HI4T trial

Prospective, parallel-group, open-label randomized controlled trial of four treatment regimens for trichuriasis in pediatric patients

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HI4T Trial - PROTOCOL SYNOPSIS

STUDY IDENTIFICATION	Prospective, parallel-group, open-label randomized controlled trial of four treatment regimens for trichuriasis in pediatric patients. HI4T trial.
TYPE AND DEVELOPMENT CLINICAL PHASE	Phase II non-inferiority randomized clinical trial
SPONSOR	Fundacion Mundo Sano, Spain
INVESTIGATOR	Dr. Lilian Sosa, Principal Invetigator Alejandro J. Krolewiecki, MD, PhD. General Coordination
STUDY CENTERS	• Universidad Autonoma de Honduras **Laboratory centers:** • Genetics Research Center. UNAH, Tegucigalpa, Honduras • Lanusse lab. CIVETAN, UNCPBA - Tandil, Argentina (pk). • Cimino lab, IIET, UNSa – Orán, Argentina (resistance)
ETHICAL COMMITTEE APPROVAL	CEI-MEIZ, UNAH, HON & Brock University, Canada.
OBJECTIVES	**Primary endpoints** Cure rate (CR) (conversion from being egg positive pre-treatment to egg negative post-treatment) for Trichuris infection will be assessed using the quadruple Kato-Katz method at 14 to 21 days post-treatment. **Secondary endpoints** • To evaluate the safety and tolerability of the interventions. • To measure the egg reduction rate of the different treatment arms against *T. trichiura*. • To validate the multi-parallel qPCR for the determination of efficacy outcomes. • To determine the presence of isolates with resistance to the study drugs in the pre and post treatment isolates. • To determine population pk parameters of IVM through a population pk approach.
DESIGN AND METHODOLOGY	Phase II, open label randomized, controlled, parallel groups clinical trial in patients infected with at *T. trichiura*.

TREATMENT ARMS	• Group 1: single dose of ALB 400 mg. (active control arm). N:39 • Group 2: single dose ALB 400mg + IVM 600µg/Kg. N: 57 • Group 3: daily dose ALB 400mg for 3 consecutive days. N:24 • Group 4: daily dose ALB 400mg + IVM 600µg for 3 consecutive days. N:57 Total Study Population: 177
INCLUSION AND EXCLUSION CRITERIA	**Inclusion Criteria** The study population will consist of participants who meet the following selection criteria: 1. Individuals of both sexes infected with *T. trichiura*. 2. Weight ≥15 kg. 3. Age: 2 to 14 years old. 4. Free acceptance to participate in the study by obtaining signed informed consent form approved by the EC. **Exclusion Criteria** Participants meeting the following criteria cannot be selected: 1. Intake ALB, mebendazole and/or IVM within the previous 3 months. 2. Background of allergy, idiosyncrasy or hypersensitivity to drugs or its excipients. 3. Acute clinical conditions (including diarrhea). 4. Participation in another clinical trial during the 3 months preceding the drug administration. 5. Pregnancy.
SAMPLES COLLECTION	Fresh stool sample in a 60ml plastic container at screening. One sample 14 to 21 days post treatment
ANALYTICAL METHODS	**Efficacy outcomes:** • Single Kato Katz. • Multiparallel qPCR **Safety:** frequency, distribution and severity of AEs and SAEs. **Resistance:** molecular biology **PK:** HPLC
Study medication	**Albendazole:** Nematel, ELEA Argentina. 400mg tabs **Ivermectin:** IVER P, ELEA Argentina. 6mg tablets

Introduction - Justification

Infection with *T. trichiura* is highly prevalent in Honduras and principally affects pediatric populations leading to growth and development impairment.

Various medications have been approved for the treatment of *T. trichiura* infection, including albendazole (ALB) and mebendazole (MBZ), both belonging to the benzimidazole family (BZ). These treatments (especially ALB) are used in Honduras during mass-drug administration campaigns.

Currently, the recommended treatment regimen is a single-dose of 400 mg of albendazole (ALB); however, the efficacy of this drug is considerably limited against *T. trichiura* infection (17%, CI of 95% 8 – 31%). This limited efficacy has raised concerns due to an increase in the

proportion of patients with this infection in areas where treatment is regularly administered. Several explanations for this limited efficacy have been explored, including lack of treatment compliance, the amount of time the parasite is exposed to the drug in the intestine, and more recently, the emergence of parasitic resistance to ALB.

Due to ALB low efficacy as well as its limited spectrum, other countries have started using ivermectin (IVM) for the treatment of helminths. Trials using ivermectin have demonstrated its high tolerability and safety. Studies involving adults using high dosages of ivermectin showed good safety profile (doses of up to 10 times (10x) the 200µg/kg).

Higher IVM doses didn't result in differences of adverse events in comparison with a placebo. Ivermectin has also been utilized for treating *Pediculosis capitis* in pediatric populations. The approved dose of 400 µg/kg in these clinical trials was well tolerated with only 1.8% of patients (7 of 398) suspending the treatment due to adverse effects (a similar proportion to the group that received 0.5% malathion lotion).

It has been demonstrated, especially in parasitic infections of veterinary importance, that using a single medication to treat parasitic infections can contribute to the emergence of anthelminthic resistance.

The combination of two different drugs is currently considered the best route for avoidance of resistance. This also helps in reaching target levels of prevalence set out by control campaigns.

In accordance with preliminary information, the combination of albendazole/ivermectin (ALB/IVM) could have increased benefits in terms of efficacy without increasing adverse effects.

The present study is proposing the use of a high dose of IVM (600 µg/kg of weight) in children, with the purpose of determining the safety, tolerability and efficacy of this treatment co-administered with albendazole.

The results of this study will help determine if the co-administration of a simplified dose of IVM/ALB is a viable treatment for *T. trichiura* infection among endemic populations.

The study communities of La Hicaca and surrounding villages are located in Honduras. Previous studies performed by our research group in these communities have found a prevalence of >60% in children up to 14 years of age.

Methodology

We propose a prospective clinical trial, with parallel control groups, randomized and incorporating four different treatment regimens (dose-ranging arms), as follows:

- **Arm 1:** Single dose of ALB* 400mg (Active control arm)
- **Arm 2:** Single dose of ALB 400mg + IVM** 600µg/Kg
- **Arm 3:** Daily dose ALB 400mg / 3 consecutive days
- **Arm 4:** Daily dose ALB 400mg + IVM 600µg/kg 3 consecutive days

*ALB (ALBENDAZOL): Nematel® 400mg tablets

**IVM (IVERMECTINA): Iver P® 6mg tablets

Pair comparisons for efficacy:

- (P1) Arm 1 vs Arm 2 (ALB vs ALB/IVM600)
- (P2) Arm 1 vs Arm 3 (ALB vs ALB x 3)
- (P3) Arm 1 vs Rama 4 (ALB vs ALB/IVM600 x3)
- (P4) Arm 2 vs Arm 4 (ALB x 3 vs ALB/IVM600 x3)

Sample size calculation

Sample Size calculation was based on the following:

H_{null} p1 = p2 = p3 = p4

$H_{Alternative}$: p2 > p1

p3 > p1

p4 > p1

p4 > p2

$$n = \frac{\left\{ z_{1-\alpha}\sqrt{\bar{p}(1-\bar{p})} - z_{\beta}\sqrt{w_2 p_1(1-p_1) + w_1 p_2(1-p_2)} \right\}^2}{w_1 w_2 \left(p_2 - p_1\right)^2}$$

ARM	Expected Cure Rate	Lost-to-follow-up	Sample Size	Inflated lost to follow up
ALB	17%	10%	35	39
IVM-ALB	55%	10%	51	57
(IVM-ALB) x3	85%	10%	51	57
ALB x3	60%	10%	21	24
Total				**177**

With this information, expected efficacy and size of the population**, we have calculated a required sample size of 177 between 2 and 14 years of age children infected with *T. trichiura*.**

Population - Study procedures

A parasitological survey will be conducted including at least 295 children within the community of La Hicaca and surroundings villages to identify infected children.

After attending an informational meeting and obtaining parental consent and children's assent, all participants will be required to provide information for a short enrollment form. They will then undergo clinical physical exam to determine their health status. Anthropometric measurements (height and weight) will also be collected to estimate standard nutritional indications, according to the following international regulations:

- Body Mass Index (BMI): (BMI for ages 5 – 19)
- Height-for-age: (5-19 years of age)
- Weight-for-age: (5-10 years of age)

Stunted growth, low weight and thinness will be determined using the Anthroplus 2007 software (version 1.0.4) and will be defined as being -2 standard deviations (SD) away from the mean height-for-age, weight-for-age and BMI for age, respectively.

As a precaution, girls who report having commenced menarche (first menstrual period), will be requested to provide a urine sample to rule out pregnancy.

Exclusion Criteria:

- Weight less than 15 kg
- Having taken antiparasitic treatment (ALB, MBZ or IVM) in the past 3 months
- History of allergies, idiosyncrasy or hypersensitivity to the medications (IVM and ALB) used in this study.
- Acute clinical conditions (including diarrhea), based on the clinician investigator judgement
- Participation in another clinical trial within the last 3 months prior to administration of the treatment
- Pregnancy

Once participants are enrolled, a stool sample will be requested to obtain baseline information regarding intestinal parasitic infections.

Those participants who are parasitized only by *T. trichiura* will be enrolled in the clinical trial. Prior to the treatment administrations, blood samples will be collected to establish baseline measurements of hepatic enzymes Alanine transaminase (ALT) and aspartate transaminase (AST) and hemoglobin. Following, participants will be randomly divided into the following groups:

- Arm 1: Single dose ALB 400mg (control group)
- Arm 2: Single dose of ALB 400mg + IVM 600µg/kg
- Arm 3: Daily dose of ALB 400mg for 3 consecutive days
- Arm 4: Daily dose of ALB 400mg + IVM 600µg/kg for 3 consecutive days

Four hours after treatment has initiated, a capillary blood sample will be collected via finger puncture (finger prick) from every participant in Arms 2 and 4 to determine the pharmacokinetics of the IVM (plasma concentration at 4, 24, and 72 hours following administration). Once the assigned regimen has been completed, each participant will undergo a clinical evaluation and a measurement of hepatic enzymes to monitor treatment safety (**safety tests**).

Anemia Diagnosis

Hemoglobin concentration will be determined by the HemoCue method (HemoCue AB, Sweden. www.hemocue.com) which requires a capillary blood sample (by finger prick).

Table 1
Haemoglobin levels to diagnose anaemia at sea level (g/l)±

Population	Non -Anaemia*	Anaemia*		
		Mild[a]	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100-109	70-99	lower than 70
Children 5 - 11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12 - 14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

± Adapted from references 5 and 6
* Haemoglobin in grams per litre
a "Mild" is a misnomer: iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent.

Hepatic Enzymes (Transaminases) (Safety Test)

Alanine transaminase (ALT) and aspartate transaminase (AST) levels will be determined by a private clinical laboratory, which will receive the anonymized samples (bearing only the participant identification code). The reference values will be determined by the laboratory but the most common ones are of the following ranges:

ALT = 0 – 40 U/L

AST = 0 – 40 U/L

Should there be any participant with altered hepatic enzymes, they will be examined clinically and undergo another test at the end of the study.

Establishing Parasitic Infection

Stool samples from study participants will be collected and kept refrigerated in coolers. Same day analysis will be done via the Kato-Katz method, following WHO recommendations. A total egg count for each helminthic species will be done and expressed as the number of eggs per gram (EPG) of stool. Based on the EPG, an intensity of infection will be determined, including the categories light, moderate or heavy. Aliquots of each sample using each 95% ethanol and 10% formalin will be preserved for molecular analysis and diagnosis of protozoan infection, respectively.

Treatment Efficacy

To determine treatment efficacy, a method determining "cure rate" (CR) will be used. Cure rate is defined the percentage of subjects who no longer pass eggs after treatment (with a 0-egg count per gram of stool at the end of the treatment period). The formula is as follows:

$$\mathrm{CR} = 100\% \times \left(1 - \frac{\text{number of subjects excreting eggs at follow-up}}{\text{number of subjects excreting eggs at baseline}}\right)$$

Comparison of Kato Katz vs multi-panel qPCR for evaluating treatment efficacy

A quantitative qPCR analysis will be done for the determination of intensity of infection in the stool samples provided by the participants, with the purpose being to compare these results with those of the Kato Katz technique. The agreement between both methods will be estimated using the Kappa statistic, which sets out to measure level of agreement between techniques. Values of κ = 0, 0.01-0.20, 0.21-0.4, 0.41-0.60, 0.61-0.80, 0.81-1 are interpreted as poor agreement, light agreement, moderate agreement, considerable agreement and excellent agreement, respectively.

Identification of genetic mutations associated with BZ resistances before and after treatment

DNA from *T. trichiura* will be extracted from the eggs found in stool samples provided by participants. This DNA will then be analyzed via the qPCR technique, using specific primers for the detection of single-nucleotide polymorphisms (SNPs) associated with resistance to benzimidazoles. The results will be presented using descriptive statistics.

The research participants will be involved in the following procedures:

1. Attend informational meeting where they will receive an invitation letter (Appendix 1) (duration: 30 min)
2. Provide with informed consent: Parents or legal guardians will sign the informed consent (Appendix 2) and children older than 9 years will provide assent (Appendix 3)
3. Fill the enrollment format (10 min) (Appendix 4)
4. Clinical history format and physical examination (15 min) (Appendix 5)
5. Anthropometric measurements (5 min) (Appendix 6)
6. Venipuncture (3 min) (protocol can be found here: https://brocku.ca/research-at-brock/wp-content/uploads/sites/73/REB-Guideline-Phlebotomy.pdf)
7. Finger prick (5 min) (protocol can be found here: https://brocku.ca/research-at-brock/wp-content/uploads/sites/73/SOP02-Finger-Prick-Blood-Sampling-edit.pdf)
8. Provide fecal samples before receiving treatment and again at 14-21 days after receiving treatment (Appendix 7).

Summary of participation

	Pre-enrollment	Enrollment	Baseline	Day 2	Day 3	Day 14-21
Day	- 30 to -2	-7 to -1	0	1	2	14-23
Stool sample	X					X
Eligibility to RTC		X				
Consent/Assent	X					
Clinical evaluation Safety		X	X	X	X	X
Anthropometry		X				
Randomization			X			
Treatment*			X	X[b]	X[b]	
Sample for PK*			X		X[b]	
Safety tests (Liver enzymes)			X		X[b]	X[c]
Urine pregnancy test		X[d]				

a. Applicable only to Arms with one-day treatment

b. Applicable only to Arms with 3-day treatment

c. Applicable only to research participants with abnormal liver enzymes in previous visits

d. Applicable only to female participants that experienced menstruation already

Adverse effects

Treatment used in the study

Oral administration of albendazole is safe but may cause rare mild and reversible adverse effects such as headache, vomit, diarrhea, abdominal pain, gastrointestinal discomfort, dizziness, hepatic function alterations, fever, leukopenia and very rarely pancytopenia. Similarly, ivermectin is a safe drug but may cause mild and reversible adverse effects such as headaches, dizziness, diarrhea, vomit, muscle pain, ocular irritation, drowsiness, hepatic function alteration and rarely postural hypertension.

Stool Sample Collection

Participants will have to collect their own stool samples, which may expose them to pathogens present in their own sample.

Venipuncture

To measure hepatic enzyme levels, 2 blood draws will be done in all participants across the four study arms. This may cause transient pain, hematoma, vasovagal attack and in extremely rare cases, infection of the puncture site.

Finger prick

To determine hemoglobin levels and IVM pharmacokinetics, various finger punctures will take place, which may cause transient pain, slight bruise, sometimes vasovagal attack and in extremely rare cases, infection of the puncture site.

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