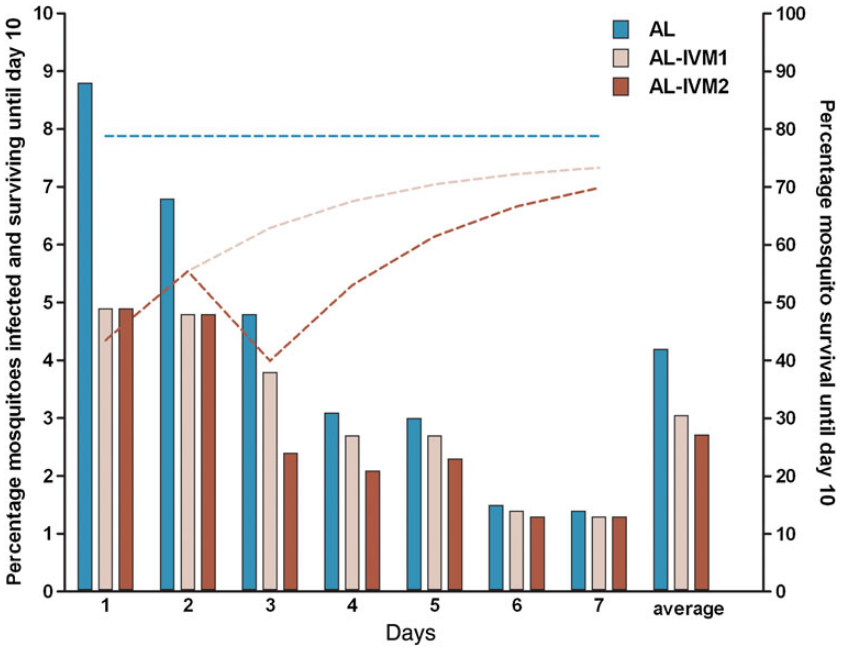

Figure 5. The estimated impact of treatment with ivermectin (IVM) on *Plasmodium falciparum* transmission for malaria patients during the first week after treatment with artemether-lumefantrine (AL). Bars indicate the percentage of mosquitoes that become infected and survive for 10 days after their blood meal for the different treatment arms and days after treatment (left y-axis). The assumptions underlying these estimates are outlined in the Supplementary Data and are based on gametocyte prevalence and density estimates from Ugandan children aged 1–10 years [7], a meta-analysis of mosquito feeding experiments [17], and IVM pharmacokinetics and mosquito survival rates presented in the current manuscript. Lines indicate mosquito survival rates for the different treatment arms (right y-axis) and were either directly estimated or based on the best fit of IVM pharmacokinetic data (Figure 2*A*) and the association between IVM plasma concentration and mosquito infection rates (Figure 3). Mosquito mortality in the AL-only arm (21% over 10 days) is considered to reflect natural mortality over this period and is assumed to be unrelated to the ingestion of gametocytes. Abbreviations: IVM1, single-dose ivermectin; IVM2, repeated-dose ivermectin.

IVM efficacy and be adequately powered to study subtle effects of IVM on sporogonic development. Most important, community trials with repeated doses of IVM are needed to confirm that IVM forms a useful adjunct to reduce and interrupt transmission [27].

In conclusion, our study indicates an incomplete but pronounced effect of IVM on the survival of malaria vectors after IVM ingestion. This effect can be extended by repeated dosing and is associated with the BMI of treated individuals. We observed no evidence for a sporontocidal effect of IVM at mosquito sublethal concentrations in *P. falciparum*–infected individuals. The transmission-blocking properties of IVM may therefore be restricted to its mosquitocidal effects.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank the study participants and members of the field team, clinical team, and entomology team at the Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso. We further acknowledge the work of Geert Jan van Gemert, Marga van de Vegte-Bolmer, Wouter Graumans, Rianne Siebelink-Stoter (Radboud University Medical Center, Nijmegen, the Netherlands), and Koen Dechering (TropIQ Health Sciences, Nijmegen, the Netherlands) for supporting in vitro work.

Disclaimer. The opinions contained herein are the private views of the authors, and are not to be construed as official, or as reflecting true views of the US Department of the Army or the Department of Defense.

Financial support. This work was supported by the Bill & Melinda Gates Foundation (grant number OPP1034789) and by the Radboud University Medical Center (Radboud Hypatia Track). Novartis provided the artemether-lumefantrine.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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