



RESEARCH ARTICLE

REVISED **Effect of high-intensity versus low-intensity praziquantel treatment on HIV disease progression in HIV and *Schistosoma mansoni* co-infected patients: a randomised controlled trial**
[version 2; peer review: 3 approved]

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Abstract

Background: It has been hypothesised that *Schistosoma* co-infection exacerbates HIV progression, and hence anthelmintic intervention in co-infected individuals will delay it. We evaluated effects of high-intensity versus low-intensity praziquantel treatment of schistosomiasis on HIV disease progression among co-infected patients from fishing populations around Lake Victoria, Uganda.

Methods: Between August 2012 and September 2015, we conducted an open-label randomised, controlled trial. Adults, antiretroviral therapy-naïve, CD4 counts ≥ 350 cells/ μ l, HIV and *S. mansoni* co-infected, were randomised 1:1 to praziquantel (40mg/kg) given quarterly (starting at enrolment) or annually (starting 12 weeks after enrolment; such that low-intensity participants were still untreated when sampled at 12 weeks). A non-randomised HIV-positive *S. mansoni*-negative comparison group was recruited. The primary outcome was mean change in plasma viral load at 12 and 60 weeks.

Results: In total 363 participants (high-intensity 113, low-intensity 113, comparison group 137) were recruited; 96 (85.0%), 97 (85.8%) and 107 (78.1%) completed 60 weeks of follow up, respectively. Adjusting for baseline age and viral load, the geometric mean ratio (aGMR [95%CI]) viral load for high-intensity vs low-intensity groups at 12 weeks was 0.90 [0.65, 1.25] $p=0.55$ and at 60 weeks 1.88 [0.78, 4.53] $p=0.16$. Results in the comparison group were similar to trial arms. High-intensity, compared to low-intensity, treatment resulted in substantially lower *S. mansoni* prevalence at all follow up visits

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($p < 0.05$).

Conclusions: In communities with a high burden of both *S. mansoni* and HIV infection, high-intensity treatment of *S. mansoni* does not delay HIV progression despite relevant benefit for parasite clearance.

Trial registration: [ISRCTN15371662](https://www.isrctn.com/ISRCTN15371662) (17/11/2016)

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

HIV, Schistosoma, co-infection, high-intensity praziquantel treatment, disease progression

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REVISED Amendments from Version 1

Following reviewers' comments, we made the following adjustments:

- Introduction section-we have added reference to Dr Watson's HEAT trial.
- Methods section-we have added a section on Allocation concealment.
- Various sections of the manuscript-we have minimally edited some sentences as reviewers suggested.

See referee reports

Introduction

HIV and helminth co-infections are common in resource constrained settings. Globally, an estimated 25% of HIV-positive individuals are reported to be co-infected¹⁻⁴. In Africa this figure is estimated at 50%⁵. Some studies have suggested that helminth co-infection could lead to faster HIV progression⁶⁻⁹. If this is true, interventions that treat helminths could help to avert HIV disease progression among co-infected people.

An observational study conducted in Ethiopia among HIV-positive individuals co-infected with *Ascaris* or *Trichuris* showed a decrease in HIV plasma viral load after treatment of helminths with albendazole¹⁰; however, a systematic review that included a randomised trial and four observational studies found that evidence regarding the benefit of anti-helminth therapy for HIV viral load, CD4 count, and clinical progression was inconclusive¹¹. Subsequently, in Entebbe, Uganda, we found that treating pregnant women with albendazole resulted in a modest decrease in HIV load¹². With the exception of the large "HEAT" trial by Watson and colleagues¹³, available studies to date have been limited in design by small sample sizes, short duration of follow-up and lack of attention to the possibility of species-specific effects¹⁴. The HEAT trial found no benefit of routine quarterly albendazole and annual praziquantel for HIV progression. However, helminth infection status was investigated only at the end of the trial at which point the prevalence of *Schistosoma* in the control arm (having received no routine anthelmintic treatment) was modest; thus, the HEAT trial offers little insight into the specific, potential benefits of treating schistosomiasis¹³.

Effects of *Schistosoma mansoni* deserve special attention: this is a systemic infection with strong immunomodulatory effects. These regulatory effects are required for the long-term survival of adult worms within the host¹⁵, but inflammation against egg antigens is also required in order for eggs to migrate from mesenteric blood vessels, through the tissues and into the intestinal lumen¹⁶. Interactions between helminths and HIV, mediated by immunological mechanisms, may therefore be especially important for schistosomiasis. In addition, HIV-*Schistosoma* co-infection is particularly common among fishing communities, such as those on the shores and islands of Lake Victoria, where *S. mansoni* infection is almost universal¹⁷ and HIV prevalence among adults is up to 37%¹⁸. These are

recognised key populations with respect to HIV infection and regarded as likely reservoirs for the continuing HIV epidemic in the general population. Therefore, any impact of *S. mansoni* co-infection on HIV replication could have far-reaching consequences.

A prospective study in Kenya with a variable duration of follow up found no benefit of treatment of *S. mansoni* on HIV load¹⁹. In Uganda, we observed a transient increase in viral load following treatment with praziquantel²⁰. However, neither we, nor our colleagues in Kenya, included an untreated control group in these initial studies and thus the impact of praziquantel treatment on HIV progression remained unknown. Kallestrup and colleagues, in Zimbabwe, included a comparison group and found that, at three months, individuals treated for schistosomiasis (predominantly *S. haematobium*) had a smaller increase in viral load than individuals who had not been treated^{21,22}.

Given these inconsistent results, we sought to evaluate the effect of high-intensity (quarterly) treatment in comparison with low-intensity (annual) praziquantel treatment on HIV disease progression, in a large, well-powered study, among patients co-infected with HIV and *S. mansoni* from fishing populations around Lake Victoria, Uganda. This was aimed at assessing possible benefits of more frequent anthelmintic treatment among hard-to-reach populations whose access to anti-retroviral treatment is limited.

Methods

Trial registration

This trial was registered with the International Standard Registered Clinical/Social Study Number (ISRCTN) registry on the 17/11/2016. Trial number: [ISRCTN15371662](https://www.isrctn.com/ISRCTN15371662). A completed CONSORT checklist is available as [Supplementary File 1](#)

Study design. This was an open label randomised controlled trial. HIV-positive adults were recruited. *Schistosoma mansoni* infected study participants were randomised to high-intensity versus low-intensity praziquantel treatment in the ratio of 1:1. The high-intensity treatment group received immediate treatment with two doses of praziquantel (40mg/kg) one week apart followed by praziquantel at 12 weeks, and then every 12 weeks. The low-intensity treatment group received a single dose of praziquantel (40mg/kg) annually (in keeping with standard Uganda government policy) the first treatment being delayed to 12 weeks from enrolment in order to determine the short-term effects of treatment by comparison with an untreated group and to replicate the Zimbabwe study²². In parallel, we recruited a comparison group of HIV-positive individuals with no detectable *S. mansoni* infection. Initially it was planned that the comparison group would not receive any praziquantel treatment; later the protocol was amended such that participants in this group received praziquantel at 12 weeks to conform with standard of care in fishing communities. All participants received albendazole 400mg at weeks 12, 36 and 60 in keeping with policy for the control of nematode infections. Participants were followed for 60 weeks. All treatments were directly observed.

Outcomes. The primary study outcome was \log_{10} plasma HIV-1 RNA level at 12 and 60 weeks of follow up. Secondary outcomes were CD4 counts, clinical progression of HIV (defined by clinical events such as opportunistic infections, and WHO staging) and mortality; and reduction of *S. mansoni* infection prevalence and intensity. Immunological investigations in this cohort will be reported separately.

Study setting. The study was conducted in fishing communities on the shores of Lake Victoria in Masaka district, Uganda, where HIV prevalence among adults was estimated to be 29% and *S. mansoni* infection more than 50%^{18,23,24}.

Inclusion and exclusion criteria. Inclusion criteria were age at least 18 years, HIV and *S. mansoni* co-infection, antiretroviral therapy (ART) naïve, not in advanced HIV WHO stage III or Stage IV, CD4 T cell count >350 cells/mm³ (i.e. not eligible for ART initiation according to prevailing guidelines at the time of the study); willing and consenting to provide laboratory specimens for stool tests, HIV viral loads, CD4 count, full blood count; available for follow up for 15 months and willing to provide locator information for tracking purposes. Participants were excluded from the study if they met any one of the following criteria: women pregnant or planning to be pregnant; had taken praziquantel in the preceding three months; had symptomatic helminth infection (Hb <8 g/dl, bloody diarrhoea, clinically apparent liver disease (vomiting blood, hepatosplenomegaly)); had high-intensity of *S. mansoni* infection (egg count >2000 eggs/g; these received immediate praziquantel treatment). Enrolment to the comparison group followed similar criteria except that participants had to be *S. mansoni* negative on analysis of three stool samples by microscopy.

Study procedures and measurements. *Screening visits:* Trained field workers mobilised the targeted population through house to house HIV counselling and testing. Those found to be HIV-infected were referred to the study clinic at Lambu fish landing site, which is the largest fishing village in the study area located about 50km from Masaka town. After written informed consent, they were requested to provide three stool samples on consecutive days to ascertain *S. mansoni* infection status. During the screening visit, blood samples were also taken for CD4 count and urine from women for pregnancy testing, to complete the eligibility assessment. Volunteers were then encouraged to return within 2 weeks for enrolment.

Randomisation (enrolment visit): During this visit, individuals who met the study criteria were enrolled and baseline clinical history and examination including WHO HIV staging were conducted (Baseline questionnaire available as [Supplementary File 2](#)). Blood samples were collected for plasma viral load levels and CD4 counts. Eligible participants were randomly allocated to one of the two treatment groups (high-intensity or low-intensity praziquantel treatment) using random permuted blocks of variable size by an independent statistician. A randomisation list containing study numbers with the allocated treatment codes was provided to the study team and participants who were eligible were assigned the next available number

until the required sample size was reached. Participants in the high-intensity group received the first praziquantel dose (directly observed) during the enrolment visit, while treatment was deferred for those in the low-intensity group to the 12 weeks' visit. At each visit, treatment was given after blood and stool samples had been collected. Neither participants nor investigators were masked as to treatment allocation.

Similar processes were followed for the comparison group except that these participants were *S. mansoni* negative on all three stool samples.

Allocation concealment: The study statistician generated two randomisation lists: i) containing trial numbers from which eligible participants were sequentially allocated the next available number ii) containing trial numbers and the allocation arms. List (i) was held at the trial clinic, while list (ii) was held by the trial statistician. When an eligible participant was recruited and allocated the next available number on the randomisation list (i), the statistician was contacted to provide the treatment allocation arm on list (ii).

Follow-up visits: From the enrolment visit, participants were scheduled to return every 12 weeks until their exit. Participants in the high-intensity group made an additional visit one week after enrolment to receive their second dose of praziquantel. At every follow-up visit, clinical evaluation, urine pregnancy testing (women), praziquantel administration for those in the high-intensity group and plasma storage were undertaken. CD4/CD8 counts, *S. mansoni* infection (single stool tests and circulating anodic antigen (CAA)) were conducted every 3 months starting from enrolment day. Plasma viral load assessments were done at enrolment, week 12 and week 60.

Laboratory analysis

Stool analysis: Each stool sample was processed and evaluated using the Kato-Katz technique²⁵. Two slides were made from each sample, each using a template designed to capture 41.7mg of stool. Slides were examined within 30 minutes of preparation for hookworm eggs, and the following day for other ova, including *S. mansoni*. The presence of other helminth eggs was recorded and the burden of infection based on the number of eggs per gram of stool calculated according to WHO criteria^{26,27}.

Blood samples: Serological testing for HIV-1 was performed using Alere determine™ rapid test HIV1/2, Cat/ref7D2343 Abbott, Japan, with all positive tests confirmed by Statpack (HIV1/2STAT-PAK DIPSTICK Cat/refHIV303 Inverness, USA) with Unigold (Trinity Biotech Uni-Gold HIV Cat/ref120652, Ireland) as tie-breaker (the prevailing Uganda Ministry of Health algorithm at the time of the study). The CD4 lymphocyte count was determined using Multiset™ software DR-DOS 5.0 system, V1.4 on a FACSCalibur machine (Becton Dickinson, USA). Plasma HIV-1 RNA was quantified using the Ampliprep/Taqman V2.0 kit Cat number; 05212294190, Roche Molecular systems Inc, Pleasanton, USA HIV-1 viral load assay, which has been shown to quantify the subtypes of HIV-1 prevalent in Uganda and had a detection level of 20 copies of viral RNA/mL. Serum

CAA was assessed, after all samples had been collected, to define *S. mansoni* infection status and intensity more precisely: Plasma CAA was measured using the up-converting phosphor lateral flow assay in three sets; (set 1) >50pg/ml was considered positive, 20–50pg/ml indecisive and <20pg/ml negative, (set 2) >30pg/ml was considered positive, 10–30pg/ml indecisive and <10pg/ml negative and (set 3) >30pg/ml was considered positive, 13–30pg/ml indecisive and <15pg/ml negative²³. All Laboratory investigations were performed at MRC/UVRI and LSHTM Uganda Research Unit clinical diagnostics laboratory.

Ethical considerations

The study was approved by Uganda Virus Research Institute (UVRI) Research Ethics Committee (REC), GC/127/12/02/01 and Uganda National Council for Science and Technology (UNCST), HS1141. To address challenges of delayed treatment among those randomised to the low-intensity group, in relation to direct, helminth-induced pathology, we excluded people who were symptomatic, or with a high egg burden (>2000epg), and likely to benefit from immediate treatment. When participants became eligible for ART (according to the prevailing Uganda Ministry of Health guidelines) they were immediately referred to a local ART provider.

Role of the funding sources

The research leading to these results was funded primarily from the European Community's Seventh Framework Programme (FP7/2007–2013) under EC-GA n° 241642. As well, the research was supported by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement. AME was supported by a Wellcome Trust senior fellowship, grant number 095778. The funders did not have access to the data and were not involved in the analysis or interpretation of the results and did not provide input regarding the decision to publish this manuscript.

Statistical methods

Sample size estimation was based on evaluation of the primary outcome: viral load measured at study exit among participants treated with high-intensity, compared to those on low-intensity, praziquantel. We aimed to recruit and follow to completion 188 HIV and *S. mansoni* co-infected participants, giving approximately 89% power to detect as significant a difference in \log_{10} viral load copies/mL at 60 weeks of 0.35 \log_{10} copies/mL. These assumptions were based on the baseline viral load in the rural community cohort in Uganda (unpublished) and a within group standard deviation in the \log_{10} copies/mL of 0.75. Due to the anticipated loss to follow up of 20% (estimated from the 18 months' fisher folk cohort)²⁸ the overall sample size was increased to 226 participants (113 per group).

Data handling and analysis: Data were double-entered and verified in Microsoft Access 2003 (Microsoft Corporation, Redmond, WA) and analysed using Stata 14 (Stata Corp, College Station, Texas, USA). Participant baseline socio-demographics and clinical characteristics were summarised using counts and

percentages, by study group, for categorical variables and means and standard deviation (SD) for continuous variables. The analysis was by intention to treat (ITT). The prevalence of *S. mansoni* and other helminth infections, and egg counts (transformed on natural logarithm), were compared between the study groups using Chi-square tests and geometric means respectively. The viral loads showed skewed distributions, with a number of results (61-overall (12 at baseline)) as undetectable. An offset from zero of 10 copies/mL was added to all the viral loads, to allow suitable logarithmic analysis. Results were transformed to \log_{10} (viral loads) and analysed by linear regression using bootstrapping with 10,000 iterations. Regression coefficients and confidence limits were back-transformed to express results as ratios of geometric means. All the primary analyses were adjusted for baseline age and viral loads and included all participants to the end of follow up, regardless of whether or not they initiated antiretroviral treatment. Similar approaches were followed for CD4 counts though the transformation was on natural logarithm and no corrections were made. A Kaplan Meier curve with log-rank test was used to compare the clinical course of HIV disease (WHO staging) between the study groups. Mortality between the groups was compared by proportions.

Two sensitivity analyses were performed: one, for the trial analysis, excluding viral loads and CD4 count results of the participants that initiated ART during the trial and those with baseline undetectable viral loads; the other for analyses of the comparison group, excluding individuals found to have *S. mansoni* infection at any time point. The exclusion in the latter first considered all with indecisive CAA results (10–30pg) as negative and secondly as positive. Similar approaches as above were followed.

Results

Study profile: Between August 2012 and September 2015, a total of 854 participants were screened and 363 (42.7 %) enrolled (113 in each of the high-intensity and low-intensity groups and 137 in the comparison group). The most common reason for exclusion was CD4 count <350 cells (Figure 1). We also excluded two participants, one in each trial group, that were randomised in error. A total of 36 participants were lost during the trial; loss was similar between the trial groups. Fifty-three (15 high-intensity, 16 low-intensity and 22 comparison group) participants initiated antiretroviral treatment during follow up, on average 3 participants per visit.

Participant characteristics at baseline: Participants' baseline characteristics are presented in Table 1. The characteristics were similar in the two trial groups except that participants in the high-intensity group were slightly younger, a smaller proportion was single (never married), and the prevalence of other helminths (Hookworm, *Ascaris*, and *Trichuris*) was lower than in the low-intensity group. The comparison group had a higher proportion of women compared to the trial groups, reflecting the lower prevalence of *S. mansoni* infection among women than men in these communities. The baseline CD4 count and viral loads were comparable in all the study groups.

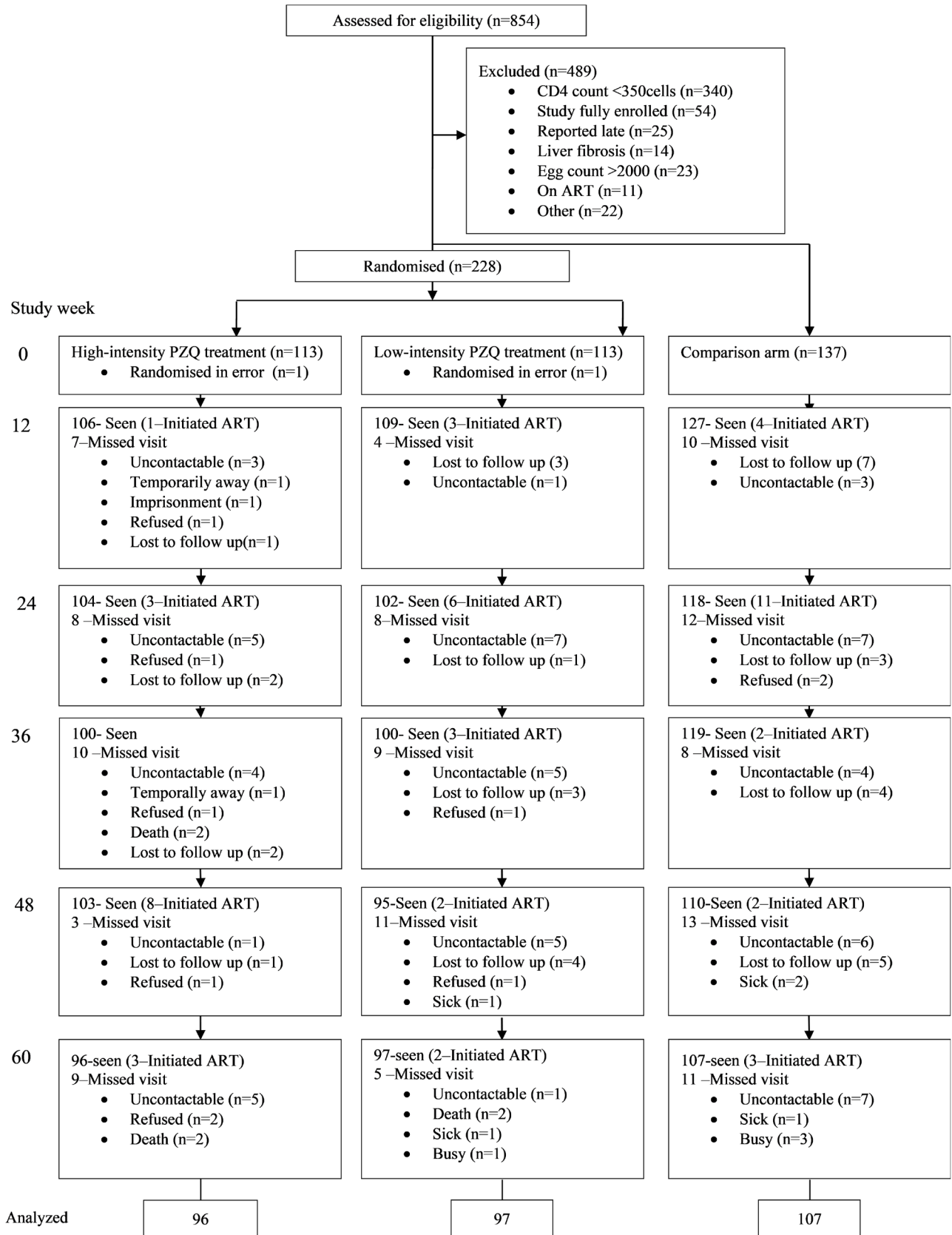


Figure 1. CONSORT flow diagram. PZQ - praziquantel.

Table 1. Baseline information by randomisation group and non-randomised comparison group.

Characteristic	Category	Number (%)		
		High-intensity PZQ (n=113)	Low-intensity PZQ (n=113)	Comparison (n=137)
Sex	Male	87(77.0)	90(79.7)	72(52.6)
	Female	26(23.0)	23(20.3)	65(47.4)
Age (years)	Median (IQR)	29 (24-33)	30 (26-36)	30 (26-36)
Age group	18–24	29(25.7)	21(18.6)	25(18.3)
	25–34	64(56.6)	55(48.7)	62(45.2)
	35–59	20(17.7)	37(32.7)	50(36.5)
Education	None	11(9.7)	10(8.9)	12(8.8)
	Primary	88(77.9)	86(76.1)	102(75.4)
	Secondary	14(12.4)	17(15.0)	23(16.8)
Marital	Single, never married	11(9.7)	20(17.7)	14(10.2)
	Married	62(54.9)	60(53.1)	82(59.8)
	Single, ever married	40(35.4)	33(29.2)	41(30.0)
Occupation	Fishing/related	88(77.9)	83(73.4)	83(73.4)
	Small scale business	9(8.0)	8(7.1)	8(7.1)
	Bar/restaurant	4(3.5)	7(6.2)	7(6.2)
	Other	12 (10.6)	15(13.3)	15(13.3)
CD4 count	Mean ln (SD)	6.5(0.33)	6.4(0.31)	6.4(0.36)
†Viral Load	Mean log ₁₀ (SD)	4.5(1.01)	4.5(0.74)	4.4(0.98)
Schistosoma (Kato Katz microscopy)	Prevalence	113(100)	113(100)	0(0.0)
	*Geometric mean egg count (95%CI)	244.2(192.3-310.1)	228.0(181.6-286.3)	N/A
Schistosoma (serum circulating anodic antigen (CAA))	Prevalence	99(87.6)	101(89.4)	47(34.3)
	*Geometric mean concentration pg/ml (95%CI)	1708.2(1178.6-2475.6)	1877.8(1277.3-2760.7)	482.2(293.3-792.7)
Other worms	Prevalence	11(9.7)	21(18.6)	22(16.1)

PZQ praziquantel. †12 volunteers (9-Low-intensity PZQ arm and 3-comparison) had undetectable viral loads at baseline. * Geometric mean among those infected. Figures in brackets are percentages unless otherwise indicated in column 2, IQR-Interquartile range.

A total of 300 (82.6%) participants completed the study follow up at 60 weeks and had the primary outcome determined. Study completion did not differ by the trial arm, standard 97 (85.8%), intensive 96 (85.0%) and comparison 107 (78.1%) $p=0.202$. A higher proportion of females (24.6%) did not complete the study follow up compared to 14.1% of the males $p=0.014$, but otherwise completers and non-completers were similar in regards to other baseline characteristics.

HIV viral load: The primary objective was to compare the effect of high-intensity versus low-intensity treatment with praziquantel on HIV disease progression by comparing viral loads between baseline and 12 weeks, and between baseline and 60 weeks in the two study groups. There was no statistical evidence of difference in mean log₁₀ viral loads between the high-intensity

and low-intensity groups at 12 weeks, $p=0.55$ (Table 2). After adjusting for baseline age group and viral load, the geometric mean ratio (aGMR) for high-intensity vs low-intensity treatment was 0.90; 95%CI (0.65, 1.25), $p=0.55$. There was a slightly higher mean log₁₀ viral load in the high-intensity group compared to low-intensity group at 60 weeks: after adjusting for baseline age group and viral load, the aGMR was 1.88; 95%CI (0.78, 4.53), $p=0.16$. Excluding those with undetectable viral load at baseline, and those that initiated ART during follow up, there was no evidence of a difference in viral load at 60 weeks between the high-intensity and low-intensity treatment groups (aGMR 1.01 95%CI (0.64, 1.95), $p=0.71$).

The comparison group had patterns of viral load change similar to the low-intensity group.

Table 2. Adjusted ratio of geometric means for the primary outcome (viral load) and CD4 counts at 12 and 60 weeks by randomisation and comparison group.

Outcome	Randomisation Group	12 weeks			60 weeks		
		Mean (SD) [§]	aGMR*	P-value	Mean (SD) [§]	aGMR*	P-value
Viral load	Low-intensity PZQ	4.2 (1.16)	1.00		3.6 (1.57)	1.00	
	High-intensity PZQ	4.3 (1.08)	0.90 (0.65-1.25)	0.55	4.0 (1.22)	1.88 (0.78-4.53)	0.16
	Comparison	4.1 (1.22)	1.18 (0.83-1.69)	0.36	3.6 (1.47)	0.92 (0.39-2.18)	0.84
CD4 count	Low-intensity PZQ	6.3 (0.38)	1.00		6.3 (0.40)	1.00	
	High-intensity PZQ	6.4 (0.38)	0.99 (0.93-1.07)	0.96	6.3 (0.40)	0.94 (0.86-1.02)	0.15
	Comparison	6.3 (0.41)	0.99 (0.93-1.07)	0.97	6.2 (0.42)	1.00(0.91-1.09)	0.98

PZQ praziquantel. *aGMR - adjusted ratio of geometric means, [§] mean -Viral load transformed on log₁₀ and CD4 on natural logarithm, adjusted for age and baseline viral load or CD4 count; "Low-intensity PZQ" was the reference group

CD4 count: There were no significant differences in mean CD4 count between the study groups at any time during follow up, even after adjusting for baseline age group and CD4 count; high-intensity vs low-intensity at 60 weeks aGMR 0.94 (0.86, 1.02), $p=0.15$ (Table 2). The comparison group did not differ from either trial group.

Schistosoma mansoni and other helminth infections: The prevalence of *S. mansoni* as assessed by microscopy was substantially lower in the high-intensity treatment group compared to the low-intensity group at 12 weeks (21.9% vs 72.5% ($p<0.01$)); as expected, given that the low-intensity group was still untreated at this time) and at 60 weeks (6.6% vs 32.3% ($p<0.01$)). Corresponding reductions in geometric mean egg counts among those infected were observed (Table 3). Although the prevalence of other helminths was somewhat higher in the high-intensity group at baseline, it did not differ significantly between the two study groups during follow up (Table 3). The prevalence of *S. mansoni* as assessed by CAA was also substantially lower in the high-intensity treatment group compared to the low-intensity at 12 weeks and 60 weeks: 74.2% vs 94.9% ($p<0.01$) and 29.2% vs 73.4% ($p<0.01$) respectively.

Although the comparison group had no evidence of *S. mansoni* infection by microscopy at baseline, infection was detected by CAA in 41.5%; in line with this result, a small proportion of comparison group participants were positive by microscopy and by CAA during follow up (CAA-positive 23.2% and 13.6% at 12 and 60 weeks, respectively; Table 3). When members of the comparison group with *S. mansoni* infection detectable by either method were excluded from the analysis of viral load, viral load measurements in this group were still similar to the low-intensity group: aGMR 0.94 (0.77–1.15), $p=0.55$ and 0.90 (0.54–1.49), $p=0.68$ at 12 and 60 weeks (all indecisive CAA results considered as negative). Similar results were obtained when indecisive CAA results were considered as positive (date not shown).

Mortality and progression to AIDS: In total six participants (4-high-intensity and 2-low-intensity group) died during follow

up. Twenty-five participants (10-high intensity, 5- low intensity and 10-comparison arm) progressed in WHO clinical staging during follow up. Based on WHO clinical staging, progression to AIDS was more likely to occur in high-intensity treatment and comparison groups compared to the low-intensity group, although this finding was not statistically significant (log-rank chi-square (low-intensity vs high-intensity) 2.08, $p=0.15$; and log-rank chi-square (low-intensity vs comparison group) 0.51, $p=0.47$ (Figure 2)).

Discussion

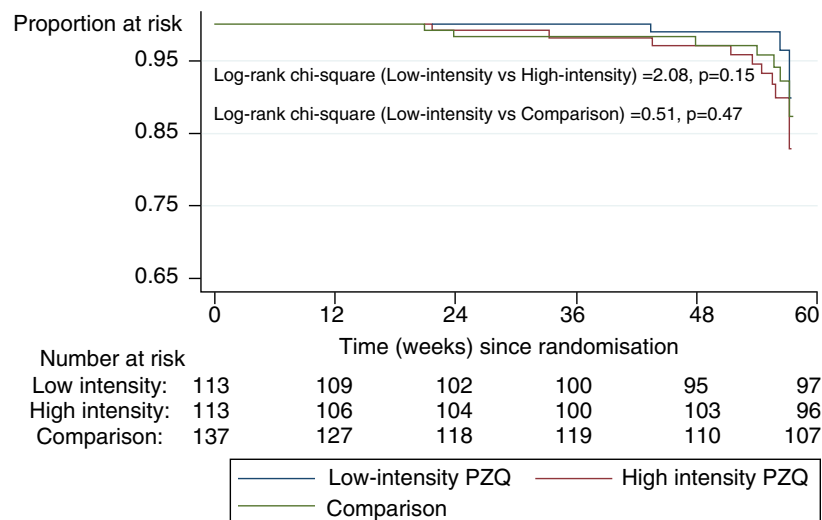
This randomised clinical trial was designed to establish whether high-intensity treatment of *S. mansoni* with praziquantel delays HIV disease progression. We used HIV viral load, CD4 count and clinical parameters as markers of disease progression. We found no benefit of praziquantel treatment of *S. mansoni* for HIV disease progression. If anything, at week 60 of follow up, HIV viral loads were slightly higher among participants who received high-intensity treatment than among those who received low-intensity treatment. In addition, analysis of outcomes in the comparison group indicated that *S.mansoni* infection *per se*, under either treatment regimen, had no effect on HIV disease progression.

Our study was not blinded, but it is unlikely that the low-intensity group received praziquantel outside the trial protocol since it is not widely available in the community clinics and pharmacies; the infection prevalence (based on microscopy) and CAA concentration at 12 weeks (i.e. prior to the first treatment in this group) remained high in this group. A marked difference in *S. mansoni* prevalence, as assessed by Kato Katz microscopy, emerged between the low-intensity and high-intensity treatment groups by 12 weeks, and persisted during follow up. The more sensitive CAA analysis showed that complete clearance of infection was slower than it appeared using microscopy of single stool samples, and this could have obscured a true effect of eliminating *S. mansoni* during the early part of follow up; however, a substantial difference had been achieved by 60 weeks. Follow up Kato Katz and CAA analyses in the comparison group indicated that some members were, in fact, *S. mansoni* infected

Table 3. Schistosoma prevalence and geometric mean egg count by study week and randomisation and comparison groups.

Time point	Prevalence geometric mean)	High-intensity PZQ (n=113)	Low-intensity PZQ (n=113)	p-value [*]	Comparison n=137	p-value [§]
12 weeks						
Kato Katz microscopy	Prevalence	23/105 (21.9%)	79/109 (72.5%)	<0.01	9/124 (7.3%)	<0.01
	*Geometric mean egg count (95%CI)	115.7 (73.9-181.1)	288.4 (215.8-385.6)	<0.01	82.3 (32.8-206.4)	0.43
CAA	prevalence	66/97 (68.0%)	86/97 (88.7%)	<0.01	13/82 (15.9%)	<0.01
	*Geometric mean pg CAA / mL (95% CI)	369.1 (247.2-551.2)	2041.5 (1395.5-2986.7)	<0.01	219.5 (100.6-478.8)	0.44
36 weeks						
Kato Katz microscopy	Prevalence	9/98 (9.2%)	22/99 (22.2%)	0.01	11/119 (9.2%)	0.99
	*Geometric mean egg count (95%CI)	61.3 (33.1-113.6)	136.1 (90.2-205.3)	0.05	38.7 (27.6-54.3)	0.17
60 weeks						
Kato Katz microscopy	Prevalence	6/91 (6.6%)	31/96 (32.3%)	<0.01	8/107 (7.5%)	0.81
	*Geometric mean egg count (95%CI)	54.6 (22.4-133.0)	191.5 (124.5-294.7)	0.01	59.1 (36.4-95.9)	0.55
CAA	prevalence	26/89 (29.2%)	69/94 (73.4%)	<0.01	14/103 (13.6%)	0.01
	*Geometric mean pg CAA / mL (95%CI)	295.5 (152.0-574.4)	695.1 (463.8-1041.6)	0.03	103.3 (62.8-169.9)	0.04
Other helminths						
12 weeks	Prevalence	6/106 (5.7%)	13/109 (11.9%)	0.11	9/124 (7.3%)	0.63
36 weeks	Prevalence	7/98 (7.1%)	7/99 (7.1%)	1.00	5/119 (4.2%)	0.37
60 weeks	Prevalence	1/91 (1%)	1/96 (1%)	0.99	0/109 (0.0%)	0.60

PZQ praziquantel. * Geometric mean among those infected, ^High-intensity PZQ to Low-intensity PZQ group, § High-intensity PZQ vs comparison, CAA-serum circulating anodic antigen

**Figure 2. Volunteers moving up in WHO staging by study group. PZQ – praziquantel.**

but a sensitivity analysis restricting the comparison group to individuals negative on all tests still showed no evidence of statistical difference relative to the trial low-intensity group.

In this study, there was a hint of an adverse effect of treating schistosomiasis on HIV load – the aGMR indicated a higher viral load in the high-intensity treatment arm, although the confidence interval was wide (aGMR 1.88 (95%CI 0.78–4.53). This is in agreement with earlier observations in Kisumu, Kenya¹⁹ and in Uganda^{20,29}. The cohort study in Kisumu demonstrated a moderate rise in mean HIV-1 plasma viral load among patients who received praziquantel treatment, but the study lacked a comparison group. Similarly, we previously demonstrated a transient rise in plasma HIV viral load in a cohort of HIV-*S. mansoni* co-infected patients in Uganda, more marked among subjects with higher intensity *S. mansoni* infections²⁰. These prior studies were limited by short follow up periods and lack of treatment randomisation. In terms of mechanism, the factors producing the type 2 responses to worm antigens released following praziquantel treatment²⁰ may affect the extracellular environment and antigen presenting cells (APC)s that determine the functional fate of naïve T cells recognizing HIV antigens, priming a phenotype less effective in hindering HIV replication. Additionally, the activated, proliferating *S. mansoni* specific CD4 T cells responding to the circulating antigen surge might themselves constitute additional targets for HIV infection and replication, supporting a transient increase in viral load.

Our findings contrast with the results of the earlier Zimbabwe study, the only similar randomised trial of praziquantel treatment to recruit individuals of confirmed *Schistosoma* infection status and to address HIV-related outcomes, which we sought to confirm. The Zimbabwe trial was a smaller study, with shorter follow up and lower power than this study. The Zimbabwe trial included participants with both *S. haematobium* and *S. mansoni*; infection intensity (at least for *S. mansoni*) was markedly lower than in our study (with mean egg counts of 3–4 epg of stool, compared to our geometric mean of >200 epg)²¹. Differences in infection intensity as well the involved species may explain differences in impact on the immune system (and hence on HIV replication). Low-intensity infections are more likely to be readily cleared by a single dose of treatment.

Our study strengths included a prolonged follow up period, sufficient sample size and randomisation of treatment. The results provide strong evidence that, in communities with a high

burden of both *S. mansoni* and HIV infection, high-intensity treatment of *S. mansoni* does not delay HIV progression despite benefits for parasite clearance. Our study limitation included a challenge that fishing communities are predominantly males and they constituted about 75% of the study population in the two randomized groups. However, a subgroup analysis stratifying by gender, though underpowered still showed that high-intensity treatment of *S. mansoni* does not delay HIV progression in males as well as females. We therefore conclude that, unfortunately, treatment of *S. mansoni* is not likely to contribute to mitigating the HIV epidemic among fishing communities.

Data availability

The MRC/UVRI and LSHTM Uganda Research Unit has a data sharing policy accessible through this link <https://www.mrcuganda.org/publications/data-sharing-policy>. The policy summarizes the conditions under which data collected by the MRC/UVRI and LSHTM Uganda Research Unit can be made available to other bona fide researchers, the way in which such researchers can apply to have access to the data and how data will be made available if an application for data sharing is approved. Should any of the other researchers need to have access to the data from which this manuscript was generated, we authors will make it available to them. The corresponding and other co-author emails have been provided and could be contacted anytime.

Grant information

This work was supported by the Wellcome Trust through a Wellcome Trust Senior Fellowship grant [095778] to AME.

This work was also supported by European Community's Seventh Framework Programme [FP7/2007–2013] under EC-GA n° 241642, and the UK Medical Research Council (MRC) and Department for International Development (DFID) as part of the MRC-DFID Condat agreement.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We would like to acknowledge the study participants and their partners, the investigators and study team. We thank W. Senyonga and Claudia de Dood for technical assistance with CAA assays.

Supplementary material

Supplementary File 1 – Completed CONSORT checklist

[Click here to access the data.](#)

Supplementary File 2 – Baseline questionnaire

[Click here to access the data.](#)

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Open Peer Review

Current Referee Status:   

Version 2

Referee Report 04 April 2019

<https://doi.org/10.21956/wellcomeopenres.16601.r35215>



Judd L. Walson 

Departments of Global Health, Medicine (Infectious Disease), Pediatrics and Epidemiology, University of Washington, Seattle, WA, USA

The authors have adequately addressed the concerns raised in my prior review. Some of the limitations remain but the authors have done a very thorough job in responding clearly to each comment.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 15 November 2018

<https://doi.org/10.21956/wellcomeopenres.15987.r34261>



Birgitte Jyding Vennervald 

Section for Parasitology and Aquatic Pathobiology (PAP), Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

This is a very interesting paper reporting the results of an open-label Randomised Controlled Trial (RCT) on the effect of intensive, 4 times per year vs. standard once yearly PZQ treatment on viral load among HIV and *Schistosoma mansoni* co-infected people living in fishing communities near lake Victoria. A non-randomised HIV-positive *S. mansoni*-negative comparison group was recruited as well.

The primary study outcome was viral load at 12 and 60 weeks of follow up. Secondary outcomes were CD4 counts and the clinical progression of the HIV infection and reduction of *S. mansoni* infection prevalence and intensity.

The results showed no statistically significant differences in viral load between the high-intensity vs low-intensity treatment groups at 12 weeks and 60 weeks and the overall conclusion of the paper is that in fishing communities with high *S. mansoni* and HIV infection prevalences, high-intensity treatment of *S. mansoni* does not delay HIV progression.

The paper is clearly and well written. Overall the study is well conducted; the results described in a clear and concise manner and the conclusions drawn based on the results are sound and justified.

I am very pleased to see that the authors report their results findings despite the fact that they found no significant differences between the two arms. This is highly important for the scientific community and generally for society that negative results are published. Well done. We should see more of that.

I have some minor questions or comments to various sections of the paper:

1. The parasitological diagnosis was based on Kato-Katz technique with preparation of two slides per stool sample. I would have liked the authors to state the amount of stool used for a slide, since this may vary (25mg to 50 mg) and have an impact of the overall sensitivity of the method.
2. At the baseline examination and randomisation participants were providing three stool samples on three consecutive days. However, as far as I can see, parasitological results at follow-up time points are all based on a single stool. This has implications for the sensitivity of the test. Kato-Katz is not a very sensitive test and sensitivity is very low with just a single stool sample post treatment. This is why the CAA assay is very useful and important to include as an additional diagnostic measure. It would have been good to include these points in the discussion.
3. I do not really see the point in having the group of *S. mansoni* negatives. Parasitological and CAA analysis reveal that some of them are in fact infected at 12 weeks and they are treated with PZQ just like the low-intensity PZQ group. Furthermore, since they are *S. mansoni* negative or very slightly infected despite living in a high transmission fishing community means that they may differ from the two randomisation groups with respect to parameters, which have not been investigated but which may be of importance.
4. I am amazed to see that despite very intense PZQ treatment (every 12 weeks) it is not possible to bring *S. mansoni* infection down to almost nothing in this group of adults. *S. mansoni* is a tough parasite to treat. I am wondering if *Schistosoma haematobium* is easier and if this may play a role when comparing with the Zimbabwean *S. haematobium* study?
5. I do not quite understand figure 2 based on the figure legend. Maybe the legend could be expanded.
6. Could this maybe be re-phrased: "producing the type 2 bias of responses to worm antigens". Maybe just remove "bias of". Whenever I read it I stumble on type 2 bias and try to figure out how statistics come into this.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Human parasitology, schistosomiasis immunology, schistosomiasis morbidity

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 26 Mar 2019

Andrew Abaasa, MRC/UVRI and LSHTM Uganda Research Unit, Uganda

Effect of high-intensity versus low-intensity praziquantel treatment on HIV disease progression in HIV and *Schistosoma mansoni* co-infected patients: a randomised controlled trial

Abaasa et al

Response to the reviewer's comments

Reviewer Two

Birgitte Jyding Vennervald, Section for Parasitology and Aquatic Pathobiology (PAP), Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Approved

This is a very interesting paper reporting the results of an open-label Randomised Controlled Trial (RCT) on the effect of intensive, 4 times per year vs. standard once yearly PZQ treatment on viral load among HIV and *Schistosoma mansoni* co-infected people living in fishing communities near lake Victoria. A non-randomised HIV-positive *S. mansoni*-negative comparison group was recruited as well.

The primary study outcome was viral load at 12 and 60 weeks of follow up. Secondary outcomes were CD4 counts and the clinical progression of the HIV infection and reduction of *S. mansoni* infection prevalence and intensity.

The results showed no statistically significant differences in viral load between the high-intensity vs low-intensity treatment groups at 12 weeks and 60 weeks and the overall conclusion of the paper is that in fishing communities with high *S. mansoni* and HIV infection prevalences, high-intensity treatment of *S. mansoni* does not delay HIV progression.

The paper is clearly and well written. Overall the study is well conducted; the results described in a clear and concise manner and the conclusions drawn based on the results are sound and justified. I am very pleased to see that the authors report their results findings despite the fact that they found no significant differences between the two arms. This is highly important for the scientific community and generally for society that negative results are published. Well done. We should see more of that.

I have some minor questions or comments to various sections of the paper:

1. The parasitological diagnosis was based on Kato-Katz technique with preparation of two slides per stool sample. I would have liked the authors to state the amount of stool used for a slide, since this may vary (25mg to 50 mg) and have an impact of the overall sensitivity of the method.

Response: Thank you for this observation, the amount of the stool used for slides was 41.7 mg. This has been included in the manuscript.

2. At the baseline examination and randomisation participants were providing three stool samples on three consecutive days. However, as far as I can see, parasitological results at follow-up time points are all based on a single stool. This has implications for the sensitivity of the test. Kato-Katz is not a very sensitive test and sensitivity is very low with just a single stool sample post treatment. This is why the CAA assay is very useful and important to include as an additional diagnostic measure. It would have been good to include these points in the discussion.

Response: In our second paragraph of the discussion section, we allude to this.

3. I do not really see the point in having the group of *S. mansoni* negatives. Parasitological and CAA analysis reveal that some of them are in fact infected at 12 weeks and they are treated with PZQ just like the low-intensity PZQ group. Furthermore, since they are *S. mansoni* negative or very slightly infected despite living in a high transmission fishing community means that they may differ from the two randomisation groups with respect to parameters, which have not been investigated but which may be of importance.

Response: It is plausible that an infection such as schistosomiasis exacerbates HIV progression and that the effect is not reversible by treatment - because of persistence of helminth antigen, for example, and/or lasting impact on the immune system. As indicated in the discussion, we consider the results from the comparison group useful to address this possibility - there was no substantial difference in progression between the comparison group and either treatment arm. We do agree, however, that there were important (and largely inevitable) differences between the comparison group and the infected groups and we acknowledge that all comparisons with that group should be taken with caution and as secondary results. We draw our major findings from the two randomized arms.

4. I am amazed to see that despite very intense PZQ treatment (every 12 weeks) it is not possible to bring *S. mansoni* infection down to almost nothing in this group of adults. *S. mansoni* is a tough parasite to treat. I am wondering if *Schistosoma haematobium* is easier and if this may play a role when comparing with the Zimbabwean *S. haematobium* study?

Response: We thank the reviewer for this interesting comment.

5. I do not quite understand figure 2 based on the figure legend. Maybe the legend could be expanded.

Response: The legend has been expanded to align PZQ with high-intensity not to give an impression it is with the comparison arm.

6. Could this maybe be re-phrased: "producing the type 2 bias of responses to worm antigens". Maybe just remove "bias of". Whenever I read it I stumble on type 2 bias and try to figure out how statistics come into this.

Response: “bias of” has been removed

Competing Interests: I declare that i have no competing interests

Referee Report 19 October 2018

<https://doi.org/10.21956/wellcomeopenres.15987.r33727>



Paul Garner 

Liverpool School of Tropical Medicine (LSTM), Liverpool, UK

1. The authors examine the question of whether helminth infection-with Schistosomiasis-exacerbates HIV infection. The authors give PZ to S mansoni infected people, and those on the low intensity schedule were untreated at 12 weeks so a direct comparison of no treatment with PZ 40 dose was possible in terms of mean change in geometric mean of viral load. The treatment reduced S mansoni but did not show any impact on mean viral load change.
2. This is an important study and is highly relevant in a research question where there seem to be strong beliefs there is an effect, yet effects to date have been mixed but always quite small, and as such the evidence base is at risk of selective publication and selective reporting. The authors have therefore done a service to science in ensuring this study, which does not demonstrate an effect, has been published. They also appear to have adhered to the protocol and not sought secondary outcomes or subgroup analyses that risk generating spurious results.
3. It is a fascinating also because the authors were able to evaluate the effect of PZ and treating the infection in people with HIV that was not suppressed by ARVs. This was because it was conducted prior to the WHO recommendation to treat all people living with HIV with ARVs irrespective of CD counts. So this study is “as good as it will ever get” in testing whether treatment has any influence on HIV progression.
4. The study is well-written. The background explains studies to date and the gap in the literature leading to this study. Whilst this is a basic expectation of the background section, so many authors do not do this or do it badly, surprisingly; I will use this as an example of good practice in our teaching! and the methods are clearly explained. The follow up is good and the results well presented.
5. It is appropriately reported without any attempt to overinterpret the results. Given the complexity of the study the authors have good numbers recruited. Very few people were started on ARVs during the course of the study and the sensitivity analysis showed this did not, by chance, influence the results, which might have happened if there was chance imbalance in the numbers treated in comparator groups.
6. The one point that would really help understand the context-and this is a broader concern with these studies of this kind around treating helminths in HIV (including the studies of albendazole used for soil transmitted helminth infection in people with HIV) is the ambiguity around the purpose of the study: is it truly believed by the authors that this could be potentially important component of treatment by delaying progression of the disease as stated in the first sentence of the discussion? Or that treatment of schisto could have some public health impact on transmission as outlined at the end of paragraph 3 in the introduction? Or is it simply a randomised explanatory trial to elucidate immune mechanisms with helminth infection? This is the only strongly recommended change I would want to see in the amended version.

7. With the absence of any demonstrable effect in this study, it seems most unlikely, given the dramatic effectiveness of ARVs in viral suppression, that further studies would be worthwhile. Indeed, given patients would need to be on ARVS, with such small putative possible effects of the treatment, the studies would have to be extremely large, probably so large that no-one would fund them. I think it would be extremely worthwhile reporting in their discussion.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence synthesis, particularly in infectious diseases common in tropical and low income settings.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 26 Mar 2019

Andrew Abaasa, MRC/UVRI and LSHTM Uganda Research Unit, Uganda

Effect of high-intensity versus low-intensity praziquantel treatment on HIV disease progression in HIV and *Schistosoma mansoni* co-infected patients: a randomised controlled trial

Abaasa et al

Response to the reviewer's comments

Reviewer Three

Paul Garner, Liverpool School of Tropical Medicine (LSTM), Liverpool, UK

Approved

1. The authors examine the question of whether helminth infection-with Schistosomiasis-exacerbates HIV infection. The authors give PZ to S mansoni infected people, and those on the low intensity schedule were untreated at 12 weeks so a direct comparison of no treatment with PZ 40 dose was possible in terms of mean change in geometric mean of viral load. The treatment reduced S mansoni but did not show any impact on mean viral load change.
2. This is an important study and is highly relevant in a research question where there seem to be strong beliefs there is an effect, yet effects to date have been mixed but always quite small, and as such the evidence base is at risk of selective publication and selective reporting. The authors have therefore done a service to science in ensuring this study, which does not demonstrate an effect, has been published. They also appear to have adhered to the protocol and not sought secondary outcomes or subgroup analyses that risk generating spurious results.
3. It is a fascinating also because the authors were able to evaluate the effect of PZ and treating the infection in people with HIV that was not suppressed by ARVs. This was because it was conducted prior to the WHO recommendation to treat all people living with HIV with ARVs irrespective of CD counts. So this study is “as good as it will ever get” in testing whether treatment has any influence on HIV progression.
4. The study is well-written. The background explains studies to date and the gap in the literature leading to this study. Whilst this is a basic expectation of the background section, so many authors do not do this or do it badly, surprisingly; I will use this as an example of good practice in our teaching! and the methods are clearly explained. The follow up is good and the results well presented.
5. It is appropriately reported without any attempt to overinterpret the results. Given the complexity of the study the authors have good numbers recruited. Very few people were started on ARVs during the course of the study and the sensitivity analysis showed this did not, by chance, influence the results, which might have happened if there was chance imbalance in the numbers treated in comparator groups.
6. The one point that would really help understand the context-and this is a broader concern with these studies of this kind around treating helminths in HIV (including the studies of albendazole used for soil transmitted helminth infection in people with HIV) is the ambiguity around the purpose of the study: is it truly believed by the authors that this could be potentially important component of treatment by delaying progression of the disease as stated in the first sentence of the discussion? Or that treatment of schisto could have some public health impact on transmission as outlined at the end of paragraph 3 in the introduction? Or is it simply a randomised explanatory trial to elucidate immune mechanisms with helminth infection? This is the only strongly recommended change I would want to see in the amended version.

Response: Much as we are fascinated by the immunomodulating effects of helminths, and the wider implications of this for human health, we confirm that our intention in conducting this relatively large trial was to obtain conclusive information (to the extent possible) on whether treating schistosomiasis has significant benefit for controlling HIV replication and progression. Therefore we believe that the statements in the introduction reflect our true position prior to conducting the trial.

7. With the absence of any demonstrable effect in this study, it seems most unlikely, given the dramatic effectiveness of ARVs in viral suppression, that further studies would be worthwhile. Indeed, given patients would need to be on ARVs, with such small putative possible effects of the treatment, the studies would have to be extremely large, probably so large that no-one would fund them. I think it would be extremely worthwhile reporting in their discussion.

Response: This is a thought provoking comment. We agree that it is not likely to be worth testing the effects of treatment of S. mansoni on HIV progression any further. However, although antiretroviral treatment is recommended on a “test and treat” basis in high HIV transmission settings, such as fishing communities, this is not easy to implement. So complementary interventions which may be easier to implement would be worth consideration.

Competing Interests: I declare that i have no competing interests

Referee Report 26 July 2018

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Judd L. Walson 

Departments of Global Health, Medicine (Infectious Disease), Pediatrics and Epidemiology, University of Washington, Seattle, WA, USA

This is an interesting manuscript presenting the results of a randomized trial comparing high-intensity treatment (frequent quarterly treatment) vs low intensity (annual) of schistosomiasis in HIV co-infected individuals. This paper adds to a previous RCT demonstrating lack of benefit with the use of empiric quarterly praziquantel in HIV infected individuals¹. Overall, this was an ambitious attempt to conduct a rigorous trial given considerable challenges in the selection of appropriate patients, potential for alternative treatments (such as ART) to impact the outcomes and need for high retention.

Unfortunately, there are a number of critical issues with the design and conduct of the trial that make the interpretation of these data difficult.

1. Overall, one cannot expect to see differences in HIV VL above and beyond reductions that would be expected with initiation of ART in antiretroviral naïve individuals. As such, the actual population for whom any expected benefit would need to exclude these individuals (which was done in a secondary analysis). Including these individuals in the primary analysis is problematic as they are not going to benefit from the intervention and they only serve to dilute the impact amongst the population who may benefit. Per my calculations, removing these individuals would leave 81 individuals per arm who were treated and did NOT receive ART. This suggests that the actual study was dramatically underpowered to detect the effect size for which it was designed. This is a significant limitation of the study. In addition, the fact that 12 individuals had undetectable VL at baseline is concerning, suggesting either that there were individuals who were included that had already initiated ART or that there were some fundamental issues with the laboratory in detecting VL. While it would be expected that some individuals in a population could be long-term non-progressors and have low to undetectable VL in the absence of treatment, the number observed here is quite high and raises some concerns.
2. The inclusion of a group of HIV infected, schisto negative “controls” does not add to the study. These individuals are likely to be different in many unmeasured ways from the coinfecting population and any comparison of this group is likely subject to considerable confounding. I found that the inclusion of this group detracted from the quality of the overall study.

3. The very high rates of LTFU in this study are concerning. Other RCTs with a similar length of follow up in East Africa among HIV infected adults achieve retention rates of greater than 90-95%. The high rates of LTFU suggest that there may have been differential loss and have introduced significant bias.
4. Important to note that the intervention also included albendazole – any observed effect could also have been attributed to this.
5. The exclusion of individuals with high intensity infection, while perhaps ethically necessary, is problematic for the interpretation of these data. It is likely that these are the individuals most likely to benefit from the intervention and the exclusion of this group makes it difficult to draw any conclusions from these results.
6. Please explain how allocation concealment was maintained. It appears that study staff were provided the randomization lists and allowed to sequentially assign groups. This is subject to bias and may not have resulted in true random allocation. If this was indeed the case, please restate that this was a pseudorandomized trial.
7. Please explain what the authors mean when they say that in each group one participant was “randomized in error”.
8. In table 2, please clarify the CD4 count values presented.
9. The authors suggest that there was previously only one RCT in Zimbabwe evaluating HIV outcomes. This is not the case (as noted above). Please review the literature to ensure that all relevant prior trials are summarized and included in the discussion.

References

1. Walson J, Singa B, Sangaré L, Naulikha J, Piper B, Richardson B, Otieno P, Mbogo L, Berkley J, John-Stewart G: Empiric deworming to delay HIV disease progression in adults with HIV who are ineligible for initiation of antiretroviral treatment (the HEAT study): a multi-site, randomised trial. *The Lancet Infectious Diseases*. 2012; **12** (12): 925-932 [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Mar 2019

Andrew Abaasa, MRC/UVRI and LSHTM Uganda Research Unit, Uganda

Effect of high-intensity versus low-intensity praziquantel treatment on HIV disease progression in HIV and *Schistosoma mansoni* co-infected patients: a randomised controlled trial

Abaasa et al

Response to the reviewer's comments

Reviewer One

Judd L. Walson, Departments of Global Health, Medicine (Infectious Disease), Pediatrics and Epidemiology, University of Washington, Seattle, WA, USA

Approved with Reservations

This is an interesting manuscript presenting the results of a randomized trial comparing high-intensity treatment (frequent quarterly treatment) vs low intensity (annual) of schistosomiasis in HIV co-infected individuals. This paper adds to a previous RCT demonstrating lack of benefit with the use of empiric quarterly praziquantel in HIV infected individuals¹. Overall, this was an ambitious attempt to conduct a rigorous trial given considerable challenges in the selection of appropriate patients, potential for alternative treatments (such as ART) to impact the outcomes and need for high retention.

Unfortunately, there are a number of critical issues with the design and conduct of the trial that make the interpretation of these data difficult.

1. Overall, one cannot expect to see differences in HIV VL above and beyond reductions that would be expected with initiation of ART in antiretroviral naïve individuals. As such, the actual population for whom any expected benefit would need to exclude these individuals (which was done in a secondary analysis). Including these individuals in the primary analysis is problematic as they are not going to benefit from the intervention and they only serve to dilute the impact amongst the population who may benefit. Per my calculations, removing these individuals would leave 81 individuals per arm who were treated and did NOT receive ART. This suggests that the actual study was dramatically underpowered to detect the effect size for which it was designed. This is a significant limitation of the study. In addition, the fact that 12 individuals had undetectable VL at baseline is concerning, suggesting either that there were individuals who were included that had already initiated ART or that there were some fundamental issues with the laboratory in detecting VL. While it would be expected that some individuals in a population could be long-term non-progressors and have low to undetectable VL in the absence of treatment, the number

observed here is quite high and raises some concerns.

Response: This is a good observation, however, it may not invalidate the trial findings because

i) When you exclude from the analysis participants that initiated ART during follow up, which we did in the sensitivity analysis, given that the numbers come to 81, the study power becomes 84.4%, which is below the assumed 89% at the trial onset but above the conventional 80%. With 84.4% power, and under similar assumptions stated in the sample size estimation in the paper, we would still expect to demonstrate a difference if it truly existed.

ii) Indeed the 12 individuals were long-term non-progressors and had low or undetectable VL throughout follow up. We retested them for HIV sero-status to confirm they were truly positive and revisited them to make sure they were not on ART treatment. It is unlikely that the laboratory had issues in detecting VL because the undetectable VL was consistent for the 12 participants. Furthermore, the median and interquartile VL for participants that started ART was 51474 copies (IQR=16361 – 151520) before starting ART and reduced to 66 copies (IQR 10 - 371) at their last assessment after ART initiation.

2. The inclusion of a group of HIV infected, schisto negative “controls” does not add to the study. These individuals are likely to be different in many unmeasured ways from the coinfecting population and any comparison of this group is likely subject to considerable confounding. I found that the inclusion of this group detracted from the quality of the overall study.

Response: It is plausible that an infection such as schistosomiasis exacerbates HIV progression and that the effect is not reversible by treatment - because of persistence of helminth antigen, for example, and lasting impact on the immune system. As indicated in the discussion, we consider the results from the comparison group useful to address this possibility – there was no substantial difference in progression between the comparison group and either treatment arm. We do agree, however, that there were important (and largely inevitable) differences between the comparison group and the infected groups and we acknowledge that all comparisons with that group should be taken with caution and as secondary results. We draw our major findings from the two randomized arms.

3. The very high rates of LTFU in this study are concerning. Other RCTs with a similar length of follow up in East Africa among HIV infected adults achieve retention rates of greater than 90-95%. The high rates of LTFU suggest that there may have been differential loss and have introduced significant bias.

Response: The retention of 96 (85.9%) in the high intensity, 97 (85.8%) in the standard treatment arms and 107 (78.1%) in the comparison group at 60 weeks were greater than the average 75% reported in longitudinal studies in the fishing communities (a population which is highly mobile due to fluctuations in the fishing seasons). In fact, at the study onset, we assumed a loss to follow up of 20% based on the studies in the fishing communities. The reference is indicated in the sample size estimation section in the methods. It is true that other non-fishing populations have better retention rates because they tend to be more stable than the fishing population. As we report, the number of participants lost to follow up was similar between the trial arms 15.1% in the high intensity and 14.2% in the standard group. Both below the assumed 20% at the trial design stage.

4. Important to note that the intervention also included albendazole – any observed effect could also have been attributed to this.

Response: In our background, we describe previous results on effects of albendazole. However, none was given in this study until after the primary outcome measurement at 12 weeks, Thereafter it was given to all groups at the same time points and therefore would be unlikely to influence the comparisons made.

5. The exclusion of individuals with high intensity infection, while perhaps ethically necessary, is problematic for the interpretation of these data. It is likely that these are the individuals most likely to benefit from the intervention and the exclusion of this group makes it difficult to draw any conclusions from these results.

Response: It is good the reviewer acknowledges that participants with high worm load benefited from immediate treatment. Indeed this was done for ethical reasons. We acknowledge that the results of this paper may not directly be applicable to HIV Schistosoma co-infected patients with egg count >2000 eggs/g. Of note, however, this was the reason for exclusion for only 23 participants, so a minority group.

6. Please explain how allocation concealment was maintained. It appears that study staff were provided the randomization lists and allowed to sequentially assign groups. This is subject to bias and may not have resulted in true random allocation. If this was indeed the case, please restate that this was a pseudorandomized trial.

Response: This is a good observation. We have edited the manuscript to reflect the randomisation process as it happened. Allocation concealment only happened at the point of treatment allocation. Treatment was not concealed since it was directly observed, and with varying schedules.

We have therefore included this statement in the manuscript to improve clarity.

The study statistician generated two randomisation lists: i) containing trial numbers to which eligible participants would be allocated the next available number sequentially ii) containing trial numbers and the allocation arms. List (i) was held at the trial clinic, while list (ii) was held by the trial statistician. When an eligible participant was recruited on the next available number on the randomisation list (i), the statistician was contacted for the treatment allocation on list (ii).

7. Please explain what the authors mean when they say that in each group one participant was “randomized in error”.

Response: As a quality control measure, a clinician that did not participate in the assessment of eligibility and randomisation exercise revisited the eligibility procedures for each participant before treatment was given. Two ineligible participants were identified by this control measure and excluded from the trial before being treated, although they had been allocated a trial number. Coincidentally, the two participants would have been allocated to the different randomisation arms.

8. In table 2, please clarify the CD4 count values presented.

Response: The VL were transformed to log base 10 while the CD4 were transformed on

the natural logarithm. These have been clarified in the Table 2's footnote.

9. The authors suggest that there was previously only one RCT in Zimbabwe evaluating HIV outcomes. This is not the case (as noted above). Please review the literature to ensure that all relevant prior trials are summarized and included in the discussion.

Response: We focused on the RCT in Zimbabwe because it was the only previous trial to examine effects of treatment among individuals of confirmed Schistosoma infection status. We have clarified this in the discussion. We have also added reference to Dr Walson's HEAT trial in the introduction, and apologise for our earlier omission of this.

Competing Interests: I declare that i have no competing interests