Species-specific treatment effects of helminth/HIV-1 co-infection: a systematic review and meta-analysis

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SUMMARY

In sub-Saharan Africa, over 22 million people are estimated to be co-infected with both helminths and HIV-1. Several studies have suggested that de-worming individuals with HIV-1 may delay HIV-1 disease progression, and that the benefit of de-worming may vary by individual helminth species. We conducted a systematic review and meta-analysis of the published literature to determine the effect of treatment of individual helminth infections on markers of HIV-1 progression (CD4 count and HIV viral load). There was a trend towards an association between treatment for *Schistosoma mansoni* and a decrease in HIV viral load (Weighted mean difference (WMD) $= -0{\cdot}10$; 95% Confidence interval (CI): $-0{\cdot}24$, $0{\cdot}03$), although this association was not seen for *Ascaris lumbricoides*, hookworm or *Trichuris trichiura*. Treatment of *A. lumbricoides*, *S. mansoni*, hookworm or *T. trichiura* was not associated with a change in CD4 count. While pooled data from randomized trials suggested clinical benefit of de-worming for individual helminth species, these effects decreased when observational data were included in the pooled analysis. While further trials are needed to confirm the role of anthelmintic treatment in HIV-1 co-infected individuals, providing anthelmintics to individuals with HIV-1 may be a safe, inexpensive and practical intervention to slow progression of HIV-1.

Key words: Helminth, HIV-1, co-infection, meta-analysis, Kenya.

INTRODUCTION

Over 2 billion individuals are infected with one or more helminth species, making them among the most prevalent infections of humans (Hotez *et al*. 2006; de Silva *et al*. 2003). In many resource-limited settings, these helminth infections directly contribute to significant morbidity, particularly among young children and pregnant women (WHO, 2010). In addition, growing evidence suggests important immunological interactions between helminths and other diseases, including HIV-1, malaria and tuberculosis (Fincham *et al*. 2003; Mwangi *et al*. 2006; Brooker *et al*. 2007; Elias *et al*. 2007, 2008; Troye-Blomberg and Berzins, 2008; Labeaud *et al*. 2009; Moreau and Chauvin, 2010; Roussilhon *et al*. 2010). In sub-Saharan Africa, where the vast majority of HIV-1 infected individuals reside, over 22 million people are estimated to be co-infected with both helminths and HIV-1 (Fincham *et al*. 2003; UNAIDS, 2007). Evidence from several studies suggests that de-worming individuals co-infected with HIV-1 may delay HIV-1 disease progression by reducing HIV-1 viral load and/or increasing CD4 counts (Wolday *et al*. 2002; Brown *et al*. 2004;

Kallestrup *et al*. 2005; Modjarrad *et al*. 2005; Nielsen *et al*. 2007; Walson *et al*. 2008, 2009). The magnitude of changes in HIV-1 viral load documented in both individual randomized trials and in a pooled analyses of all available data ($0{\cdot}3$–$0{\cdot}5$ $\log_{10}$ copies/mL) may increase the annual risk of progression to an AIDS-defining illness or death by as much as 25%–44% (Modjarrad *et al*. 2008; Baggaley *et al*. 2009). It is plausible that providing anthelmintics to individuals with HIV-1 may be a safe, inexpensive and practical intervention to slow progression of HIV-1.

Variability in the geographical distribution of individual helminth species, as well as species-specific differences in the host response to helminth infection, may influence the relative benefit of de-worming in co-infected individuals (Brooker *et al*. 2000, 2009; Anthony *et al*. 2007; Hewitson *et al*. 2009; Bourke *et al*. 2010; WHO, 2010). Two randomized trials examining the effect of treating helminths on markers of HIV-1 progression have suggested significant benefit with the treatment of specific helminth species. In a randomized double-blind, placebo-controlled trial conducted in Kenya, significantly higher CD4 counts and a trend towards lower plasma HIV-1 viral load were reported following treatment with albendazole among individuals with documented *Ascaris lumbricoides* at baseline (Walson *et al*. 2008). In this study, significant benefit was not observed following the treatment of other species of soil-transmitted helminths. In addition,

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another randomized trial conducted in Zimbabwe also suggested a significant attenuation of plasma HIV-1 viral load increase following the treatment of *Schistosoma mansoni* (Kallestrup *et al.* 2005). It is unclear whether these differences in effect associated with the treatment of individual helminth species represent species-specific differences in the host immune response to de-worming, differences in the effectiveness of treatment regimens used for each species, or a failure to adequately power these studies to detect other important species-specific differences in treatment effects. It is important to examine the effect of eradicating individual helminth species on markers of HIV-1 disease transmission in order to target de-worming strategies to provide maximum benefit to co-infected individuals.

We previously reported data from a systematic review and meta-analysis of the published literature documenting benefit following helminth treatment among HIV-1 co-infected individuals (Walson *et al.* 2009). Given the possible differences in effect observed with individual helminth species, we have conducted a meta-analysis of these data to determine the effect of treatment of individual helminth infections on markers of HIV-1 progression. In addition, we examined strengths and limitations of available studies and suggest important considerations for the design and methodology of future studies evaluating the impact of de-worming among HIV-1-infected individuals. Determining if the effect of de-worming on markers of HIV-1 progression varies by helminth species may improve our understanding of host immunity and inform the development of effective interventions for HIV-1/helminth co-infected individuals.

MATERIALS AND METHODS

Searching strategy

We conducted a systematic review of the literature using the methods of the Cochrane Collaboration (Higgins and Green, 2009). The full text of the search strategy employed has been published previously (Walson and John-Stewart, 2008). The search was updated in January 2010 using MEDLINE (1966–2010), EMBASE (1980–2010), CENTRAL online (1980–2010) and AIDSearch online (1980–2010) to identify research studies that investigated the association between helminth co-infection and HIV-1 disease progression. The references of all identified articles, as well as review articles were examined to locate additional studies not identified during the computerized search. Studies published in all languages and in all countries were considered.

Selection

Each study was reviewed independently by the authors and included if it met all 5 of the following criteria: (1) study population included HIV-1 sero-positive individuals with documented helminth co-infection; (2) helminth infection was documented by direct stool microscopy, concentration techniques, other microscopic methods (such as Kato-Katz), culture of stool samples, antigen testing methods (e.g. ELISA kits), modified Knott's concentration methods for microfilaria, or other immunochromato-graphic testing methods; (3) anthelmintic therapy was defined as any intervention approved for use in the eradication of helminth infection in humans, including benzimidazoles, ivermectin, praziquantel, diethylcarbamazine, bithionol, oxamniquine, pyrantel and nitazoxanide; (4) studies utilized an appropriate control group including comparison to another anthelmintic drug, placebo, no treatment, or helminth uninfected individuals; and (5) study design was limited to either a randomized control trial comparing treatment to placebo among helminth-infected individuals, or a prospective cohort design comparing treatment among helminth-infected individuals to non-treated, non-helminth-infected individuals. The above criteria were selected to increase comparability between the studies.

Quality assessment

Quality assessments of observational and randomized trials have been previously published (Walson and John-Stewart, 2008; Walson *et al.* 2009). Quality of the studies varied both within study design and between study designs. Randomized studies were of the highest quality of included studies. Quality scores were not assigned.

Data abstraction

Separate standardized data abstraction forms were used for randomized trials and cohort studies. Authors JW and GJS independently extracted the following data elements: author(s), year of publication, year in which study was conducted, study design, study duration, completeness of follow-up for cohort studies, country and location of the study, setting (e.g. urban or rural, hospital or clinic), method(s) of recruitment; number of participants, characteristics of participants (age, gender, socio-economic status, HIV-1 stage if available), details of intervention (medication, dose, duration, number of treatments), details of outcomes (change in HIV-1 RNA, change in CD4 count, change in rate of clinical HIV-1 disease progression, changes in WHO or CDC staging, mortality), and quality assessment.

Where data were incomplete, attempts were made to contact the original authors for clarification of relevant information. Authors were asked to provide data when outcomes or populations included in this
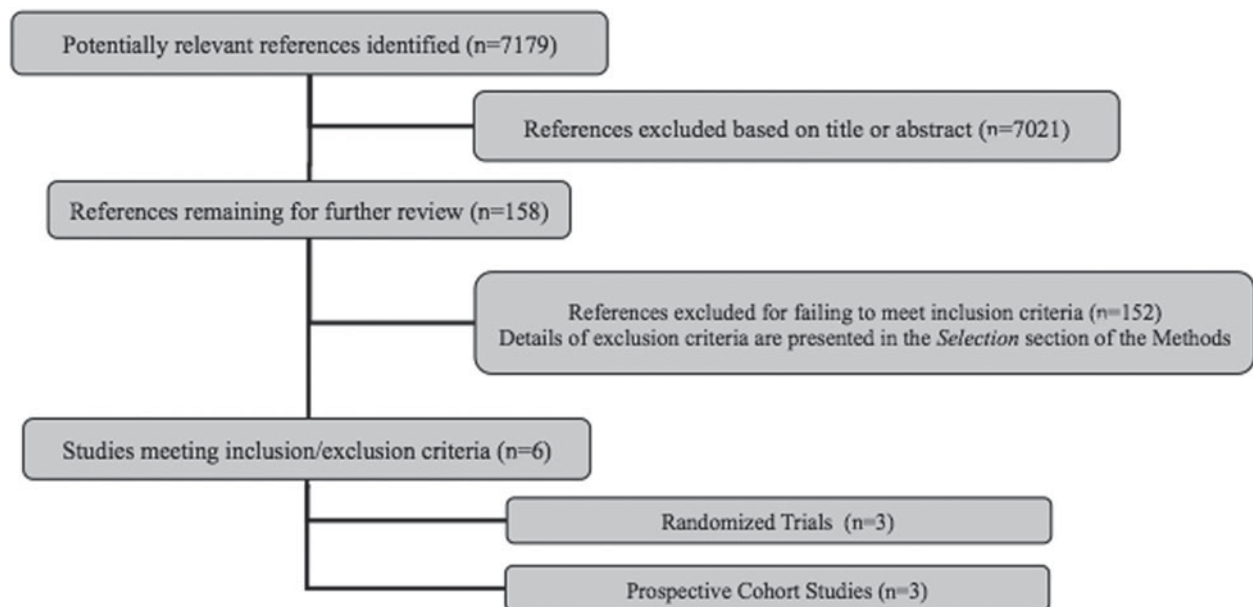
Fig. 1. Flow diagram of study selection with number of permissive articles.

review were not clearly defined in published manuscripts.

Study characteristics

Classification of studies. Study design was classified as either prospective cohort or randomized-controlled trial (RCT). Prospective cohort studies compared HIV-1 and helminth-co-infected individuals who were treated with anthelmintics to an internal comparison group consisting of HIV-1 infected, helminth uninfected individuals who did not receive anthelmintics. Randomized controlled trials were those studies in which assignment to treatment group (active drug or placebo) was determined by random allocation.

Outcome. The primary outcomes of interest were changes in plasma HIV-1 RNA levels and changes in absolute CD4 counts before and after use of anthelminthic therapy. Secondary outcome measures included markers of clinical disease progression, adverse events and mortality.

Quantitative data synthesis

Results from a systematic review and meta-analysis of the data by species are presented for those species evaluated in multiple studies and treated according to a standardized treatment recommendations. This is followed by a summary of results for species evaluated in only one study, or species-specific infections not treated according to the recommended treatment guidelines (Anonymous, 2007). CD4 and viral load outcomes included in this review were reported using similar continuous scales of measurement. CD4 counts were measured in cells/mm^3 and viral load was measured as $\log_{10}$ copies/mL. A weighted mean difference (WMD) and 95% confidence interval (CI) were computed as the change in CD4 count and change in $\log_{10}$ HIV-1 RNA after anthelmintic treatment (compared to participants who were helminth uninfected and untreated). WMDs of CD4 count and HIV viral load were evaluated between baseline and 12 weeks post-treatment in treatment and placebo groups in randomized trials (Kallestrup *et al*. 2005; Nielsen *et al*. 2007; Walson *et al*. 2008). The length of time between baseline and post-treatment follow-up used in the calculation of WMDs varied slightly in cohort studies from either 4 months (Elliott *et al*. 2003; Modjarrad *et al*. 2005), or 6 months (Brown *et al*. 2004) and comparisons were between helminth infected/treated and uninfected/untreated (Elliott *et al*. 2003; Brown *et al*. 2004; Modjarrad *et al*. 2005). The meta-analysis used a DerSimonian and Laird random effects model to compute pooled WMDs of CD4 count and HIV viral load. The Cochrane's chi-squared test for heterogeneity set at a significance of $P < 0.10$ was evaluated. The extent of heterogeneity was measured using tau squared, a measure of between-study variance. Data were analyzed using Stata 11 (Stata Corporation, College Station, TX) and figures were created using Stata version 11.

RESULTS

Using the search criteria outlined above, we identified 7,179 published studies of which 6 articles met the pre-specified inclusion criteria (Fig. 1). The study population included HIV-1-infected adults co-infected with at least one helminth species. The number of studies evaluating each helminth

Table 1. Summary of included studies

Author (Year)	Study design	County: Study Period	Sub-group analysis population	Intervention or treatment group	Comparison group	Time point of evaluation
Kallestrup (2005)	RCT	Zimbabwe: Oct 2001 to June 2003	HIV-1 (+) adults (18 years and older) co-infected with S. *mansoni*	HIV/*S. mansoni* co-infection Praziquantel 40 mg/kg at baseline	HIV/*S. mansoni* co-infection and placebo	Baseline and 12 weeks
Nielsen (2007)	RCT	Tanzania: May to Nov 2002	HIV-1 (+) adults (18–70 years) co-infected with *W. bancrofti*	HIV/*W. bancrofti*: co-infection Diethylcarbamazine 6 mg/kg at baseline	HIV/*W. bancrofti* co-infection and placebo	Baseline and 12 weeks
Walson (2008)	RCT	Kenya: March 2006 to June 2007	HIV-1 (+) adults co-infected with *A. lumbricoides*, hookworm, or *T. trichiura*	HIV/*A. lumbricoides* co-infection HIV/Hookworm co-infection HIV/*T. trichiura* co-infection Albendazole 400 mg/day × 3 days at enrollment	HIV/any helminth co-infection (*A. lumbricoides*, hookworm, or *T. trichiura*) and placebo	Baseline and 12 weeks
Brown (2004)	Prospective cohort study	Uganda: Feb 2001 to Mar 2002	HIV-1 (+) adults co-infected with *S. mansoni*, hookworm, *T. trichiura*, *S. stercoralis*, or *M. perstans* and HIV-1 (+) adults without co-infection	HIV/Hookworm; HIV/*T. trichiura*; HIV/*M. perstans*: Albendazole 400 mg at enrollment; HIV/*S. mansoni*: Praziquantel 40 mg/kg month 1; HIV/*S.stercoralis*: Albendazole 800 mg/day × 3 days at enrollment	HIV/helminth uninfected and untreated	Baseline and 6 months
Elliott (2003)	Prospective cohort study	Uganda: Nov 1999 to Jan 2000	HIV-1 (+) adults co-infected with *S. mansoni*, *A. lumbricoides*, hookworm, *T. trichiura* and HIV-1 (+) adults without co-infection	HIV/*S. mansoni*: Praziquantel, 40 mg/kg at enrollment. HIV/*A. lumbricoides*, HIV/hookworm, HIV/*T. trichiura*: Mebendazole, 200 mg/day × 3 days at enrollment	HIV/helminth uninfected and untreated	Baseline and 4 months
Modjarrad (2005)	Prospective cohort study	Zambia: Mar to Dec 2003	HIV-1 (+) adults (19–45 years) co-infected with *S. mansoni*, *A. lumbricoides*, hookworm, *S. stercoralis* and HIV-1 (+) adults without co-infection	HIV/*A. lumbricoides*, HIV/Hookworm, HIV/*S. stercoralis*: Albendazole 400 mg × 1 day and 200 mg × 2 days (weeks 1 and 4); HIV/*S. mansoni*: Praziquantel 40 mg/kg	HIV/helminth uninfected and untreated	Baseline and 4 months

Table 2. Recommended treatment regimen by helminth species

Helminth	Treatment regimens used in included studies	Recommended adult treatment[1]
S. mansoni	Praziquantel 40 mg/kg × 1d	Praziquantel: 40 mg/kg PO in 2 doses × 1d Oxamniquine: 15 mg/kg PO once
A. lumbricoides	Albendazole 400 mg × 1d Albendazole 400 mg × 3d Mebendazole 200 mg × 3d	Albendazole: 400 mg PO once Mebendazole: 100 mg bid PO × 3d or 500 mg once Ivermectin: 150-200mcg/kg PO once
Hookworm	Albendazole 400 mg × 1d Albendazole 400 mg × 3d Mebendazole 200 mg × 3d	Albendazole: 400 mg PO once Mebendazole: 100 mg PO bid × 3d or 500 mg once Pyrantel pamoate: 11 mg/kg (max 1 g) PO × 3d
T. trichiura	Albendazole 400 mg × 1d Albendazole 400 mg × 3d Mebendazole 200 mg × 3d	Preferred drug: Mebendazole: 100 mg bid PO × 3d or 500 mg once Alternatives: Albendazole: 400 mg PO × 3d Ivermectin: 200 mcg/kg PO × 3d
S. stercoralis	Albendazole 800 mg × 3d Albendazole 400 mg × 1d + 200 mg × 2d	Preferred drug: Ivermectin: 200 mcg/kg/d PO × 2d Alternative: Albendazole: 400 mg PO bid × 7d
M. perstans	Albendazole 400 mg × 1d	Albendazole: 400 mg PO bid × 10d Mebendazole: 100 mg PO bid × 30d
W. bancrofti	Diethylcarbamazine 6 mg/kg × 1d	Diethylcarbamazine: 6 mg/kg/d PO in 3 doses × 12d

Key to abbreviations: d: Day; PO: By mouth; BID: Twice a day.
[1] Source: Anon. (2007). Drugs for parasitic infections. *Medical Letter on Drugs and Therapeutics,* **5 (Suppl)**, e1–e15.

Table 3. Weighted mean differences (WMDs) of CD4 count outcomes by species

Worm	Author (Year)	Study design	Treatment	Control	CD4 WMD (95% CI)
A. lumbricoides	Walson (2008)	RCT	26	28	−120·0 (−190·9, −49·1)
	Elliott (2003)	Observational	2	34	−47·0 (−368·2, 274·2)
	Modjarrad (2005)	Observational	27	57	3·0 (−82·2, 88·2)
	Pooled		55	119	−60·4 (−159·9, 39·1)
S. mansoni	Kallestrup (2005)	RCT	64	66	−33·5 (−118·2, 51·2)
	Brown (2004)	Observational	118	171	−8·0 (−70·9, 54·9)
	Elliott (2003)	Observational	24	34	−47·0 (−206·6, 112·6)
	Modjarrad (2005)	Observational	5	57	10·0 (−176·3, 196·3)
	Pooled		211	328	−17·9 (−64·5, 28·7)
Hookworm	Walson (2008)	RCT	76	72	−22·0 (−73·5, 29·5)
	Brown (2004)	Observational	79	171	2·0 (−75·2, 79·2)
	Elliott (2003)	Observational	14	34	−80·0 (−278·2, 118·2)
	Modjarrad (2005)	Observational	24	57	103·0 (−19·4, 225·4)
	Pooled		193	334	0·14 (−51·1, 51·4)
T. trichiura	Walson (2008)	RCT	12	12	−41·0 (−190·1, 108·1)
	Brown (2004)*	Observational	15	171	−6·0 (−136·1, 124·1)
	Elliott (2003)	Observational	6	34	−109·0 (−394·4, 176·4)
	Pooled		18	46	−55·6 (−187·7, 76·6)
S. stercoralis	Brown (2004)	Observational	41	171	−8·0 (−89·7, 73·6)
	Modjarrad (2005)	Observational	4	57	−5·0 (−87·3, 77·3)
M. perstans	Brown (2004)	Observational	23	171	−2·0 (−96·3, 92·3)
W. bancrofti	Nielsen (2007)	RCT	6	6	−5·2 (−17·6, 7·3)

* Not included in pooled estimate because of treatment regimen.

species is as follows; (*S. mansoni* (n = 4) (Elliott *et al.* 2003; Brown *et al.* 2004; Kallestrup *et al.* 2005; Modjarrad *et al.* 2005), *Strongyloides stercoralis* (n = 2) (Brown *et al.* 2004; Modjarrad *et al.* 2005), hookworm species (n = 4) (Elliott *et al.* 2003; Brown *et al.* 2004; Modjarrad *et al.* 2005; Walson *et al.* 2008), *Trichuris trichiura* (n = 3) (Elliott *et al.* 2003; Brown *et al.* 2004; Walson *et al.* 2008), *A. lumbricoides*

(n = 3) (Elliott *et al.* 2003; Modjarrad *et al.* 2005; Walson *et al.* 2008), *Wuchereria bancrofti* (n = 1) (Nielsen *et al.* 2007), and *Mansonella perstans* (n = 1)) (Brown *et al.* 2004). All of the studies included were conducted in sub-Saharan Africa and all were published between 2003 and 2008.

A total of 3 randomized controlled trials (Kallestrup *et al.* 2005; Nielsen *et al.* 2007; Walson

Table 4. *Weighted mean differences (WMDs) of viral load outcomes by species*

Worm	Author (Year)	Study design	Treatment	Control	VL WMD (95% CI)
A. lumbricoides	Walson (2008)	RCT	26	28	−0·85 (−1·46, −0·24)
	Elliott (2003)	Observational	2	34	0·19 (−0·73, 1·11)
	Modjarrad (2005)	Observational	27	57	−0·12 (−0·42, 0·18)
	Pooled		55	119	−0·29 (−0·83, 0·25)
S. mansoni	Kallestrup (2005)	RCT	64	66	−0·21 (−0·40, −0·02)
	Brown (2004)	Observational	79	126	0·04 (−0·19, 0·27)
	Elliott (2003)	Observational	24	34	−0·06 (−0·54, 0·42)
	Modjarrad (2005)	Observational	5	57	−0·09 (−0·68, 0·50)
	Pooled		172	283	−0·10 (−0·24 to 0·03)
Hookworm	Walson (2008)	RCT	76	72	0·02 (−0·30, 0·34)
	Brown (2004)	Observational	55	126	−0·11 (−0·37, 0·15)
	Elliott (2003)	Observational	14	34	0·11 (−0·55, 0·77)
	Modjarrad (2005)	Observational	24	57	0·03 (−0·35, 0·41)
	Pooled		169	289	−0·03 (−0·20, 0·15)
T. trichiura	Walson (2008)	RCT	12	12	0·34 (−0·42, 1·10)
	Brown (2004)*	Observational	10	126	−0·17 (−0·69, 0·35)
	Elliott (2003)	Observational	6	34	−0·05 (−0·69, 0·59)
	Pooled		18	46	0·11 (−0·38, 0·60)
S. stercoralis	Brown (2004)	Observational	26	126	0·00 (−0·31, 0·31)
	Modjarrad (2005)	Observational	4	57	−0·07 (−0·60, 0·46)
M. perstans	Brown (2004)	Observational	18	126	−0·04 (−0·47, 0·39)
W. bancrofti	Nielsen (2007)	RCT	5	6	−0·08 (−0·93, 0·77)

* Not included in pooled estimate because of treatment regimen.

et al. 2008) and 3 prospective cohort studies (Elliott *et al*. 2003; Brown *et al*. 2004; Modjarrad *et al*. 2005) were included. Study methodology was similar among randomized trials and prospective cohort studies regardless of the helminth species investigated. Details of the methodology used in each study are listed in Table 1.

Treatment courses for nematode infections varied between studies; consisting of either 400 mg of albendazole/day for 3 days (Walson *et al*. 2008), 400 mg of albendazole on the first day followed by 200 mg per day for 2 days (Modjarrad *et al*. 2005), a single dose of 400 mg of albendazole (Brown *et al*. 2004), or 200 mg of mebendazole per day for 3 days (Elliott *et al*. 2003). One study prescribed 800 mg of albendazole for 3 days for infections with *S. stercoralis* (Brown *et al*. 2004). Schistosome infections were evaluated in 4 studies and all used a standard dose of 40 mg/kg of praziquantel for treatment (Elliott *et al*. 2003; Brown *et al*. 2004; Kallestrup *et al*. 2005; Modjarrad *et al*. 2005).

Pooled analyses were performed on the 4 helminth species in which; (1) results were available from more than 1 study and (2) treatments followed currently recommended guidelines for each of the included species (*A. lumbricoides, S. mansoni*, Hookworm and *T. trichiura* - Elliott *et al*. 2003; Brown *et al*. 2004; Modjarrad *et al*. 2005; Walson *et al*. 2008 – see Table 2). Results of the pooled-estimates evaluating the effect of helminth treatment on CD4 count and HIV viral load are presented below for each species separately. Heterogeneity was minimal ($P > 0·2$) in all

of the analyses presented with the exception of change in CD4 count and viral load among individuals with *A. lumbricoides* (results described below). CD4 results for each species are presented in Table 3, and HIV viral load results are presented in Table 4.

Species-specific effects of treatment

A. lumbricoides. Three studies evaluated the effect of treatment for *A. lumbricoides* on CD4 count (n = 174) and HIV viral load (n = 174) (Elliott *et al*. 2003; Modjarrad *et al*. 2005; Walson *et al*. 2008). Details of the study design and methodology are summarized in Table 1. Using a random effects model, treatment for *A. lumbricoides* was not associated with CD4 count (WMD = − 60·4; 95% CI: −159·9, 39·1) (Fig. 2A), or HIV viral load (WMD = − 0·29; 95% CI: −0·83, 0·25) (Fig. 2B). The test for heterogeneity was statistically significant in both the analysis of HIV viral load ($P = 0·07$, tau squared = 0·14) and CD4 count ($P = 0·09$, tau squared = 0·00).

S. mansoni. Four studies evaluated the effect of treatment for *S. mansoni* on CD4 (n = 539) and HIV viral load (n = 455) (Elliott *et al*. 2003; Brown *et al*. 2004; Kallestrup *et al*. 2005; Modjarrad *et al*. 2005) (Table 1). Using a random effects model, treatment for *S. mansoni* was not associated with CD4 count (WMD = − 17·9; 95% CI: −64·5, 28·7) (Fig. 3A), however there was a trend towards an association
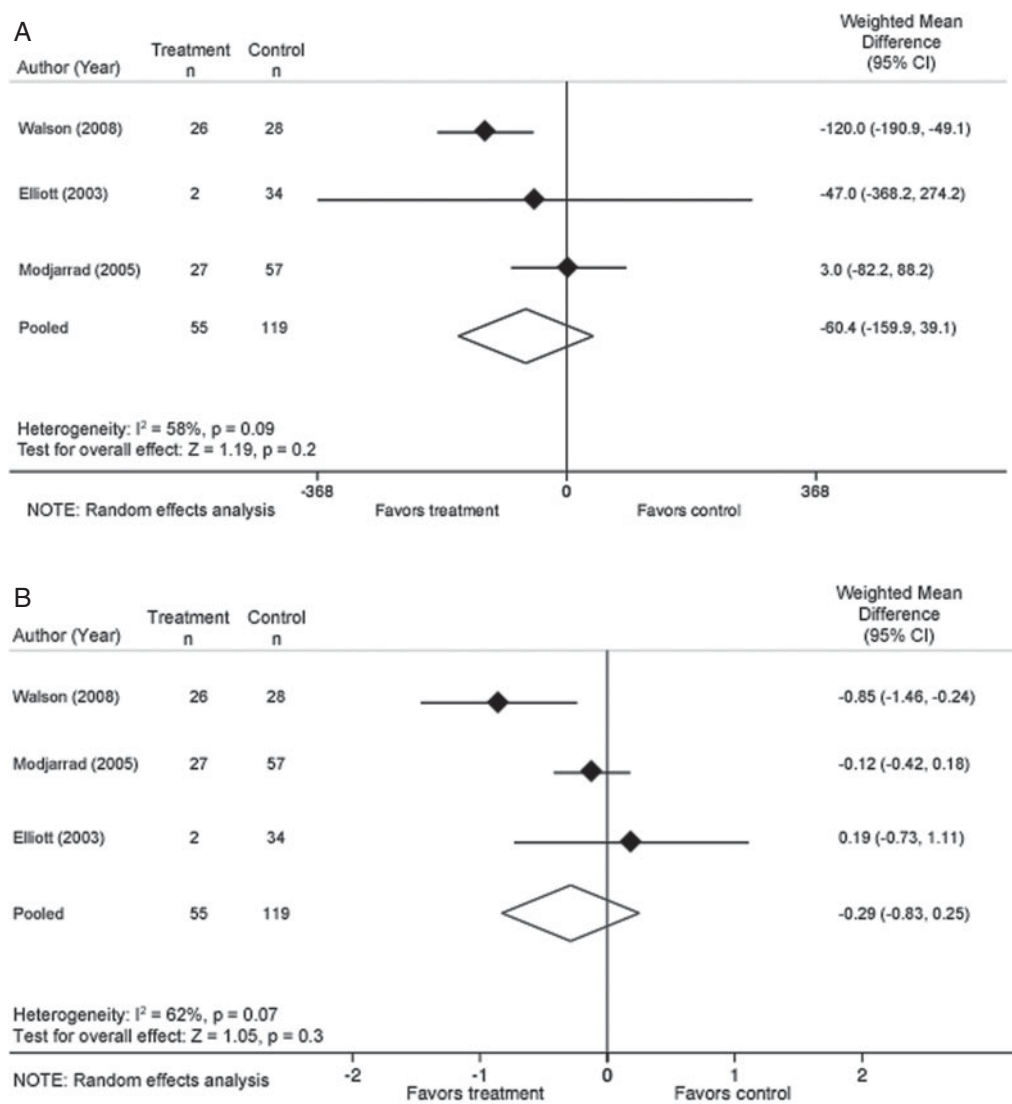
Fig. 2. Treatment effect of *A. lumbricoides* on HIV disease progression. A. *A. lumbricoides*: Change in CD4 count after treatment or no treatment. B. *A. lumbricoides*: Change in Log_{10} HIV-1 RNA after treatment or no treatment.

between treatment for *S. mansoni* and a decrease in HIV viral load (WMD = − 0·10; 95% CI: −0·24, 0·03) (Fig. 3B).

Hookworm. Four studies evaluated the effect of treatment for hookworm on CD4 (n = 527) and HIV viral load (n = 458) (Elliott *et al.* 2003; Brown *et al.* 2004; Modjarrad *et al.* 2005; Walson *et al.* 2008) (Table 1). Using a random effects model, treatment for hookworm was not associated with CD4 count (WMD = 0·14; 95% CI: −51·1, 51·4) (Fig. 4A) or HIV viral load (WMD = − 0·03; 95% CI: −0·20, 0·15) (Fig. 4B).

T. trichiura. While 3 studies included in this review evaluated the effect of treatment for *T. trichiura* on CD4 and HIV viral load, the pooled data are limited to the 2 studies which gave the recommended treatment course of either 200 mg of mebendazole for 3 days (Elliott *et al.* 2003) or 400 mg of albendazole for 3 days (Walson *et al.* 2008). A total

of 64 subjects are included in the viral load analysis and 64 are included in the analysis of CD4 count (Elliott *et al.* 2003; Brown *et al.* 2004; Walson *et al.* 2008) (Table 1). Using a random effects model, treatment for *T. trichiura* was not associated with CD4 count (WMD = − 55·6; 95% CI: −187·7, 76·6) (Fig. 5A) or HIV viral load (WMD = 0·11; 95% CI: −0·38, 0·60) (Fig. 5B).

M. perstans. One prospective cohort study evaluated the effect of treatment of *M. perstans* on CD4 count and HIV viral load (n = 144) (Brown *et al.* 2004), therefore, pooled data are unavailable. Treatment in this study consisted of a single dose of 400 mg of albendazole. Treatment of *M. perstans* was not associated with CD4 count (WMD = − 2·0; 95% CI: −96·3, 92·3) or HIV viral load in this study (WMD = − 0·04; 95% CI: −0·47, 0·39).

W. bancrofti. One randomized clinical trial evaluated the effect of treatment of *W. bancrofti* on CD4
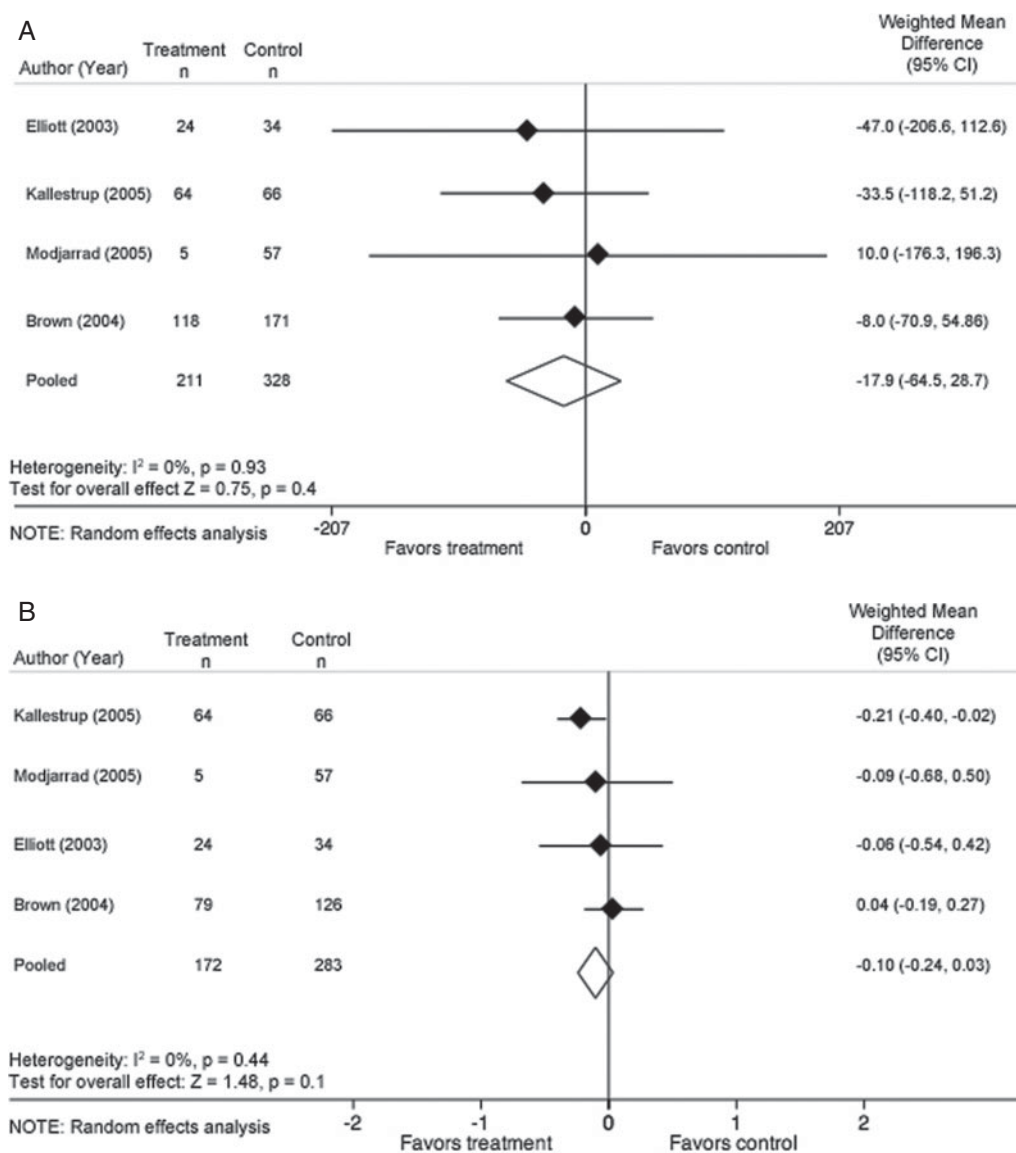
Fig. 3. Treatment effect of *S. mansoni* on HIV disease progression. A. *S. mansoni*: Change in CD4 count after treatment or no treatment. B. *S. mansoni*: Change in Log_{10} HIV-1 RNA after treatment or no treatment.

count and HIV viral load (n = 17) (Nielsen *et al.* 2007), therefore pooled data are unavailable. Infections with treated with 6 mg/kg of diethylcarbamazine. Treatment of *W. bancrofti* was not associated with CD4 count (WMD = −5·2; 95% CI: −17·6, 7·3) or HIV viral load (WMD = −0·08; 95% CI: −0·93, 0·77) in this study.

S. stercoralis. Two cohort studies evaluated the effect of treatment for *S. stercoralis* on CD4 (n = 273) and viral load (213) (Brown *et al.* 2004; Modjarrad *et al.* 2005). HIV-1-infected individuals in these studies were treated with either 800 mg of albendazole for 3 days (Brown *et al.* 2004), or 400 mg of albendazole on the first day and 200 mg for 2 subsequent days (Modjarrad *et al.* 2005). Because neither of these studies utilized the current recommended dose of 400 mg of albendazole per day for 7 days (Anonymous, 2007), these data were not

pooled. Lastly, neither of these studies found a treatment effect on CD4 count or HIV viral load.

DISCUSSION

Data from several randomized trials have suggested species-specific differences exist in the observed benefit associated with de-worming, specifically among individuals infected with *A. lumbricoides* and *S. mansoni*. In this analysis, we stratified data from studies evaluating the effect of de-worming on markers of HIV-1 disease progression by helminth species and conducted a pooled analysis including data from both randomized and observational studies. Data from sub-group analyses from studies examining the treatment of *A. lumbricoides*, *S. mansoni*, hookworm, *T. trichiura*, *M. perstans* and *W. bancrofti* in HIV-co-infected individuals were included. In this pooled analysis, no significant
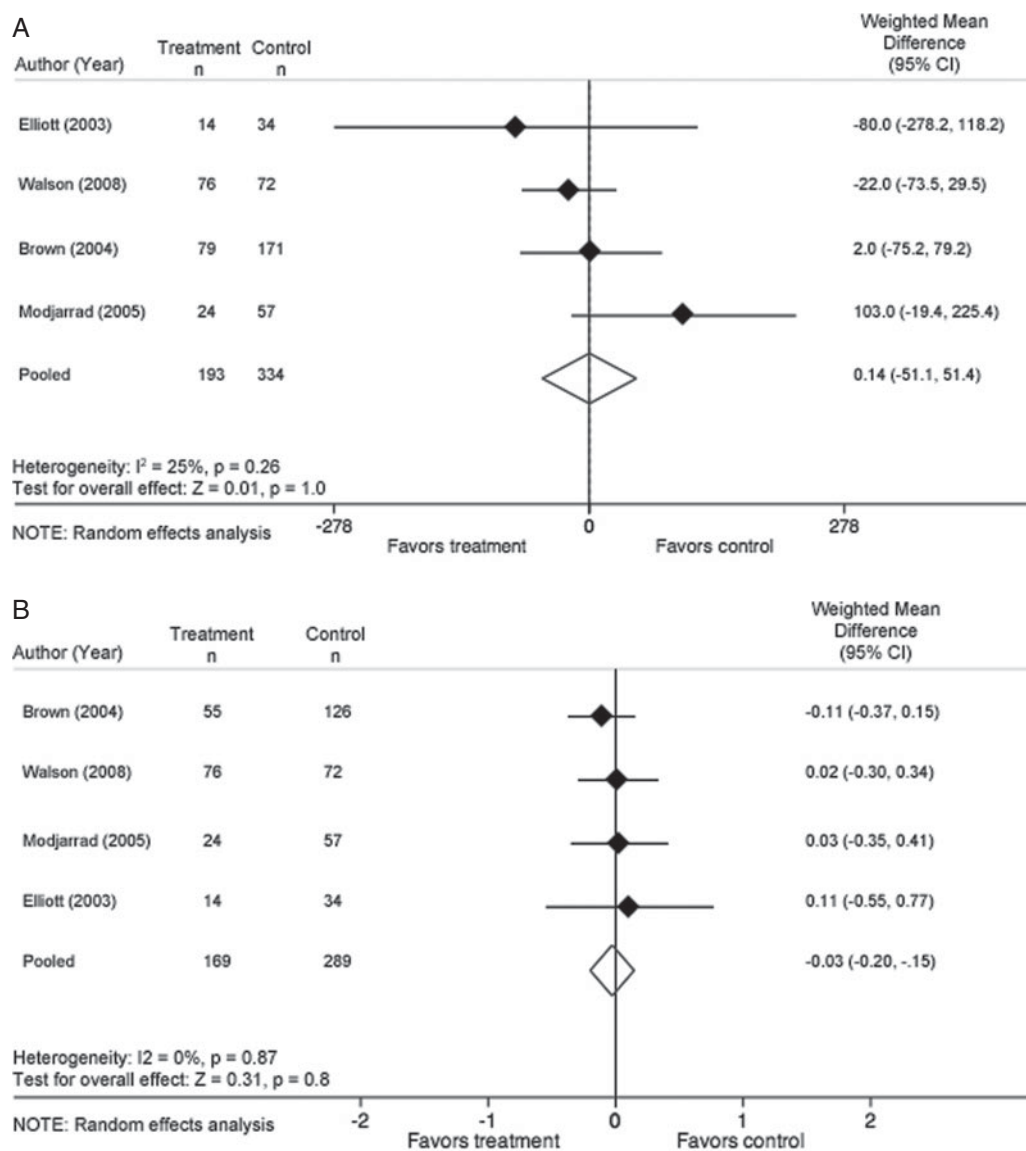
Fig. 4. Treatment effect of Hookworm on HIV disease progression. A. Hookworm: Change in CD4 count after treatment or no treatment. B. Hookworm: Change in Log_{10} HIV-1 RNA after treatment or no treatment.

benefits on markers of HIV-1 disease progression were observed with the treatment of any individual helminth species.

It is possible that the observation of benefit observed in the randomized trials following treatment of *A. lumbricoides* and *S. mansoni* was a result of type I error. However, as the randomized trial design provides the strongest level of evidence, the highly significant improvement in CD4 count and trend towards a reduction in viral load following deworming in *A. lumbricoides* and HIV-1-co-infected individuals seen in one randomized trial (Walson *et al.* 2008), and the significant attenuation in viral load observed following treatment for schistosomiasis in another randomized trial (Kallestrup *et al.* 2005), suggest that type I error is unlikely. It appears more likely that the inclusion of observational studies in the pooled analysis may have resulted in type II

errors, as many of these studies had notable limitations in their design and methodology.

There are several possible explanations for why benefit was observed in randomized trials following treatment of *A. lumbricoides* and *S. mansoni,* but not with other helminth species. *A. lumbricoides*-infected individuals, when compared to helminth uninfected controls, have been observed to have lower levels of TH1 cytokines and higher levels of TH2, pro-inflammatory, and immunosuppressive cytokines (Malla *et al.* 2006). These differences in TH2 polarization appear to be more prominent with *A. lumbricoides* infection than with hookworm or *Trichuris* (Cooper *et al.* 2000; Pit *et al.* 2001; Bradley and Jackson, 2004; Jackson *et al.* 2004; Geiger *et al.* 2007). HIV-1- infected individuals co-infected with *A. lumbricoides* who received albendazole displayed significantly larger reductions in
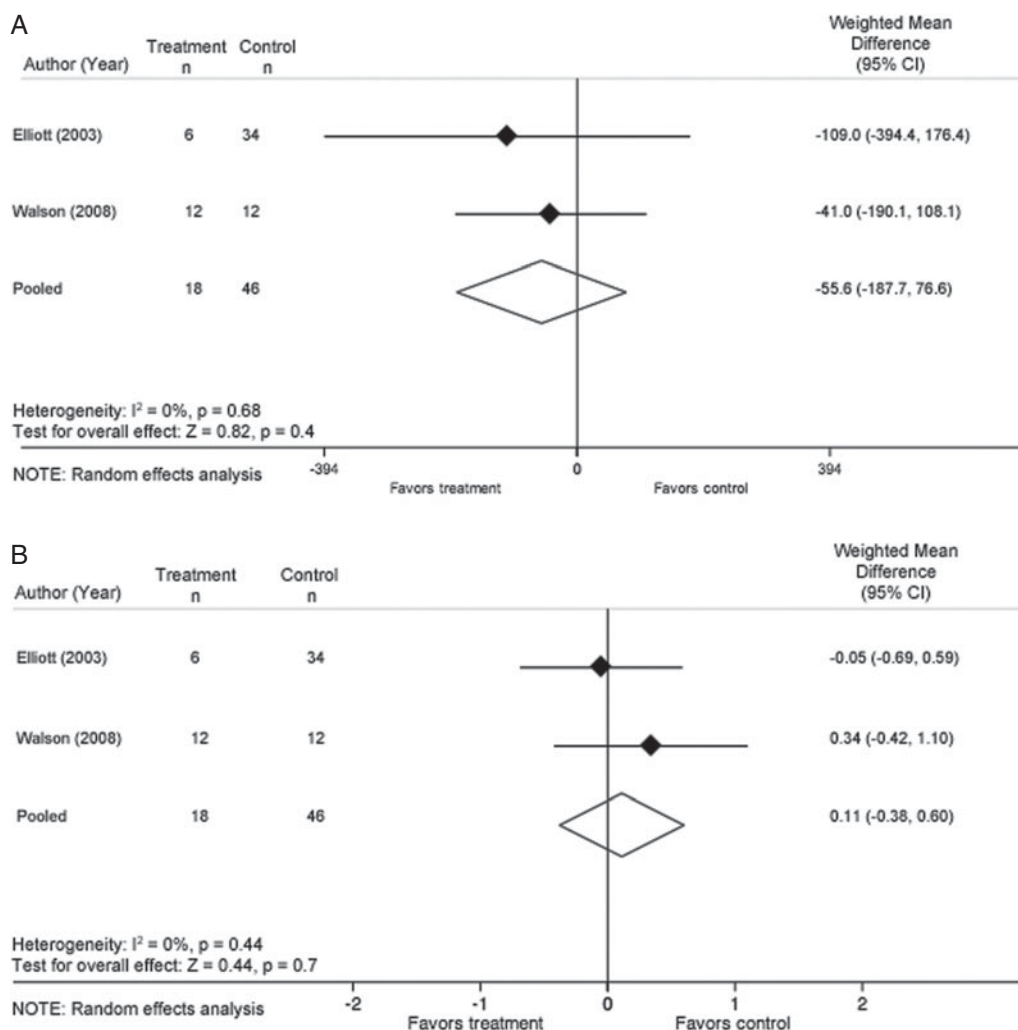
Fig. 5. Treatment effect of *T. trichiura* on HIV disease progression. A. *T. trichiura*: Change in CD4 count after treatment or no treatment. B. *T. trichiura*: Change in Log_{10} HIV-1 RNA after treatment or no treatment.
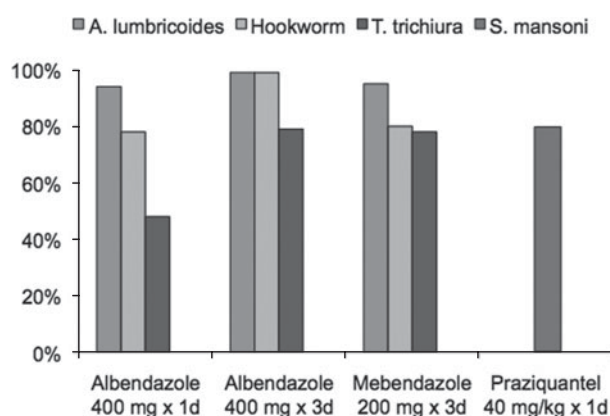

Fig. 6. Previously published data on the proportion of patients cured by treatment regimen.(Footnote to Fig. 6): Data Sources: (Marti *et al*., 1996; Bennett and Guyatt, 2000; Horton, 2000; Ferrari *et al*., 2003; Keiser and Utzinger, 2008).

interleukin-10 (IL-10) when compared to those receiving placebo, suggesting treatment of *A. lumbricoides* may reduce IL-10- mediated immunosuppression (Blish *et al*. 2010). Similarly, a predominant

TH2 response is also thought to occur among individuals with early schistosomiasis, followed by IL-10 mediated hyporesponsiveness during chronic infection (Burke *et al*. 2009; Taylor *et al*. 2009). The strong TH2 polarization and IL-10-mediated hyporesponsiveness seen with these infections may significantly affect the hosts ability to control HIV-1 replication and may explain the observation of benefit following de-worming of *A. lumbricoides* and *S. mansoni*-infected individuals.

The failure to detect an association between de-worming and markers of HIV-1 progression may also have been influenced by the variation in efficacy of the treatment regimens used for each species. The efficacy of a single 400 mg dose of albendazole is significantly different for each of these individual helminth species (Fig. 6). While this treatment regimen is highly effective against *A. lumbricoides* (cure >94%) (Bennett and Guyatt, 2000; Horton, 2000; Keiser and Utzinger, 2008), cure rates are significantly lower for hookworm (cure 78%) (Horton, 2000) and *T. trichiura* (cure 28–48%) (Bennett and Guyatt, 2000; Horton, 2000; Keiser

and Utzinger, 2008). The lower efficacy of treatment of hookworm and *T. trichiura* infection may have reduced the ability of this analysis to detect an effect, as many of these individuals who were randomized to albendazole may not actually have been cured of their infection. These individuals would effectively dilute the effect of treatment observed in the analysis.

Finally, it is important to note that many studies conducted to date have not been designed to evaluate species-specific effects among individual sub-groups of patients. In retrospectively evaluating the power of published studies, we determined that less than 35% of sub-group analyses had adequate power (> 80%) to detect meaningful differences when stratified by individual helminth species. It is plausible that species-specific differences have not consistently been observed due to inadequate power in these studies.

Due to the wide heterogeneity of methodologies used in HIV/helminth co-infection treatment studies, we applied stringent inclusion criteria, resulting in only six studies being included in this review. Many studies conducted to date have included inappropriate comparison groups, limiting the ability of these studies to make valid comparisons. Some studies have compared individuals who test negative for helminths at follow-up to those who test positive for helminths at follow-up. There may be important differences in the immunological responses to helminth infection between individuals who successfully clear helminth infection following therapy and those who do not (Mutapi, 2001; Anthony *et al.* 2007). These differences may also be related to individual immune control of HIV-1. Differences in factors associated with risk of re-exposure to helminth infection are also likely to exist between participants who are rapidly re-infected with helminths compared to those who are not. Given that both re-infection and/or decreased immune control of HIV-1 are likely to dilute the treatment effect, this methodology may result in a significant bias towards the null.

Insufficient data from individual trials exist to determine the effect of treating individual helminths on markers of HIV-1 progression. As a result, we sought to increase the effective sample size of each comparison by pooling data from multiple prospective studies. While this approach may add power to the analysis of each comparison, differences in study design and methodology between included studies are an important limitation of this analysis. In addition, while randomized trials of anthelminthic therapy provide the strongest level of evidence to determine the possible benefit of such treatment, the analysis of sub-groups within these cohorts reduces the benefit of randomization. We also included several observational studies, all of which may be limited by bias. The lack of standardized treatment regimens included in the analysis likely resulted in

differences in treatment efficacy by study and by species. Finally, study sample sizes were relatively small and species-specific analyses from individual studies lacked power to detect meaningful effects.

While the implications of these data may be important for all HIV-1-infected individuals, HIV-1-infected children may benefit disproportionately. In addition to harbouring a large burden of helminth infections, HIV infection is often undiagnosed and untreated in young children in many resource-limited settings. Without effective antiretroviral therapy, mortality approaches 50% in the first two years of life for these children. It is critical that practical and effective approaches to delay immuno-suppression be examined and implemented in pediatric populations in order to maximize benefit.

Conclusions

Understanding differences in the treatment effects among helminth species may lead to better clinical and therapeutic management of these infections. It is important to determine the relative benefit of treating individual helminth species on markers of HIV-1 progression. Further trials are needed to confirm the possible role of anthelmintic treatment in HIV-1 co-infected individuals, particularly in populations most likely to benefit, such as young children. Such studies should be rigorously designed and adequately powered to detect species-specific effects.

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CORRIGENDUM

Species-specific treatment effects of helminth/HIV-1 co-infection: a systematic review and meta-analysis – CORRIGENDUM

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Please note the correct spelling of the second author's name, Bradley R. Herrin.

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