

Efficacy and safety of albendazole and high-dose ivermectin co-administration in school-aged children infected with *Trichuris trichiura* in Honduras: A Randomized Controlled Trial

Gabriela Matamoros<sup>1-2</sup>, Ana Sánchez<sup>1-2</sup>, José Antonio Gabrie<sup>2</sup>, Marisa Juárez<sup>3</sup>, Laura Ceballos<sup>4</sup>, Andrés Escalada<sup>3</sup>, Carol Rodríguez<sup>5</sup>, Helena Martí-Soler<sup>6</sup>, María Mercedes Rueda<sup>5</sup>, Maritza Canales<sup>5</sup>, Carlos Lanusse<sup>4</sup>, Pamela Cajal<sup>3</sup>, Luis Álvarez<sup>4</sup>, Rubén O. Cimino<sup>3</sup>, Alejandro Krolewiecki<sup>3-4</sup>

<sup>1</sup> Instituto de Investigaciones en Microbiología, Universidad Nacional Autónoma de Honduras

<sup>2</sup> Faculty of Applied Health Sciences, Brock University, Ontario, Canada.

<sup>3</sup> Instituto de Investigaciones de Enfermedades Tropicales (IIET-CONICET), Sede Regional Orán, Universidad Nacional de Salta, Argentina.

<sup>4</sup> Laboratorio de Farmacología, Centro de Investigación Veterinaria de Tandil (CIVETAN), UNCPBA-CICPBA-CONICET, Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires, Tandil, Argentina.

<sup>5</sup> Escuela de Microbiología, Universidad Nacional Autónoma de Honduras

<sup>6</sup> ISGlobal, Hospital Clínic- Universitat de Barcelona, Barcelona, Spain,

**Corresponding author:** Alejandro Krolewiecki. Instituto de Investigaciones de Enfermedades Tropicales. UNSa. Alvarado 751 (4530). Orán, Argentina. TE: +5491131838673. Email: alekrol@hotmail.com

**Key Points.** The combination of albendazole and high-dose ivermectin in this randomized clinical trial demonstrated significant superiority and good tolerability for the treatment of *Trichuris trichiura* infections compared to albendazole monotherapy, the current standard of practice in mass drug administration campaigns.

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## Abstract

### Background

The efficacy of currently available anthelmintics against *Trichuris trichiura* infections is significantly lower than for other soil-transmitted helminths (STH). 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 one of the following treatments: (Arm 1) single-dose ALB 400 mg; (Arm 2) single-dose ALB 400 mg/IVM 600 µg/kg; (Arm 3) ALB 400 mg for 3 consecutive days; or (Arm 4) ALB 400 mg/IVM 600 µg/kg for 3 consecutive days. Efficacy was measured through egg reduction rate (ERR) and cure rate (CR), 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

A total of 176 children were randomized to one of the 4 treatment arms, 117 completed treatment and follow-up. The ERR for Arms 1 to 4 were: 47.7%, 96.7%, 72.1% and 100%, respectively; with p-values <0.001 between IVM groups and ALB only arms. The CRs were 4.2%, 88.6%, 33.3% and 100%, respectively. A total of 48 (85.4% mild) AEs 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 a significantly improved treatment for the control of this infection.

**Keywords:** ivermectin; albendazole; soil-transmitted helminths; anthelmintic; *Trichuris trichiura*

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## Introduction

Human infections by *Trichuris trichiura* are still widespread in tropical and subtropical impoverished regions of the world, with an estimated prevalence of over 460 million cases affecting mostly school-age 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 helminths (STH) infections targeted for control by the WHO led strategy, which recommends preventive chemotherapy (PC) through mass drug administration (MDA) of benzimidazoles for school and pre-school age children in communities with an STH prevalence  $\geq 20\%$  [4]. Since the introduction of these large scale programs in 2012, over 2.8 billion tablets of these drugs have been distributed for their implementation [5]; still, the Global Burden of Disease Study estimated an almost no reduction in the prevalence of *T. trichiura* [2].

The efficacy of currently available anthelmintic drugs against *T. trichiura* is significantly lower than for other STH such as *Ascaris lumbricoides* and hookworms. In a systematic review, the efficacy of albendazole (ALB) in single-dose regimens was calculated to produce cure rates (CR) of 31% (95%CI 21-42), and egg reduction rates (ERR) of 50% (95%CI 39-61). For mebendazole (MEB), the CR was 42% (95%CI 26-60) and ERR 66% (95%CI 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. Further, modelling 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 to either drug alone. Such combination is promising since IVM is also effective for *Strongyloides stercoralis* and other neglected tropical diseases (NTDs) 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, or height, based dosing regimen, unlike ALB or MEB which are prescribed in fixed doses for any person  $\geq 2$  years old. This study presents safety and efficacy results of a trial comparing 3 experimental regimens that tested 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**

Phase II randomized, open label, controlled, outcome assessor blinded, clinical trial.

### **Ethical approvals**

The study received clearance from the research ethics committee of the master program in Infectious and Zoonotic Diseases (CEI-MEIZ) at the National Autonomous University of Honduras, the Brock University Research Ethics Board, and the Sanitary Regulation Agency of Honduras. Additionally, the study was authorized by the regional office of the Honduran Health Ministry. Participants provided written parental consent and children's assent (for children  $\geq 9$  years-old) prior to their enrollment. The study was registered at ClinicalTrials.gov # NCT04041453.

## Study area

The clinical trial took place in two 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 between 2-14 years of age infected with *T. trichiura* and a body weight  $\geq 15$  kg. Exclusion criteria included: anthelmintic treatment within 3 previous months, allergies to anthelmintic drugs, acute clinical conditions (including gastrointestinal symptoms), pregnancy or 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 by a one-tail test for pairwise comparisons of the expected CR for four study groups — ALB, CR: 17%; ALB+IVM, CR: 55%; ALB+IVM x 3d, CR: 85%; ALB x 3d, CR: 60% — with an overall significance level of 5% adjusted for multiple tests by Bonferroni's correction, 80% power and inflated for 10% lost-to-follow-up. The estimated sample size was of 177 participants (single dose ALB: 39, single dose ALB/IVM: 57, 3-dose ALB: 24, 3-dose ALB/IVM: 57).

## Baseline procedures to determine eligibility

All children aged 2-14 years from La Hicaca and children enrolled in first through third grade in San Juan Pueblo were invited to participate in the study. Upon enrollment, weight (kg) and height (cm) were recorded to calculate height-for-age Z-score (HAZ), weight-for-age Z-score

(WAZ), and body-mass-index-for-age Z-score (BMIZ) using WHO AnthroPlus version 1.0.4 (WHO, Geneva, Switzerland).

To identify trichuriasis, a single fecal sample was collected from each participant and examined through the Kato-Katz method within 30–60 min 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 was negative for *T. trichiura* but positive for any other STH 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 one of the four treatment arms. Group assignments were concealed from researchers doing the diagnostic tests.

### **Intervention**

Treatments were administered by physicians. Participants were randomly assigned to one of the four following treatments: (1) single-dose ALB 400 mg; (2) single-dose ALB 400 mg + IVM 600 µg/kg; (3) ALB 400 mg for 3 consecutive days; or (4) ALB 400 mg + 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, Argentina). IVM 6 mg scored tablets were used in all cases at a dose of 0.6mg/kg/day based on baseline weight rounding to the lower full (6mg) or half (3mg) dose. Prior to treatment, a standard meal with an approximate nutritional value of 377 Cal (47% carbohydrates, 36% fat and 17% protein) was provided, 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:

i) adverse events (AE) and ii) laboratory determination of ALT and AST. Physical examination was performed by physicians immediately before and 4 h after treatment. Participants were monitored for 4 h, after receiving medication in view of the proposed link between  $C_{max}$  and toxicity for IVM [15]. A structured questionnaire to identify visual disturbances was included.

Blood samples for laboratory analysis were collected 4 h after drug administration on the first and last day of treatment (in cases of 3-day treatment arms), and abnormalities were classified following the National Institute of Health (NIH) 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 post-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 h after treatment (approximate time to peak blood concentration for ALB and IVM in humans), 2 droplets (~70  $\mu$ L) of blood were transferred onto filter paper cards (Western blotting filter paper,

Thermo scientific USA) and dried at room temperature, placed in sealed plastic bags with silica gel desiccant and stored at room temperature for further HPLC analysis.

To extract ALB/metabolites and IVM, blood samples were punched from dried blood spot (DBS) cards and transferred to a polypropylene tube (5 mL). The samples were spiked with 10  $\mu$ L of oxibendazole or moxidectin internal standard (IS), respectively. Followed by 1 mL of acetonitrile/water (4:1 v/v). After shaking (15 min), sonication (90 min) in an ultrasonic bath (90 min), and centrifugation (2300  $\times$ g, 10 min, 4  $^{\circ}$ 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  $^{\circ}$ C in a water bath. The chromatographic conditions for ALB and IVM analysis were previously reported by Ceballos *et al.*, [19] and Lifschitz *et al.*, [20], respectively.

A complete validation of the analytical procedures for the extraction and quantification of ALB and its metabolites, ALB sulphoxide (ALBSO) and ALB sulphone (ALBSO<sub>2</sub>) and IVM in DBS was performed. 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  $\mu$ L drops of human blood previously fortified, transferred onto filter paper and dried for 1 h. The calibration curves of all analytes showed good linearity with correlation coefficients >0.995. The calibration range was between 0.2-2  $\mu$ g/mL (ALB, ALBSO and ALBSO<sub>2</sub>) and 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 CV <20%, accuracy of  $\pm$  20% and absolute recovery <70%, was 0.2 mg/mL for ALB/metabolites and 5 ng/mL for IVM.

## Statistical Analysis

Statistical analyses were done using STATA (Stata SE version 16.1 StataCorp, USA). CRs were calculated as the percentage of *T. trichiura* positive participants at baseline who became egg-negative after treatment, considering a 95% confidence interval (CI). Arithmetic mean egg counts were calculated for each treatment arm before and after treatment to assess the corresponding ERR, using the following formula:  $ERR = (1 - [\text{mean EPG at follow-up} / \text{mean EPG at baseline}]) \times 100$ . CIs for ERR were calculated using bootstrap resampling methods with 10,000 replicates [21]. Descriptive statistics for continuous variables and frequency (proportions) for categorical variables were used to describe demographic, nutritional, and parasitological characteristics of the studied population. A one-way ANOVA with Bonferroni correction was conducted to determine if nutritional characteristics differed between infection intensities. Differences in proportions were determined by Chi-square 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 one of the 4 treatment arms (Figure 1). Enrollment for each arm in both communities were for arms 1 to 4, respectively: 38 (97%), 57 (100%), 23 (96%), and 58 (102%), representing 99% of the recruitment target. However, due 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 (Fig 1). This was communicated to the Data Safety and Monitoring Board (DSMB), which based on preliminary analysis of the available data, recommended that the study be terminated, and 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 to a significantly lower mean value of -0.239, on those participants with moderate to heavy intensity ( $p = 0.036$ ). No significant difference was identified in BMIZ score values in children with low-intensity trichuriasis versus those without infection ( $p > 0.99$ ).

### **Study Population**

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

### **Efficacy**

CRs and ERRs against *T. trichiura* for the 117 participants that completed treatment and follow-up are shown in Table 2. Low CR of just 4.2% (95% CI: 0.7-20.2) was observed in Arm 1 (ALB 400 mg single-dose). All experimental arms demonstrated significantly higher CRs against *T. trichiura* compared to Arm 1 (Table 2). ALB 400 mg during 3 consecutive days (Arm 3) resulted in a greater CR when compared to ALB single-dose (Arm 1) (33.3% vs

4.2%,  $p < 0.05$ ). 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 ERR compared to monotherapy arms, showing a reduction of 96.7% (95% CI, 96.2-96.9) and 100% (95% CI, 96.3-100), for arm 2 and arm 4, respectively ( $p < 0.001$ ). Egg reduction after treatment with 3-day ALB was significantly higher than with single-dose ( $p < 0.05$ ).

### **Drug concentrations**

Both ALB (and metabolites) and IVM were detectable 4 h 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 (36) participants reported 48 adverse events (AE). 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 frequency in the experimental arms (Table 4). Photophobia was only reported by four participants, one of them receiving IVM. Overall, 41/48 (85.4%) of the reported AEs were mild and 7/48 (14.6%) were moderate. All AEs resolved without medical intervention within 48 h of treatment completion. Based on the physicians' judgment and timing of AEs onset with respect to drug intake, it was determined that 22 out of 48 reported AEs (45.8%) were possibly related to treatment administration.

Mean blood concentrations of IVM were not statistically different between children with and without treatment-related AEs ( $p = 0.8197$ ). Similarly, no statistically significant differences were identified in the occurrence of AEs between groups with and without IVM ( $p = 0.560$ ).

Conversely, mean ALB blood concentrations were significantly different between children with and without AEs ( $p < 0.05$ ). A logistic regression analysis—controlled by age and sex—identified a significant association between AEs and ALB blood levels, with an OR = 2.25 (95% CI: 1.26-3.99,  $p < 0.05$ ) for increments of 0.5  $\mu\text{g/mL}$  of blood drug concentration.

## DISCUSSION

This trial found a significant positive impact of high-dose IVM on the efficacy of ALB when co-administered at either single or 3-day regimens compared to the standard of practice in public health interventions. Despite the trial interruption due to the COVID-19 pandemic (117 children completed the trial, 53 did not), statistical differences still reached 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 (ALB/IVM 1-day and ALB/IVM 3-day).

Previous studies have reported STH prevalences above 50% in multiple regions of Honduras [11, 22, 23] and according to a recent 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* is 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].

Controlling *T. trichiura* infections remains challenging and new treatment approaches with adequate efficacies across STH are needed [24]. Multiple studies have explored the benefits of anthelmintic combination therapy [8, 25-29] and IVM has been of particular interest due to its broad-spectrum [10, 30, 31]. In fact, WHO has recently added IVM to its Essential Medicine List for the treatment of STH [32]. CRs in this trial demonstrate the superior efficacy of ALB+IVM at single-dose against trichuriasis, (88.6%) compared to a significantly lower CR of ALB monotherapy (4.2%). Extremely low CR of ALB against *T. trichiura* has

been previously documented [28], and although ALB efficacy improves if administered for 3 days, it is still significantly lower than combined treatments. Through the determination of ALB plasma concentration, a low oral bioavailability of the product was ruled out to explain the low efficacy of ALB, which was found at levels consistent with previous ALB pharmacokinetic data [33, 34]. *T. trichiura* resistance to benzimidazoles remains to be investigated among the study participants, but a recent study in the same area documented the absence of  $\beta$ -tubulin related mutations [23].

Ascending doses (200  $\mu\text{g}/\text{kg}$ , 400  $\mu\text{g}/\text{kg}$  and 600  $\mu\text{g}/\text{kg}$ ) of IVM monotherapy have been recently studied versus placebo, demonstrating poor efficacies throughout the dosing range [26]. Our results on the systemic exposure of high-dose IVM are consistent with previous reports, although unlike them, we did not find a correlation between drug concentration and thinness (as assessed by BMIZ) [33], probably due 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 AE, 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 suggest that combination therapy with a high dose of IVM could be safely administered to children.

Similar to previous reports, 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 co-administration of IVM. This finding was unexpected and suggests that a greater absorption of ALB and its metabolites might result in an increase incidence of AEs.

Among the limitations of this trial, we did not explore the added value of high-dose rather than standard doses of 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 to the baseline intensity of infection due to daily fluctuation in ova excretion, a single Kato-Katz as used in this study, has demonstrated adequate performance in drug-efficacy assessments [39, 40]. Another limitation to consider is the study interruption due to the COVID-19 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 a significant efficacy and good tolerability for the treatment of *T. trichiura* infections, thus offering a significantly improved treatment for the control of this STH species, which is notoriously refractory to the current standard of care.

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## NOTES

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### **Authors contributions**

Study design: GM, AS, AK

Writing protocol: AK, GM, ROC, AS

Literature search: GM, ROC, AK

Data collection: MJ, CR, LA, PC, MMR

Database maintenance and supervision: GM, AK, MJ, LA

Laboratory analyses: GM, LS, AE, CR, MMR, MC, CL, PC, LA, LC

Data analysis: HMS, JAG, GM

Data interpretation: GM, AK, AS, LA

Writing: GM, AS, AK

Coordination: AS, AK

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#### Potential conflicts:

AK: received honoraria for lectures by Elea/Phoenix laboratories. AK, ROC, MJ, AE, LA, CL, LC, PC: received grant support from Elea/Phoenix laboratories for other research projects to their Institutions. GM no conflict, AS no conflict, JAG no conflict, CR no conflict, HMS no conflict, MMR no conflict, MC no conflict.

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Table 1. Characteristics of population recruited to participate in the study per treatment arm (n=117)

Characteristics	Single dose		3 days dose		p value <sup>a</sup>
	ALB n=24	ALB+IV M n=35	ALB n=18	ALB+IV M n=40	
Age — mean (SD)	8.8 (2.9)	8.1 (2.5)	8.9 (2.1)	8.2 (2.5)	0.611 <sup>b</sup>
Girls	12 (50%)	15 (42.9%)	10 (55.6%)	20 (50%)	0.835
<b>Nutritional indicators</b>					
Stunting (< -2 SD HAZ)	9 (37.5%)	7 (20%)	2 (11.1%)	11 (27.5%)	0.238
Underweight (< -2 SD WAZ) <sup>c</sup>	2 (13.3%)	2 (8.3%)	0 (0%)	5 (16.1%)	0.543
Thinness (< -2 SD BMIZ)	1 (4.2%)	1 (2.9%)	1 (5.6%)	0 (0%)	0.439
Hemoglobin (g/dL) — mean (SD)	13 (0.6)	12.9 (0.8)	12.9 (0.7)	12.9 (0.8)	0.887 <sup>b</sup>
<b>Parasitic profile</b>					
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)	0.960 <sup>b</sup>
Moderate-to-heavy infections by <i>Trichuris trichiura</i>	3 (12.5%)	7 (20%)	5 (27.8%)	10 (25%)	0.602

<sup>a</sup> Calculated from Pearson Chi2 or Fisher's exact test. <sup>b</sup> Calculated from one-way ANOVA. <sup>c</sup> Not calculated in children older than 10 years of age as per WHO recommendation (ALB, n=15; ALB+IVM, n=24; ALB x 3 days, n=12; ALB+IVM x 3 days, n=31). SD: standard deviation; HAZ: height-for-age Z-scores; WAS: weight-for-age Z-scores; BMIZ: body mass-index-for-age Z-score.

Table 2. Cure rates and egg reduction rates for treatment arms (n=117)

	Single dose		3-day dose	
	ALB (Control arm)	ALB+IVM	ALB	ALB+IVM
<b>CURE RATE (CR)</b>				
Positive before treatment	24	35	18	40
Cured after treatment	1	31	6	40
CR (95% CI)	4.2% (0.7-20.2)	88.6% (74.0-95.5)	33.3% (16.3-56.2)	100.0% (96.3-100.0)
<i>P</i> -value vs control arm <sup>a</sup>	-	< 0.001	<0.05	<0.001
<b>EGG REDUCTION RATE (ERR)</b>				
EPG Before treatment — <i>mean</i> (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 — <i>mean</i> (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)
<i>P</i> -value vs control arm <sup>b</sup>	-	<0.001	0.012	<0.001

CR: Cure rate; EPG: eggs per gram of stool; ALB: albendazole IVM: Ivermectin

<sup>a</sup> Calculated from Fisher's exact test, <sup>b</sup> Calculated from Dunn's pairwise comparison test

Table 3. Albendazole sulphoxide (ALBSO) and Ivermectin (IVM) blood concentration

	Single Dose		3-day dose			
	ALB	ALB+IVM	ALB		ALB+IVM	
			Day 1	Day 3	Day 1	Day 3
ALBSO ( $\mu\text{g/mL}$ )	$0.64 \pm 0.24^a$	$0.94 \pm 0.57^a$	$0.67 \pm 0.25$	$0.66 \pm 0.27$	$0.71 \pm 0.25$	$0.76 \pm 0.29$
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 ( $\text{ng/mL}$ )		$35.5 \pm 17.9$			$42.9 \pm 25.9$	$50.4 \pm 29.7$
Range		9.17- 83.3			10-131.7	4.30-141.3

Concentrations are expressed as (mean  $\pm$  SD and range) measured at 4 h post-treatment in children treated with IVM (0.6 mg/kg) as a single oral dose (Arm 2) or during 3 consecutive days (Arm 4) and with albendazole (ALB, 400 mg) as a single oral dose (Arm 1 and 2) or during 3 consecutive days (Arm 3 and 4).

<sup>a</sup> Statistically significant difference between mean value concentration of arm 2 vs arm 1 ( $p < 0.05$ )

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**Table 4.** Safety profile for treatment arms (n=175)

	Single dose				3-day dose				Total events
	ALB (n=38)		ALB+IVM (n=56)		ALB (n=23)		ALB+IVM (n=58)		
	Affected/at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	
Total		1		15		13		19	48
<b>Eye disorders</b>									
Photophobia	0	0	0	0	13	3	1.7	1	4
Blurred vision	0	0	0	0	4.3	1	0	0	1
<b>Gastrointestinal disorders</b>									
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
<b>Respiratory disorders</b>									
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
<b>General disorders</b>									
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
<b>Liver enzymes</b>									
Grade 2 toxicity*	2.6	1	0	0	0	0	1.7	1	2

\*AST and ALT = 2.6-5 x upper limit of normal for serum (ULN)



**Figure 1.** Flow diagram of the randomized controlled trial assessing efficacy and safety of albendazole and high-dose ivermectin co-administration in school-aged children infected with *Trichuris trichiura* in Honduras

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Figure 1

