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Efficacy and Safety of Albendazole and High-Dose Ivermectin Coadministration in School-Aged Children Infected With *Trichuris trichiura* in Honduras: A Randomized Controlled Trial

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Background. The efficacy of currently available anthelminthics against *Trichuris trichiura* infections is significatively lower than for other soil-transmitted helminths. The combination of ivermectin (IVM) and albendazole (ALB) has shown significant improvements in efficacy.

Methods. Safety and efficacy randomized controlled clinical trial comparing 3 experimental regimens against ALB monotherapy for the treatment of *T. trichiura* infections in northern Honduras. Infected children were randomized to 4 treatment arms: arm 1, single-dose ALB (400 mg); arm 2, single-dose ALB (400 mg) plus IVM (600 μg/kg); arm 3, ALB (400 mg) for 3 consecutive days; or arm 4, ALB (400 mg) plus IVM (600 μg/kg) for 3 consecutive days. Efficacy was measured based on the egg reduction and cure rates, both assessed 14–21 days after treatment, using the Kato-Katz method. Safety was evaluated by analyzing the frequency and severity of adverse events.

Results. Of 176 children randomized to 1 of the 4 treatment arms, 117 completed treatment and follow-up. The egg reduction rates for arms 1, 2, 3, and 4 were 47.7%, 96.7%, 72.1%, and 100%, respectively; with *P* values <.001 for comparisons between IVM groups and ALB-only arms. The cure rates were 4.2%, 88.6%, 33.3%, and 100%, respectively. A total of 48 adverse events (85.4% mild) were reported in 36 children.

Conclusions. The combined use of ALB and high-dose IVM is a highly effective and well tolerated treatment for the treatment of *T. trichiura* infections, offering significantly improved treatment for the control of this infection.

Clinical Trials Registration. NCT04041453.

Keywords. ivermectin; albendazole; soil-transmitted helminths; anthelminthic; *Trichuris trichiura*.

Human infections by *Trichuris trichiura* are still widespread in tropical and subtropical impoverished regions of the world, with an estimated prevalence of >460 million cases, affecting mostly school-aged children [1, 2]. Although commonly asymptomatic, the infection can cause asthenia, abdominal pain, diarrhea, anemia, and the more severe *Trichuris* dysentery syndrome [1]. Chronicity of these infections can affect cognition and school performance [3]. Trichuriasis is included in the group of soil-transmitted helminth (STH) infections targeted for control by the World Health Organization (WHO)–led strategy, which recommends preventive chemotherapy through mass drug administration (MDA) of benzimidazoles for school- and preschool-aged children in communities with an STH prevalence ≥20% [4]. Since the introduction of these large scale programs in 2012, >2.8 billion tablets of these drugs have been distributed for implementation [5]; still, the Global Burden of Disease Study estimated almost no reduction in the prevalence of *T. trichiura* [2].

The efficacy of currently available anthelminthic drugs against *T. trichiura* is significantly lower than for other STHs, such as *Ascaris lumbricoides* and hookworms. In a systematic review, the efficacy of albendazole (ALB) in single-dose regimens was calculated to produce a cure rates (CR) of 31% (95% confidence interval [CI], 21%–42%) and an egg reduction rates (ERR) of 50% (95% CI, 39%–61%). For mebendazole (MEB), the CR was 42% (95%

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CI, 26%–60%), and the ERR 66% (55%–77%) [6]. As an additional concern, the same systematic review identified significantly reduced CRs for both drugs in studies published after the year 2000. Furthermore, modeling studies estimating the number of MDA rounds required for *T. trichiura* control concluded that, given the current effectiveness of these drugs, breaking transmission for this parasite would not be attainable [7]. Added to improvements in drug efficacy, provision of adequate water and sanitation are critical for a sustainable control of STH.

The addition of ivermectin (IVM) to either ALB or MEB treatment has shown significant, although suboptimal, improvements in efficacy compared with either drug alone. Such combination is promising since IVM is also effective for *Strongyloides stercoralis* and other neglected tropical diseases, such as lymphatic filariasis, onchocerciasis, and scabies [8, 9]. With a favorable safety profile and a wide therapeutic index [10], IVM is currently prescribed in weight-based, or height-based, dosing regimens, unlike ALB or MEB, which are prescribed in fixed doses for any person ≥2 years old. This article presents safety and efficacy results from a trial comparing experimental multiple-day regimens and high-dose IVM drug combinations against ALB monotherapy for the treatment of *T. trichiura* infections in children from endemic areas of Honduras.

METHODS

Study Design

The study was a phase II randomized, open-label, controlled, outcome assessor–blinded, clinical trial.

Ethical Approval

The study received clearance from the research ethics committee of the master's program in infectious and zoonotic diseases at the National Autonomous University of Honduras, the Brock University Research Ethics Board, and the Sanitary Regulation Agency of Honduras. In addition, it was authorized by the regional office of the Honduran Health Ministry. Participants provided written parental consent and children's assent (for children ≥9 years old) before enrollment. The study was registered at ClinicalTrials.gov (NCT04041453).

Study Area

The clinical trial took place in 2 Honduran rural villages, La Hicaca and San Juan Pueblo. Both sites had been identified with STH prevalences >50% [11, 12]. In La Hicaca, sustained transmission of *T. trichiura* has been observed, with the latest study reporting >60% prevalence for this species [13].

Eligibility Criteria

The study included children 2–14 years of age infected with *T. trichiura* and with a body weight ≥15 kg. Exclusion criteria included anthelminthic treatment within the 3 previous months, allergies to anthelminthic drugs, acute clinical conditions (including gastrointestinal symptoms), pregnancy, and puerperium.

Sample Size

Sample size was calculated estimating the efficacy of the different experimental drug or combinations and gathering the individual samples sizes for the study. The sample size was calculated using a 1-tailed test for pairwise comparisons of the expected CRs for 4 study groups—17% for single-does ALB, 55% for single-dose ALB-IVM, 85% for 3-dose ALB-IVM, and 60% for 3-dose AL—with an overall significance level of 5% adjusted for multiple tests by Bonferroni correction and 80% power and inflated for 10% loss to follow-up. The estimated sample size was 177 participants, included 39 participants for single-dose ALB (arm 1), 57 for single-dose ALB-IVM (arm 2), 24 for 3-dose ALB (arm 3), and 57 for 3-dose ALB-IVM (arm 4).

Baseline Procedures to Determine Eligibility

All children aged 2–14 years from La Hicaca and children enrolled in grades 1–3 in San Juan Pueblo were invited to participate in the study. On enrollment, weight (in kilograms) and height (in centimeters) were recorded to calculate height-for-age *z* score, weight-for-age *z* score, and body mass index–for-age *z* score (BMIZ), using WHO AnthroPlus software, version 1.0.4.

To identify trichuriasis, a single fecal sample was collected from each participant and examined through the Kato-Katz method within 30–60 minutes of preparation. Quality control reexamination was performed in 100% of the negative and 10% of the positive samples. Infection intensities were classified as light, moderate, or heavy infections, according to WHO guidelines [14]. Children whose Kato-Katz result was negative for *T. trichiura* but positive for any other STHs were provided 3-day ALB treatment free of charge.

Randomization Phase

Simple centralized randomization was performed through a computer-based random generated list (with varying random blocks) to assign children to 1 of the 4 treatment arms. Group assignments were concealed from researchers performing the diagnostic tests.

Intervention

Treatments were administered by physicians. Participants were randomly assigned to the 4 treatment arms: arm 1, single-dose ALB (400 mg); arm 2, single-dose ALB (400 mg) plus IVM (600 μg/kg); arm 3, ALB (400 mg) for 3 consecutive days; or arm 4, ALB (400 mg) plus IVM (600 μg/kg) for 3 consecutive days. The drugs administered were ALB (400-mg tablets) and IVM (6-mg scored tablets) (Nematel and Iver-P, respectively, by Elea/Phoenix). The IVM 6-mg scored tablets were used in all cases at a dose of 0.6 mg/kg/d, based on baseline weight rounding to the lower full (6-mg) or half (3-mg)

dose. Before treatment, a standard meal was provided. with an approximate nutritional value of 377 Cal (47% carbohydrates, 36% fat, and 17% protein), to assure optimal systemic availability of the drugs in all participants and to prevent bias related to different oral absorption of study medication between participants. At the end of the trial, participants remaining positive for *T. trichiura* received an additional 3-day ALB (400 mg) treatment.

Safety Assessment

To assess drug safety, the following data were gathered and classified according to severity: (1) adverse events (AEs) and (2) laboratory determinations of alanine aminotransferase and aspartate aminotransferase levels. Physical examination was performed by physicians immediately before and 4 hours after treatment. Participants were monitored for 4 hours after receiving medication, in view of the proposed link between the maximum concentration and toxicity for IVM [15]. A structured questionnaire to identify visual disturbances was included.

Blood samples for laboratory analysis were collected 4 hours after drug administration on the first and last days of treatment (in cases of 3-day treatment arms), and abnormalities were classified according to National Institutes of Health guidelines [16]. Hemoglobin concentrations were measured, and anemia was determined based on hemoglobin values according to age [17].

Efficacy Assessment

The primary outcome of this clinical trial was CR against *T. trichiura* at 14–21 days after treatment in a single Kato-Katz specimen, based on WHO guidelines [18]. The secondary outcome was *T. trichiura* ERR at the same end point.

Drug Concentration Assessment

To determine systemic drug concentrations from each participant at 4 hours after treatment (approximate time to peak blood concentration for ALB and IVM in humans), 2 droplets (approximately 70 µL) of blood were transferred onto filter paper cards (Western blotting filter paper; Thermo Scientific) and dried at room temperature, placed in sealed plastic bags with silica gel desiccant, and stored at room temperature for further high-performance liquid chromatographic analysis.

To extract ALB/metabolites and IVM, blood samples were punched from dried blood spot cards and transferred to a polypropylene tube (5 mL). The samples were spiked with 10 µL of oxibendazole or moxidectin internal standard, respectively, followed by 1 mL of acetonitrile-water (4:1 vol/vol). After shaking (15 minutes), sonication (90 minutes) in an ultrasonic bath (90 minutes), and centrifugation (2300*g* for 10 minutes at 4°C), the liquid fraction was transferred to a 5-mL glass tube and evaporated to dryness under a gentle stream of dry nitrogen at 56°C in a water bath. The chromatographic conditions for ALB and IVM analyses were previously reported by Ceballos et al [19] and Lifschitz et al [20], respectively.

A complete validation was performed of the analytical procedures for the extraction and quantification of ALB and its metabolites, ALB sulfoxide (ALBSO) and ALB sulfone and IVM in dried blood spots. The chromatographic identification of either ALB and its metabolites or IVM was undertaken by comparison with retention times of pure reference standards. The linearity of the method was tested after elaboration of analytical calibration curves using 70-µL drops of human blood, previously fortified, transferred onto filter paper, and dried for 1 hour. The calibration curves of all analytes showed good linearity with correlation coefficients >0.995. The calibration range was 0.2–2 µg/mL (ALB, ALBSO, and ALB sulfone) or 5–200 ng/mL (IVM).The extraction efficiency of the analytes was determined by comparison of the peak areas from fortified blank samples with the peak areas from direct injections of equivalent quantities of standards. Mean absolute recovery percentages ranged between 80% and 92.1%. The limit of quantification defined as the lowest measured concentration with a coefficient of variation of <20%, accuracy of ±20%, and an absolute recovery of <70%, was 0.2 mg/mL for ALB/metabolites and 5 ng/mL for IVM.

Statistical Analysis

Statistical analyses were done using Stata software (Stata SE version 16.1; StataCorp). CRs were calculated as the percentage of *T. trichiura*–positive participants at baseline who became egg negative after treatment, with a 95% CI. Arithmetic mean egg counts were calculated for each treatment arm before and after treatment to assess the corresponding ERR, using the following formula: ERR = [1 – (mean EPG at follow-up/mean EPG at baseline)] × 100, where EPG represents eggs per gram of stool. CIs for ERR were calculated using bootstrap resampling methods with 10 000 replicates [21]. Descriptive statistics for continuous variables and frequency (proportion) for categorical variables were used to describe demographic, nutritional, and parasitological characteristics of the studied population. One-way analysis of variance with Bonferroni correction was conducted to determine if nutritional characteristics differed between infection intensities. Differences in proportions were determined by means χ^2 or Fisher exact test for categorical variables and Student *t* test for continuous variables following a normal distribution. Statistical associations to determine the relationship between drug concentrations and frequency of AEs were estimated through logistic regression analysis adjusted by age and sex.

RESULTS

Recruitment

A total of 377 participants were assessed for eligibility: 279 from La Hicaca and 98 from San Juan Pueblo. Of those, 176 were enrolled and randomized to 1 of the 4 treatment arms (Figure 1), including 38 participants in arm 1 (97% of recruitment target), 57 in arm 2 (100%), 23 in arm 3 (96%), and 58 in arm 4 (102%), representing 99% of the recruitment target overall. However, owing to the emergence of the COVID-19 pandemic in Honduras in March 2020, the research team was unable to return to San Juan Pueblo and assess treatment efficacy in 53 participants. Altogether, 117 children completed participation for the assessment of treatment efficacy, and 117 stool samples were analyzed to determine CR and ERR (Figure 1). This was communicated to the Data Safety and Monitoring Board, which, based on preliminary analysis of the available data, recommended that the study be terminated, and the data analyzed.

Screened Population

Among the screened participants (N = 377), trichuriasis was the most prevalent infection (52%), with 25% of these infections of moderate to heavy intensity. In terms of nutritional indicators, it was observed that the mean BMIZ value in participants with low-intensity infections was 0.259, compared with a significantly lower mean value of −0.239, in participants with infections of moderate to heavy intensity ($P = .04$). No significant difference was identified in BMIZ between children with low-intensity trichuriasis and those without infection ($P > .99$).

Study Population

The baseline characteristics of the study population included in the efficacy analysis (n = 117) are shown in Table 1. No significant differences were found between treatment arms for any of the evaluated characteristics, demonstrating the homogeneity between groups.

Efficacy

CRs and ERRs against *T. trichiura* for the 117 participants who completed treatment and follow-up are shown in Table 2. A low CR of just 4.2% (95% CI, .7–20.2) was observed in arm 1 (single-dose ALB [400 mg]). All experimental arms demonstrated significantly higher CRs against *T. trichiura* compared with arm 1 (Table 2). ALB (400 mg) for 3 consecutive days (arm 3) resulted in a higher CR than single-dose ALB (arm 1) (33.3% vs 4.2%, respectively; $P < .05$). No significant associations between intensity of infection and CRs were found in any of the treatment arms.

Combined administration of IVM/ALB resulted in a significantly higher ERRs compared with monotherapy arms, showing reductions of 96.7% (95% CI, 96.2%–96.9%) and 100% (95% CI, 96.3%–100%), for arms 2 and 4, respectively ($P < .001$). The

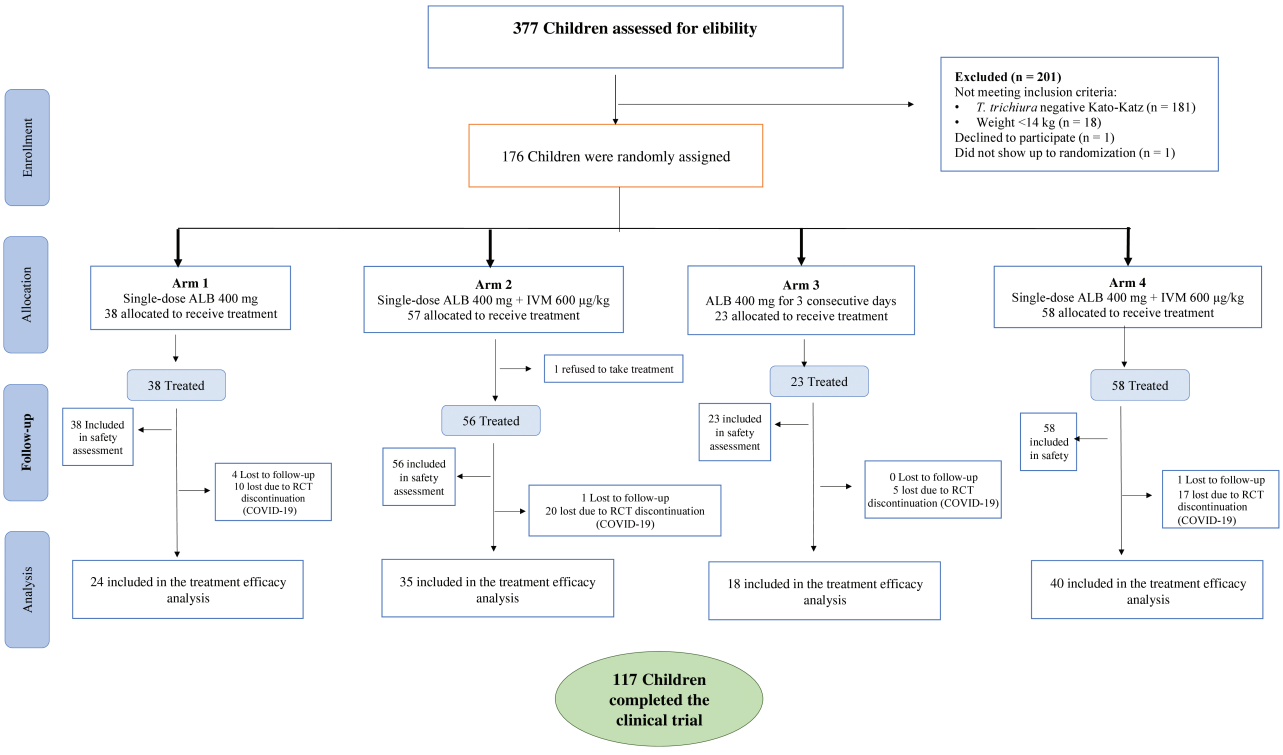

Figure 1. Flow diagram of the randomized controlled trial (RCT) assessing efficacy and safety of albendazole (ALB) and high-dose ivermectin (IVM) coadministration in school-aged children infected with *Trichuris trichiura* in Honduras. Abbreviation: COVID-19, coronavirus disease 2019.

Table 1. Characteristics of Population Recruited to Participate in the Study, by Treatment Arm (n = 117)

Characteristic	Single Dose		3 Daily Doses		*P* Value[a]
	Arm 1: ALB (n = 24)	Arm 2: ALB- IVM (n = 35)	Arm 3: ALB (n = 18)	Arm 4: ALB-IVM (n = 40)	
Age, mean (SD), y	8.8 (2.9)	8.1 (2.5)	8.9 (2.1)	8.2 (2.5)	.61[b]
Female sex, no. (%)	12 (50)	15 (42.9)	10 (55.6)	20 (50)	.84
Nutritional indicators, no (%)[c]					
Stunting	9 (37.5)	7 (20)	2 (11.1)	11 (27.5)	.24
Underweight	2 (13.3)	2 (8.3)	0 (0)	5 (16.1)	.54
Thinness	1 (4.2)	1 (2.9)	1 (5.6)	0 (0)	.44
Hemoglobin, mean (SD), g/dL	13 (0.6)	12.9 (0.8)	12.9 (0.7)	12.9 (0.8)	.89[b]
Parasitic profile					
EPG, mean (95% CI)	1402.4 (1383.8–1421.0)	1593.5 (1580.6–1606.4)	1233.1 (1219.5–1246.8)	1159.7 (1149.2–1170.3)	.96[b]
Moderate-to-heavy *Trichuris trichiura* infection, no. (%)	3 (12.5)	7 (20)	5 (27.8)	10 (25)	.60

Abbreviations: CI, confidence interval; EPG, eggs per gram of stool; IVM, ivermectin; SD, standard deviation.

[a]Calculated with Pearson χ^2 or Fisher exact tests unless otherwise noted.

[b]Calculated with 1-way analysis of variance.

[c]Stunting was defined as height-for-age *z* score <2 SDs below the mean; underweight, as weight-for-age *z* score <2 SDs below the mean; and thinness, as body mass index–for-age z score <2 SDs below the mean. Underweight was not calculated in children >10 years of age, per World Health Organization recommendation; these included 15 children in arm 1, 24 in arm 2, 12 in arm 3, and 31 in arm 4.

ERR after treatment with 3-day ALB was significantly higher than that after single-dose ALB ($P < .05$).

Drug Concentrations

Both ALB (and metabolites) and IVM were detectable 4 hours after treatment. ALBSO was the main analyte detected in blood samples after ALB administration, and IVM was detected in all blood samples of children from arms 2 and 4 (Table 3).

Safety Assessment

A total of 175 participants were included in the safety assessment. Thirty-six participants reported 48 adverse events (AEs). No serious AEs were noted in this study, and the control arm had the lowest frequency of AEs. The most common AEs were headache and abdominal pain, both with similar frequencies in the experimental arms (Table 4). Photophobia was reported by only 4 participants, 1 receiving IVM. Overall, 41 of the 48 reported AEs (85.4%) were mild, and 7 (14.6%) were moderate. All AEs resolved without medical intervention within 48 hours of treatment completion. Based on the physicians' judgment and timing of AE onset with respect to drug intake, it was determined that 22 of 48 reported AEs (45.8%) were possibly related to treatment administration.

Mean blood concentrations of IVM did not differ significantly between children with and those without treatment-related AEs ($P = .82$). Similarly, no significant differences were identified in the occurrence of AEs between groups with or without IVM treatment ($P = .56$). Conversely, mean ALB blood concentrations differed significantly between children with and those without AEs ($P < .05$). Logistic regression analysis—controlled by age and sex—identified a significant association between AEs and ALB blood levels, with an OR of 2.25 (95% CI,

Table 2. Cure and Egg Reduction Rates by Treatment Arms (n = 117)

CRs and ERRs	Single Dose		3 Daily Doses	
	Arm 1: ALB (Control Arm)	Arm 2: ALB-IVM	Arm 3: ALB	Arm 4: ALB-IVM
CR data				
Positive before treatment, no.	24	35	18	40
Cured after treatment, No.	1	31	6	40
CR (95% CI), %	4.2 (.7–20.2)	88.6 (74.0–95.5)	33.3 (16.3–56.2)	100.0 (96.3–100.0)
P value (vs control arm)[a]	…	<.001	<.05	<.001
ERR data				
EPG before treatment, mean (95% CI)	1402.4 (1383.8–1421.0)	1593.5 (1580.6–1606.4)	1233.1 (1219.5–1246.8)	1159.7 (1149.2–1170.3)
EPG after treatment, mean (95% CI)	732.9 (726.8–739.1)	54.2 (53.3–55.1)	343.9 (339.5–348.4)	0
ERR (95% CI), %	47.7 (46.8–48.7)	96.7 (96.2–96.9)	72.1 (71.2–73.0)	100.0 (96.3–100.0)
P value (vs control arm)[b]	…	<.001	.01	<.001

Abbreviations: ALB, albendazole; CI, confidence interval; CR, cure rate; EPG, eggs per gram of stool; ERR, egg reduction rate; IVM, ivermectin.

[a]Calculated with Fisher exact test.

[b]Calculated with Dunn pairwise comparison test.

Table 3. Albendazole Sulfoxide and Ivermectin Blood Concentrations

	Single Dose		3 Daily Doses			
			Arm 3: ALB		Arm 4: ALB-IVM	
Concentration[a]	Arm 1: ALB	Arm 2: ALB-IVM	d 1	d 3	d 1	d 3
ALBSO, µg/mL						
Mean (SD)	0.64 (0.24)[b]	0.94 (0.57)[b]	0.67 (0.25)	0.66 (0.27)	0.71 (0.25)	0.76 (0.29)
Range	0.156–1.13	0.29–2.26	0.41–1.20	0.28–1.30	0.28–1.35	0.34–1.62
IVM, ng/mL						
Mean (SD)	…	35.5 (17.9)	…	…	42.9 (25.9)	50.4 (29.7)
Range	…	9.17–83.3	…	…	10–131.7	4.30–141.3

Abbreviations: ALB, albendazole; ALBSO, ALB sulfoxide; IVM, ivermectin; SD, standard deviation.

[a]Concentrations were measured 4 hours after treatment in children treated with IVM (0.6 mg/kg) as a single oral dose (arm 2) or for 3 consecutive days (arm 4) and with ALB (400 mg) as a single oral dose (arms 1 and 2) or for 3 consecutive days (arms 3 and 4).

[b]Significant difference between arms 1 and 2 ($P < .05$).

1.26–3.99; $P < .05$) for 0.5-µg/mL increments of blood drug concentration.

DISCUSSION

The current trial found a significant positive impact of high-dose IVM on the efficacy of ALB when coadministered in either single or 3-day regimens compared with the standard of practice in public health interventions. Despite the trial interruption due to the coronavirus disease 2019 pandemic (117 children completed the trial, and 53 did not), differences still reached statistical significance. This was due to the lower than estimated efficacy of the control arm (ALB [400 mg]) and the higher than estimated efficacy of both IVM-containing arms (1-day and 3-day ALB-IVM).

Previous studies have reported STH prevalences >50% in multiple regions of Honduras [11, 22, 23], and according to a 2018 review, the country—despite MDA campaigns—has an overall STH prevalence >50% in 40.6% of its municipalities [12]. In the present study, *T. trichiura* was the most prevalent STH, in agreement with previous reports [13, 22, 23]. Only 20% of *T. trichiura* infections in this study were of moderate or heavy intensity, as shown in previous reports from the same region [23].

Table 4. Safety Profile by Treatment Arm (n = 175)

	Single Dose				3 Daily Doses				
	Arm 1: ALB (n = 38)		Arm 2: ALB-IVM (n = 56)		Arm 3: ALB (n = 23)		Arm 4: ALB-IVM (n = 58)		
Type of AE	Affected/ at Risk, %	AEs, No.	Affected/ at Risk, %	AEs, No.	Affected/ at Risk, %	AEs, No.	Affected/ at Risk, %	AEs, No.	Total AEs, No.
Total	…	1	…	15	…	13	…	19	48
Eye disorders									
Photophobia	0	0	0	0	13	3	1.7	1	4
Blurred vision	0	0	0	0	4.3	1	0	0	1
GI disorders									
Abdominal pain	0	0	14	8	13	3	6.9	4	15
Vomiting	0	0	0	0	0	0	3.4	2	2
Diarrhea	0	0	1.8	1	0	0	0	0	1
Respiratory disorders									
Common cold	0	0	0	0	4.3	1	1.7	1	2
Cough	0	0	0	0	0	0	1.7	1	1
Asthma	0	0	0	0	4.3	1	0	0	1
General disorders									
Headache	0	0	8.8	5	8.7	2	13.8	8	15
Nausea	0	0	1.8	1	0	0	0	0	1
Pruritus	0	0	0	0	8.7	2	1.7	1	3
Liver enzyme disorders									
Grade 2 toxicity[a]	2.6	1	0	0	0	0	1.7	1	2

Abbreviations: AE, adverse event; ALB, albendazole; GI, gastrointestinal; IVM, ivermectin.

[a]Defined as serum aspartate aminotransferase and alanine aminotransferase levels 2.6–5 times the upper limit of normal.

Controlling *T. trichiura* infections remains challenging, and new treatment approaches with adequate efficacy across STHs are needed [24]. Multiple studies have explored the benefits of anthelminthic combination therapy [8, 25–29], and IVM has been of particular interest owing to its broad spectrum [10, 30, 31]. In fact, WHO has added IVM to its "essential medicines" list for the treatment of STHs [32]. CRs in this trial demonstrate the superior efficacy of single-dose ALB-IVM against trichuriasis, compared with ALB monotherapy (CR, 88.6% vs 4.2%, respectively). An extremely low CR for ALB against *T. trichiura* has been previously documented [28], and although the efficacy of ALB improves with 3-day administration, it is still significantly lower than that of combined treatments. The plasma ALB concentration was used to rule out low oral bioavailability as an explanation for ALB's low efficacy, which was consistent with previous ALB pharmacokinetic data [33, 34]. The resistance of *T. trichiura* to benzimidazoles remains to be investigated among study participants, but a 2019 study in the same area documented the absence of β-tubulin–related mutations [23].

Ascending doses (200, 400, and 600 μg/kg) of IVM monotherapy have been compared with placebo, demonstrating poor efficacies throughout the dosing range [26]. Our results for systemic exposure to high-dose IVM are consistent with previous reports, although unlike the previous studies, we did not find a correlation between drug concentration and thinness (as assessed by BMIZ) [33], probably owing to the homogeneity of BMIZ values in our study population and the high variability observed in blood drug concentrations.

Safety of IVM and ALB has been widely demonstrated as both have been extensively used in MDA programs [35, 36]. Previous studies report a low frequency of AEs, most of them of mild to moderate intensity [31]. Moreover, trials exploring the safety of combination therapy in comparison with ALB monotherapy do not report significant differences in the frequency or severity of AEs [8, 37]. Our results are not only consistent with previous data regarding ALB and IVM safety but they also suggest that combination therapy with a high dose of IVM could be safely administered to children.

Similar to previously reported studies, the present trial did not identify any correlation between AEs and mean IVM systemic concentrations [10, 38].We did find, however, a significant association between ALB blood levels and AEs, regardless of coadministration of IVM. This finding was unexpected and suggests that a greater absorption of ALB and its metabolites might result in an increased incidence of AEs.

Among the limitations of this trial, we did not explore the added value of high-dose rather than standard-dose IVM. With the evidence generated by this and other studies on the safety of the high-dose regimen (600 μg/kg), future trials would be in a better position to tackle this question [26]. Although multiple Katz-Katz specimens might provide more precision on the baseline intensity of infection, owing to daily fluctuation in ova excretion, a single Kato-Katz specimen, as used in the current study, has demonstrated adequate performance in drug efficacy assessments [39, 40]. Another limitation to consider is the study interruption due to the coronavirus disease 2019 pandemic, which resulted in the recruitment of a smaller sample than the original target. Finally, larger studies are required to confirm our findings.

In summary, the combined use of ALB and high-dose IVM shows significant efficacy and good tolerability for the treatment of *T. trichiura* infections, thus offering significantly improved treatment for the control of this STH species, which is notoriously refractory to the current standard of care.

Notes

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