MAJOR ARTICLE

Albendazole and Mebendazole Administered Alone or in Combination with Ivermectin against *Trichuris trichiura*: A Randomized Controlled Trial

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Background. Single-dose albendazole and mebendazole show limited efficacy in the treatment of trichuriasis. The combination of albendazole with ivermectin improves efficacy, but a mebendazole-ivermectin combination has not been previously investigated.

Methods. We performed a randomized controlled trial in 2 schools in Zanzibar, Tanzania, to assess the efficacy and safety of albendazole (400 mg) plus placebo, albendazole plus ivermectin (200 μg/kg), mebendazole (500 mg) plus placebo, and mebendazole plus ivermectin in children with a parasitologically confirmed *Trichuris trichiura* infection. Cure rate (CR) and egg reduction rate were assessed by intent-to-treat analysis. Adverse events were monitored within 48 h after treatment.

Results. Complete data records were available for 548 children. The highest CR against *T. trichiura* was achieved with a mebendazole-ivermectin combination (55%). Low CRs were observed with albendazole-ivermectin (38%), mebendazole (19%), and albendazole (10%). Compared with placebo, the use of ivermectin statistically significantly increased the CRs from 14% to 47% (odds ratio, 0.19; 95% confidence interval [CI], 0.12–0.28). The highest egg reduction rate (97%; 95% CI, 95%–98%) was observed using the mebendazole-ivermectin combination, followed by albendazole-ivermectin (91%; 95% CI, 87%–94%), mebendazole (67%; 95% CI, 52%–77%), and albendazole (40%; 95% CI, 22%–56%). The adverse events, reported by 136 children, were generally mild, with no significant difference between the treatment arms.

Conclusions. Addition of ivermectin improves the therapeutic outcomes of both albendazole and mebendazole against *T. trichiura* and may be considered for use in soil-transmitted helminth control programs and individual patient management.

Trial registration. isrctn.org Identifier: ISRCTN08336605.

An estimated 604 million to 795 million people are infected with the whipworm *Trichuris trichiura*, causing a global burden of 6.4 million disability-adjusted life-years lost [1–3]. The current strategy against *T. trichiura* and other soil-transmitted helminth infections (*Ascaris lumbricoides* and hookworm) is to regularly administer anthelmintic drugs, mainly albendazole and meben-

dazole, to school-aged children and other at-risk populations [4, 5]. Although both drugs show good therapeutic profiles against *A. lumbricoides*, mebendazole fails to effectively clear hookworm infections, and neither drug is satisfactory against *T. trichiura*. In a meta-analysis of randomized, placebo-controlled trials, the average cure rate (CR) of single-dose albendazole (400 mg) against *T. trichiura* was reported to be only 28%. Mebendazole (500 mg), with an average CR of 36%, performed slightly better [6]. Improved treatment outcomes against *T. trichiura* were observed when using triple-dose treatments of either drug [7]. Albendazole and mebendazole can be coadministered with other deworming drugs; foremost is the combination of albendazole with ivermectin (200 or 400 μg/kg) as used against lymphatic filariasis. This combination therapy

showed promising results against *T. trichiura*; observed CRs were 65% and 80% in 2 trials [8, 9]. However, a third trial found no effect by adding ivermectin to albendazole [10]. Despite the somewhat higher efficacy of mebendazole compared with albendazole against trichuriasis, the efficacy and safety of a mebendazole-ivermectin combination have yet to be investigated [7, 11].

In Zanzibar, control programs have significantly reduced the prevalence and intensity of soil-transmitted helminthiasis [12]. However, in contrast to *A. lumbricoides* and hookworm, the prevalence of *T. trichiura* infections has remained high [12, 13]. Against this background, we were motivated to assess the efficacy and safety of albendazole and mebendazole combined with ivermectin against *T. trichiura* and to compare treatment outcomes with standard monotherapies.

PATIENTS AND METHODS

Study area and population. The study was conducted in Unguja, Zanzibar Island, Tanzania, from March through May 2009. Stool samples were collected from children attending schools in Kinyasini and Kilombero, where soil-transmitted helminthiasis is highly endemic [12]. Both schools are located in district North A, 30–40 km northeast of Zanzibar Town.

Ethical considerations. Ethical approval was granted by the Ethics Committee of Basel, Switzerland (13/09), and the Ministry of Health and Social Welfare, Zanzibar (ZAMEC/0001/09). The trial was registered with Current Controlled Trials (ISRCTN08336605). Written informed consent was obtained from parents or guardians of participating children, whereas children consented orally. Participation was voluntary, and individuals could withdraw from the trial at any time.

Eligibility criteria. Children attending grades 1–7 in the 2 schools were eligible if they met all of the following inclusion criteria: written informed consent provided by parents or guardians, age of 5 years or older, sufficiently large stool sample to perform duplicate Kato-Katz thick smears at baseline survey, infection with *T. trichiura*, and submission of second stool sample subjected to duplicate Kato-Katz thick smears before treatment.

After randomization, children were excluded from treatment if fulfilling any of the following exclusion criteria: pregnant (for females), as verbally assessed by medical personnel; presence of systemic illnesses (eg, fever or severe illness); and anthelmintic treatment within the previous 4 weeks.

Sample size. Sample size calculation was based on the range of CRs of albendazole and mebendazole (20%–45%) versus albendazole plus ivermectin (65%–80%) against *T. trichiura* according to recent reviews [6, 11]. Using a significance level of .05 to detect greater efficacy of combination therapy, a power of 80%, and an equation by Fleiss [14], the minimum required number of individuals per treatment group at different CRs was 105.

The prevalence of *T. trichiura* infections was conservatively estimated to be 30% [12], and the compliance for stool submission was assumed to be 90% per sample. Hence, we estimated that ~2000 subjects were needed to identify 600 *T. trichiura*–infected individuals. However, the baseline survey revealed a prevalence of *T. trichiura* of >50% in both schools. Hence, we stopped enrolling after 1240 children had been invited.

Baseline parasitologic survey. First, the name, age, sex, and school grade of each child were recorded. Second, children received containers with unique identification numbers and were invited to bring a fresh stool sample the following morning. Within 2 weeks a total of 1240 children were invited to participate. Children with a microscopically confirmed *T. trichiura* infection were asked for a second stool sample, and their body weight was recorded.

Randomization. The trial statistician was provided with the list of identification numbers of 618 *T. trichiura*–positive children and generated a computer-based random allocation sequence (numbers 1–4). The numbers were decoded for each school by 1 of 2 researchers (S.K. for Kilombero and B.S. for Kinyasini) to assign children either to albendazole (400 mg; Laboratoria Wolfs) plus placebo (Hermes Edulcorants), albendazole plus ivermectin (200 µg/kg; Merck), mebendazole (500 mg; Janssen-Cilag) plus placebo, or mebendazole plus ivermectin. Trial medications were prepared in identical envelopes labeled with unique identification numbers and sealed. Because ivermectin is administered according to patient weight, ivermectin and placebo tablets were counted and packed according to children's weight.

On the day of treatment, eligible children were examined by medical personnel for exclusion criteria before drug administration. Administrators opening the sealed envelopes and administering the drugs were masked to group assignment. However, to the trained eye, the gravure on the albendazole or mebendazole tablets was not identical, and placebos were slightly smaller than ivermectin tablets. Children could not see the tablets because drug administrators placed the tablets directly in their mouth, but differences in palatability and taste of the tablets might exist. Drugs were swallowed with clean water and accompanied by a small food item. A clinician was present, monitored acute adverse events (AEs), and provided medical assistance if necessary. The staff of the nearby health centers had undergone pharmacovigilance training. The medical staff was informed about the date of treatment, and the health centers were provided with first aid drugs (oral and intravenous analgesics and antianaphylactics) and remained open for 24 h after treatment. Children, parents, and teachers were advised to refer to these health centers in case of AEs.

All laboratory personnel, including the outcome assessors, were masked to group assignment. Only the data examiners saw unmasked data, and 1 of them (J.H.) had no contact with

the study participants, although the success of the masking was not assessed formally.

Assessment of AEs. At 48 h after treatment, AEs due to the treatment were assessed by a pretested questionnaire. Children were interviewed by trained personnel of the Helminth Control Laboratory Unguja (HCLU), who were familiar with potential AEs resulting from anthelmintic treatment. Solicited AEs were headache, vertigo, allergic reactions (pruritus, urticaria, and anaphylaxis), shivering, abdominal cramps, nausea, vomiting, diarrhea, and fever. The AEs were recorded and graded as follows: *mild,* indicating present but not requiring any interven-

tion; *moderate,* requiring medication for symptomatic relief on request or present and interfering with normal daily activities; and *severe,* requiring medical intervention beyond symptomatic relief.

Follow-up. Three weeks after treatment, study participants were asked for 2 consecutive stool samples. Approximately 120 children were enrolled daily, and the procedure was continued for 3 weeks until, in the middle of May 2009, most treated children had provided 2 stool samples for follow-up.

Laboratory procedures. Stool samples were transferred to the HCLU and processed the same day, in accordance with
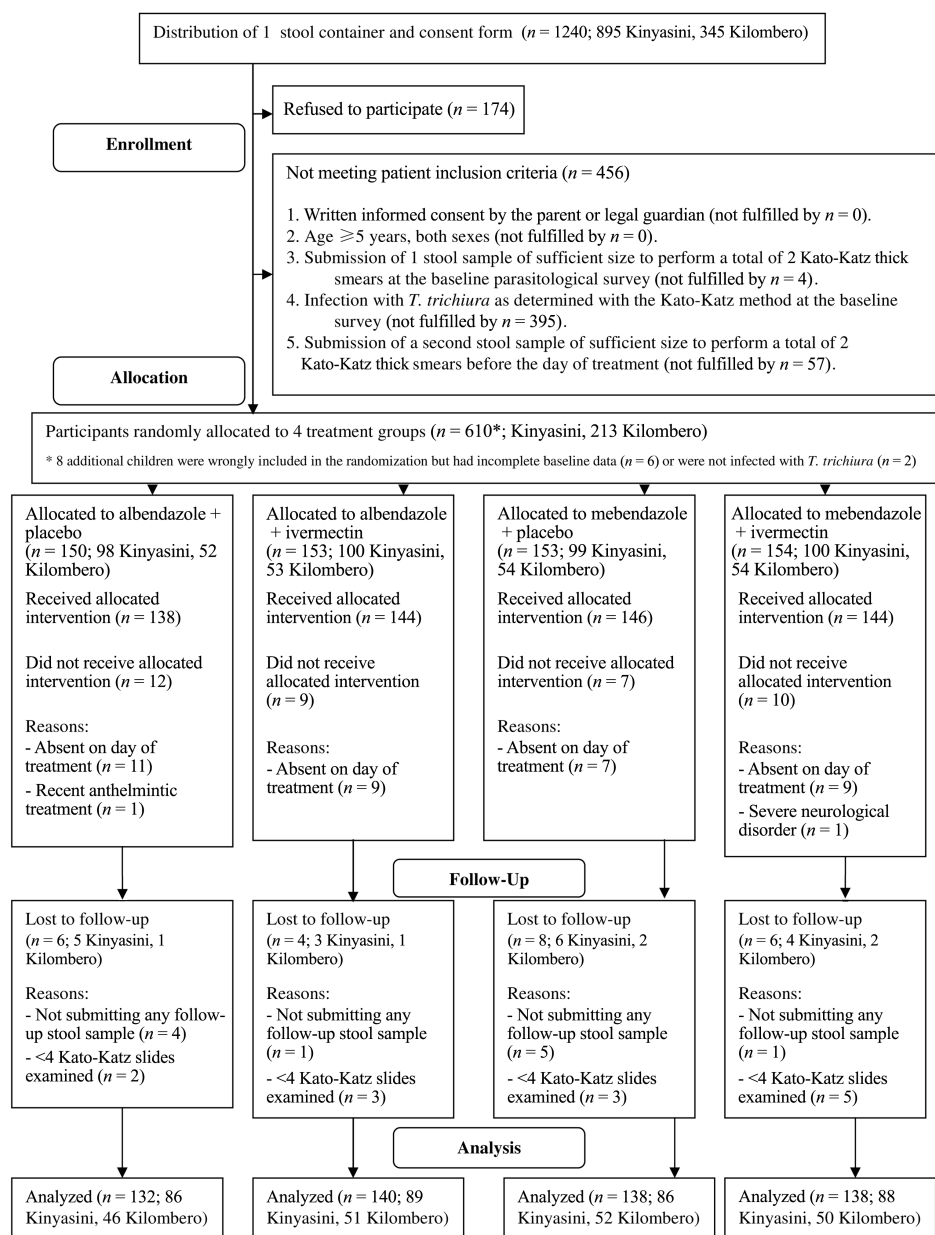
Figure 1. Flow diagram of the randomized controlled trial comparing the efficacy and safety of albendazole and mebendazole alone and in combination with ivermectin against *Trichuris trichiura* in children from primary schools in Kinyasini and Kilombero on Unguja Island, Zanzibar, in early 2009.

Table 1. Baseline Demographic and Clinical Characteristics of 610 Children in a Randomized Controlled Trial in Early 2009 in the Primary Schools of Kilombero and Kinyasini on Unguja Island, Zanzibar, Tanzania

Characteristic	Albendazole plus placebo (n = 150)	Albendazole plus ivermectin (n = 153)	Mebendazole plus placebo (n = 153)	Mebendazole plus ivermectin (n = 154)
Age, mean ± SD, years	10.9 ± 2.6	11.0 ± 2.8	10.8 ± 2.8 (152 observations[a])	11.0 ± 2.6
No. of females/no. of males	71/79	84/69	89/64	92/62
No. of participants at Kilombero/at Kinyasini	52/98	53/100	54/99	54/100
Weight, mean ± SD, kg	30.5 ± 9.9 (145 observations[a])	30.6 ± 10.2 (151 observations[a])	29.5 ± 9.2 (149 observations[a])	29.4 ± 8.9 (151 observations[a])
Infected with *Trichuris trichiura*				
No. (%) of participants	150 (100)	153 (100)	153 (100)	154 (100)
EPG				
Geometric mean	154	121	136	154
Median (range)	156 (66–302)	108 (54–276)	126 (60–282)	159 (78–273)
Infection intensity,[b] no. (%) of participants				
Light	138 (92.0)	142 (92.8)	144 (94.1)	144 (93.5)
Moderate	12 (8.0)	11 (7.2)	9 (5.9)	10 (6.5)
Infected with *Ascaris lumbricoides*				
No. (%) of participants	19 (12.7)	15 (9.8)	19 (12.4)	20 (13.0)
EPG				
Geometric mean	3401	1839	2601	381
Median (range)	4584 (1122–17,772)	2904 (774–6846)	11394 (1104–23,394)	603 (17–8183)
Infection intensity, no. (%) of participants				
Light	11 (57.9)	10 (66.7)	8 (42.1)	14 (70.0)
Moderate	7 (36.8)	4 (26.7)	11 (57.9)	5 (25.0)
Heavy	1 (5.3)	1 (6.6)	0	1 (5.0)
Infected with hookworm				
No. (%) of participants	44 (29.3)	37 (24.2)	39 (25.5)	40 (26.0)
EPG				
Geometric mean	60	66	65	64
Median (range)	60 (18–152)	66 (36–132)	48 (18–192)	51 (18–263)
Infection intensity,[b] no. (%) of participants				
Light	44 (100)	36 (97.3)	39 (100)	40 (100)
Moderate	0 (0)	1 (2.7)	0 (0)	0 (0)

NOTE. EPG, eggs per gram of stool.

[a] Data were recorded only for the indicated number of children.

[b] None had heavy intensity.

standardized, quality-controlled methods [15]. Duplicate 41.7-mg Kato-Katz thick smears were prepared [16]. Slides were quantitatively examined under a microscope for the presence of hookworm eggs after a clearing time of 20–40 min and for *T. trichiura* and *A. lumbricoides* eggs a few hours later.

Primary and secondary outcomes. Primary outcome measures were the CR and egg reduction rate (ERR) achieved by treatment with any drug regimen against *T. trichiura* infections. Secondary outcome measures were the frequencies of AEs. The CR was determined as the percentage of children excreting eggs before treatment who became negative after treatment. The ERR was calculated as the reduction in the group's geometric mean (GM) egg count, including infected and noninfected subjects at follow-up, according to World Health Organization

(WHO) guidelines [17]. Confidence intervals (CIs) for the ERR were calculated using a bootstrap resampling method with 2000 replicates.

Statistical analysis. An intention-to-treat analysis was pursued. All individuals with primary end point data records were included in the final analyses (Figure 1). The species-specific numbers of helminth eggs recorded from 4 Kato-Katz slides before and after treatment were added and multiplied by a factor of 6 to obtain the arithmetic mean of the eggs per gram of stool (EPG) for each individual. The arithmetic means were used to determine whether the intensity of infection with soil-transmitted helminths was light, moderate, or heavy, using WHO cutoffs, and to calculate the GM infection intensities as a summary measure among the treatment groups [17].

Table 2. Cure Rates (CRs) and Egg Reduction Rates (ERRs) of *Trichuris trichiura* and Infection Characteristics of *Ascaris lumbricoides* and Hookworm after Administration of Albendazole and Mebendazole Given Alone or in Combination with Ivermectin in a Tanzanian Study (*n* = 548)

Characteristic	Albendazole plus placebo	Albendazole plus ivermectin	Mebendazole plus placebo	Mebendazole plus ivermectin
Trichuris trichiura				
No. of participants positive before treatment	132	140	138	138
No. (%) of participants still positive after treatment	119 (90.2)	87 (62.1)	112 (81.2)	62 (44.9)
CR, % (95% CI)	9.8 (5.4–16.3)	37.9 (29.8–46.4)	18.8 (12.7–26.4)	55.1 (46.4–63.5)
Geometric mean EPG				
Before treatment	154	127	146	160
After treatment	92	11	49	5
ERR, % (95% CI)[a]	40.3 (21.5–55.7)	91.1 (87.2–94.0)	66.7 (52.3–76.9)	96.7 (95.0–97.9)
Hookworm				
No. of participants positive before treatment	39	30	34	35
No. (%) of participants still positive after treatment	16 (41.0)	10 (33.3)	22 (64.7)	26 (74.3)
Geometric mean EPG				
Before treatment	67	74	61	58
After treatment	4	3	13	29
Ascaris lumbricoides				
No. of participants positive before treatment	14	14	18	18
No. (%) of participants still positive after treatment	0 (0)	1 (7.1)	4 (22.2)	0 (0)
Geometric mean EPG				
Before treatment	2680	1699	2414	553
After treatment	0	1	5	0

NOTE. CI, confidence interval; EPG, eggs per gram of stool.

[a] The CIs of the ERRs were constructed by a bootstrap resampling.

The 2 × 2 factorial design enabled the determination of the treatment efficacy of the 4 regimens against *T. trichiura,* the determination of potential interactions between the interventions, and the determination of the treatment efficacy of the interventions by school, using regression analysis. Odds ratios (ORs) and respective *P* values were used to explain differences among the 4 treatment groups. Significance was given at $P < .05$.

Differences in the median time (days) from treatment to the last collected stool sample at follow-up between the schools and the 4 treatment groups were assessed using the Wilcoxon test. Drug-related AEs were analyzed using ordinal logistic regression with the untoward effect classified as absent, mild, moderate, or severe and the factorial treatment regimens (without interaction term) as predictor variables.

Data were double-entered and discrepancies were removed in tracing back to original records. Statistical analyses were performed using Stata software, version 10 (StataCorp); bootstrap CIs were calculated using R 2.9.1 (R Development Core Team).

RESULTS

Study cohort. Among 1240 children invited for the baseline screening, 174 did not participate, and 456 were excluded (Figure 1). The remaining 610 children were randomly assigned to 1 of the 4 treatment arms. An additional 8 children were wrongly included in the randomization, although they were not infected with *T. trichiura* (*n* = 2) or had incomplete parasitological data (*n* = 6). These children were excluded from subsequent analyses. Thirty-eight children did not receive the assigned intervention because they either were absent during the treatment (*n* = 36) or met 1 of the exclusion criteria at the day of treatment (*n* = 2). Twenty-four children were lost to follow-up. Complete data records for the final analysis were available for 548 children. AEs were determined from 564 (99%) of the 572 treated children.

Baseline parasitologic survey. Overall, 1066 children submitted a stool sample for Kato-Katz examination at baseline. The prevalence of *T. trichiura* was 63%. Hookworm and *A. lumbricoides* infections were diagnosed in 20% and 9% of the children, respectively.

Baseline characteristics. The mean age of the 610 randomized children was 11 years (Table 1). Children's mean weight was similar in all groups (range, 29.4–30.6 kg). The proportion of girls differed slightly among groups (range, 47%–60%). The GMs of *T. trichiura* infections were similar in the 4 treatment groups (121–154 EPG), and infection intensities were mainly light (92%–94%).

Table 3. Multiple Regression Analysis for the 2 × 2 Factorial Design to Assess the Risk of a Persistent *Trichuris trichiura* Infection after Treatment in 548 Schoolchildren from Kilombero and Kinyasini in Tanzania

Type of analysis	OR (95% CI)	*P*
Primary analysis (*n* = 548)		
Albendazole (vs mebendazole)	2.05 (1.38–3.04)	<.001
Placebo (vs ivermectin)	5.40 (3.55–8.22)	<.001
Kinyasini (vs Kilombero)	1.08 (0.72–1.63)	.702
2-way analysis (*n* = 548)		
Albendazole (vs mebendazole)	1.47 (0.72–2.99)	.285
Placebo (vs ivermectin)	8.54 (3.73–19.59)	<.001
Kinyasini (vs Kilombero)	1.08 (0.57–2.07)	.806
Ivermectin × mebendazole (vs ivermectin × albendazole)	1.03 (0.43–2.44)	.950
Albendazole × Kinyasini (vs albendazole × Kilombero)	1.66 (0.72–3.83)	.236
Ivermectin × Kinyasini (vs ivermectin × Kilombero)	0.49 (0.20–1.20)	.118
Adjusted analysis (*n* = 548)		
Albendazole (vs mebendazole)	2.02 (1.35–3.00)	.001
Placebo (vs ivermectin)	5.40 (3.54–8.25)	<.001
Kinyasini (vs Kilombero)	0.98 (0.54–1.78)	.951
Female sex (vs male sex)	0.68 (0.45–1.02)	.059
Age	0.97 (0.90–1.05)	.407
Days from treatment to last follow-up stool sample	1.01 (0.96–1.07)	.642

NOTE. Two-way interactions between the effects of the medications (interaction term: ivermectin × albendazole, ivermectin × mebendazole) and between the effects of schools and medications (interaction term: ivermectin × Kinyasini, albendazole × Kinyasini) were assessed. The outcome variable was a *T. trichiura* infection after treatment. Explanatory variables in parentheses ("vs variable") indicate the baseline of comparison. CI, confidence interval; OR, odds ratio.

The proportion of children coinfected with hookworm (range, 24%–29%) and the intensity of hookworm infection (range, 60–66 EPG) were similar in all groups. Concurrent infections with *A. lumbricoides* were found in 10%–13%; the GM was highest in the albendazole-placebo group (3401 EPG) and lowest in the mebendazole-ivermectin group (381 EPG).

Time difference for follow-up. Stool samples for follow-up were collected 22–39 days after treatment. The median follow-up period was 23 days in Kilombero and 30 days in Kinyasini (*P* < .001). The median follow-up period for the 4 treatment groups was 29 days for all groups (*P* = .954).

***CR and ERR against* T. trichiura.** By design, all children included in the primary analysis were infected with *T. trichiura* before treatment. The highest CR (55%) was achieved with a mebendazole-ivermectin combination, followed by albendazole-ivermectin (38%). Particularly low CRs were achieved when administering albendazole and mebendazole alone (10% and 19%, respectively) (Table 2).

Because there was no evidence of a statistically significant interaction between the effects of the medications (OR, 1.03; 95% CI, 0.43–2.44; Table 3), the effect of each drug on *T. trichiura* can be interpreted individually according to the results of the primary analysis. Mebendazole cured statistically significantly more *T. trichiura* than albendazole (OR, 2.05; 95% CI, 1.38–3.04), and ivermectin cured significantly more *T. trichiura* than placebo (OR, 5.40; 95% CI, 3.55–8.22). Hence, ivermectin has an additive effect on both albendazole and mebendazole. After adjusting for sex, age, and days to last follow-up stool sample, none of the estimates changed significantly. The addition of ivermectin to albendazole or mebendazole improved the CR from 14% to 47%, compared with placebo (Figure 2). Mebendazole, regardless of whether combined with ivermectin or placebo, showed a higher CR than the albendazole analogous treatments (37% vs 24%).

The pattern observed for ERRs was similar to that for CRs (Table 2). Medication with mebendazole-ivermectin resulted in the highest ERR (97%; bootstrap 95% CI, 95%–98%). Treatment with albendazole-ivermectin resulted in a statistically significant lower ERR (91%; 95% CI, 87%–94%), as indicated by nonoverlapping bootstrap CIs. Lowest ERRs were achieved when applying mebendazole (67%; 95% CI, 52%–77%) or albendazole (40%; 95% CI, 22%–56%) alone.

***Treatment outcome on hookworm and* A. lumbricoides.** Concurrent hookworm and *A. lumbricoides* infections were found in 25% and 12%, respectively, of the 548 children included in the primary analysis. The highest decreases in prevalence and intensity of hookworm infections were found within the albendazole-treated groups (Table 2). No drug combination was superior to albendazole treatment against *A. lumbricoides*.

AEs. Abdominal cramps were reported by 13% (72 of 564)
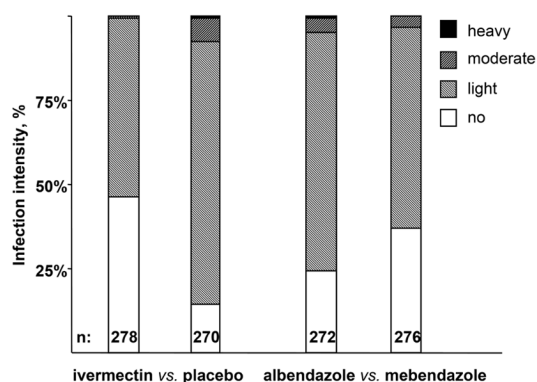
Figure 2. Independent treatment effects of albendazole versus mebendazole and of ivermectin versus placebo on infection intensities of *Trichuris trichiura* (administration of albendazole and mebendazole alone and in combination with ivermectin in a 2 × 2 factorial design). Infection intensities were classified according to World Health Organization cutoffs [17]. Intensity class *no* represents the cure rate; *light,* light infection intensities after treatment; *moderate,* moderate infection intensities after treatment, and *heavy,* heavy infection intensities after treatment.

of the participants, headache and fatigue by 5% (27 of 564), nausea by 5% (26 of 564), diarrhea and vertigo by 3% (19 of 564), and allergic reactions by 1.4% (8 of 564) (Table 4). Four children reported pruritus without rash, 4 had localized urticaria, and 6 reported shivering. Most AEs (72%; 166 of 229) were mild, the remaining 28% (63 of 229) were moderate. AEs were mainly self limiting. Relief through drugs was sought by 29 children, and 3 used local remedies.

The proportion and intensity of abdominal cramps were

slightly higher in the treatment regimens containing ivermectin, without statistical significance (OR, 1.30; 95% CI, 0.79–2.14) (Table 4). Girls reported vertigo statistically significantly less often than boys (OR, 0.22; 95% CI, 0.06–0.76). Older children were more likely to experience fatigue (OR, 1.53; 95% CI, 1.04–2.26) but reported less vomiting (OR, 0.71; 95% CI, 0.53–0.95) and diarrhea (OR, 0.81; 95% CI, 0.67–0.98). Children with moderate *T. trichiura* infection intensities at baseline were more likely to report shivering than those with light infections (OR, 6.76; 95% CI, 1.20–38.11).

DISCUSSION

We found low CRs with standard single-dose albendazole and mebendazole against *T. trichiura* infections among schoolchildren in Zanzibar, confirming results from a meta-analysis of randomized, placebo-controlled trials [6]. An albendazole-ivermectin combination resulted in a statistically significant higher CR against *T. trichiura*, hence supporting findings from 2 previous trials [8, 9]. A mebendazole-ivermectin combination—used for the first time against *T. trichiura*—resulted in statistically higher CRs and ERRs than any of the other treatments. High ERRs are particularly relevant for morbidity control.

Our results confirm previous findings reviewed by Olsen [11] (ie, elevated efficacy against *T. trichiura* when albendazole was combined with ivermectin) but contrast to findings from a Ugandan trial in which concurrent administration of ivermectin failed to enhance efficacy in curing *T. trichiura* infections in pregnant women [10]. However, in the Ugandan study, only 17 individuals were infected with *T. trichiura*; hence, results

Table 4. Adverse Events (AEs) Reported 48 Hours after Treatment with Albendazole or Mebendazole in Combination with Ivermectin or Placebo by Schoolchildren from Kinyasini and Kilombero on Unguja Island, Zanzibar (*n* = 564)

Characteristic	Albendazole plus placebo (n = 136) AEs	AEs of moderate intensity	Albendazole plus ivermectin (n = 144) AEs	AEs of moderate intensity	Mebendazole plus placebo (n = 143) AEs	AEs of moderate intensity	Mebendazole plus ivermectin (n = 141) AE	AEs of moderate intensity
Abdominal cramps	15 (11.0)	3	21 (14.6)	12	17 (11.9)	3	19 (13.5)	6
Fatigue	8 (5.9)	NA	4 (2.8)	NA	6 (4.2)	NA	9 (6.4)	NA
Headache	8 (5.9)	5	5 (3.5)	3	7 (4.9)	1	7 (5.0)	2
Nausea	5 (3.7)	1	11 (7.6)	4	3 (2.1)	2	7 (5.0)	0
Diarrhea	6 (4.4)	0	4 (2.8)	2	5 (3.5)	1	4 (2.8)	0
Vertigo	6 (4.4)	2	2 (1.7)	2	6 (4.2)	1	5 (3.5)	0
Fever	4 (2.9)	1	6 (4.2)	3	4 (2.8)	2	2 (1.4)	0
Vomiting	3 (2.2)	0	3 (2.1)	1	3 (2.1)	0	0 (0)	0
Allergic reaction	2 (1.7)[a]	0	5 (3.5)[a, b]	3	1 (0.7)[b]	1	0 (0)	0
Shivering	3 (2.2)	0	3 (2.1)	2	0 (0)	0	0 (0)	0
Total	60	12	64	32	52	11	53	8

Note. Data are no. or no. (%) of children who experienced AEs. NA, not applicable.
[a] Pruritus without rash.
[b] Localized urticaria.

have to be interpreted with caution. Compared with other trials, our trial found considerably lower CRs and ERRs with albendazole and mebendazole alone and an albendazole-ivermectin combination against *T. trichiura* [6, 10, 11]. A plausible explanation is that we used a more rigorous diagnostic approach with 4 Kato-Katz thick smears examined before and after treatment. Indeed, CRs would have been considerably higher if only duplicate Kato-Katz thick smears were examined before and after treatment: 60% for mebendazole-ivermectin, 53% for albendazole-ivermectin, 30% for mebendazole, and 21% for albendazole. A potential onset of drug resistance should be kept in mind, not least because of high anthelmintic drug pressure in Zanzibar during the past 15 years [12, 18, 19]. The low efficacy of albendazole against *T. trichiura* in our study is worrying also, because a prior spot-check had revealed a low CR of 25% in preschool-aged children, using a less rigorous diagnostic approach [18]. Although a trial conducted on the neighboring island Pemba in 1992–1993 had revealed similarly low CRs of albendazole and mebendazole against *T. trichiura* as found in our study, the ERR of albendazole against *T. trichiura* had been significantly higher (73%) [20]. An ERR <50% raises concern and should trigger more detailed investigations (eg, in vitro tests for further clarification of whether resistance is emerging), as has been previously suggested for schistosomiasis [21]. With the exception of the egg hatch assay for human hookworm [22, 23], in vitro tests for the biological confirmation of anthelmintic resistance have yet to be developed for human nematode infections.

Compared with CRs of other treatment options against *T. trichiura* (eg, combination therapies with pyrantel-oxantel [CR, 32%] [24] or mebendazole-levamisole [CR, 23%] or treatment with levamisole [CR, 10%] [19] or tribendimdine alone [CR, 0] [25]), the CRs observed in our study for the 2 ivermectin combined therapies were considerably higher.

The small groups for assessment of treatment outcomes of the 4 treatment regimens against hookworm and *A. lumbricoides* resulting from low prevalences of coinfections are a limitation of our study. The highest decrease in both prevalence and infection intensity was achieved with albendazole, regardless of whether it was combined with ivermectin, in line with previous findings [6, 26].

Regarding the helminth reinfection potential in Zanzibar, the follow-up period of 3–5 weeks after treatment might be considered another limitation of our study. Anthelmintic drug efficacy should be monitored 2–3 weeks after treatment [27]. However, an increase in time until the last follow-up stool sample after treatment was collected showed no association with *T. trichiura* infection in our study. Hence, potential reinfections should not have confounded our results.

The different treatments investigated here were safe, and AEs were transient and mostly mild. Nevertheless, compared with a previous review in which only gastrointestinal AEs occurred with a frequency of >1% [28], not only did we observe abdominal cramps and diarrhea, but also most other solicited AEs showed frequencies >1%. However, the frequency of AEs in our study may be overestimated because we did not assess pretreatment conditions, which may allow distinguishing between treatment-related and treatment-unrelated AEs. Importantly, the prevalence and intensity of soil-transmitted helminth infections in Zanzibar have significantly decreased during the past 15 years [12]. Because there might be higher rates of AEs in populations with higher infection rates and no previous treatment history, similar studies are needed to ensure like-for-like comparisons.

In conclusion, the addition of ivermectin to albendazole and mebendazole improves treatment outcomes against *T. trichiura* and will have an extra beneficial effect against an often coendemic but neglected soil-transmitted helminth, *Strongyloides stercoralis*, and against coendemic ectoparasites. These drug combinations may be considered in soil-transmitted helminth control programs and individual patient management.

Acknowledgments

References

1. Chan MS. The global burden of intestinal nematode infections—fifty years on. Parasitol Today **1997**; 13:438–443.
2. Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet **2006**; 367: 1521–1532.
3. Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis **2009**; 3:e412.
4. World Health Organization. Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. Geneva: World Health Organization, **2006**.
5. Smits HL. Prospects for the control of neglected tropical diseases by mass drug administration. Expert Rev Anti Infect Ther **2009**; 7:37–56.
6. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. JAMA **2008**; 299:1937–1948.
7. Keiser J, Utzinger J. The drugs we have and the drugs we need against major helminth infections. Adv Parasitol **2010**; 73:197–230.
8. Belizario VY, Amarillo ME, de Leon WU, de los Reyes AE, Bugayong MG, Macatangay BJ. A comparison of the efficacy of single doses of

albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp. Bull World Health Organ **2003**; 81:35–42.

9. Beach MJ, Streit TG, Addiss DG, Prospere R, Roberts JM, Lammie PJ. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. Am J Trop Med Hyg **1999**; 60:479–486.

10. Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. Am J Trop Med Hyg **2008**; 79:856–863.

11. Olsen A. Efficacy and safety of drug combinations in the treatment of schistosomiasis, soil-transmitted helminthiasis, lymphatic filariasis and onchocerciasis. Trans R Soc Trop Med Hyg **2007**; 101:747–758.

12. Knopp S, Mohammed KA, Rollinson D, et al. Changing patterns of soil-transmitted helminth infections in Zanzibar in the context of national control programs. Am J Trop Med Hyg **2009**; 81:1071–1078.

13. Knopp S, Mohammed KA, Khamis IS, et al. Spatial distribution of soil-transmitted helminths, including *Strongyloides stercoralis,* among children in Zanzibar. Geospat Health **2008**; 3:47–56.

14. Fleiss JL. The measurement of interrater agreement: statistical methods for rates and proportions. 2nd ed. New York: Wiley, 1981:212–236.

15. Knopp S, Mohammed KA, Stothard JR, et al. Patterns and risk factors of helminthiasis and anemia in a rural and a periurban community in Zanzibar, in the context of helminth control programs. PLoS Negl Trop Dis **2010**; 4:e681.

16. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in schistosomiasis mansoni. Rev Inst Med Trop São Paulo **1972**; 14:397–400.

17. Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioli L. Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level. Geneva: World Health Organization, **1998**.

18. Stothard JR, Rollinson D, Imison E, Khamis IS. A spot-check of the efficacies of albendazole or levamisole, against soil-transmitted helminthiases in young Ungujan children, reveals low frequencies of cure. Ann Trop Med Parasitol **2009**; 103:357–360.

19. Albonico M, Bickle Q, Ramsan M, Montresor A, Savioli L, Taylor M. Efficacy of mebendazole and levamisole alone or in combination against intestinal nematode infections after repeated targeted mebendazole treatment in Zanzibar. Bull World Health Organ **2003**; 81:343–352.

20. Albonico M, Smith PG, Hall A, Chwaya HM, Alawi KS, Savioli L. A randomized controlled trial comparing mebendazole and albendazole against *Ascaris, Trichuris* and hookworm infections. Trans R Soc Trop Med Hyg **1994**; 88:585–589.

21. World Health Organization. The World Health Report 1999: making a difference. Geneva: World Health Organization, **1999**.

22. Albonico M. Methods to sustain drug efficacy in helminth control programmes. Acta Trop **2003**; 86:233–242.

23. Albonico M, Wright V, Ramsan M, et al. Development of the egg hatch assay for detection of anthelminthic resistance in human hookworms. Int J Parasitol **2005**; 35:803–811.

24. Albonico M, Bickle Q, Haji HJ, et al. Evaluation of the efficacy of pyrantel-oxantel for the treatment of soil-transmitted nematode infections. Trans R Soc Trop Med Hyg **2002**; 96:685–690.

25. Steinmann P, Zhou XN, Du ZW, et al. Tribendimidine and albendazole for treating soil-transmitted helminths, *Strongyloides stercoralis* and *Taenia* spp.: open-label randomized trial. PLoS Negl Trop Dis **2008**; 2:e322.

26. Marti HP, Haji HJ, Savioli L, et al. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. Am J Trop Med Hyg **1996**; 55:477–481.

27. Scherrer AU, Sjöberg MK, Allangba A, et al. Sequential analysis of helminth egg output in human stool samples following albendazole and praziquantel administration. Acta Trop **2009**; 109:226–231.

28. Horton J. Albendazole: a review of anthelmintic efficacy and safety in humans. Parasitology **2000**; 121(suppl):S113–132.