Published in final edited form as:

Cochrane Database Syst Rev. ; (3): CD006419. doi:10.1002/14651858.CD006419.pub3.

Deworming helminth co-infected individuals for delaying HIV disease progression

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Abstract

Background—The HIV-1 pandemic has disproportionately affected individuals in resource-constrained settings where other infectious diseases, such as helminth infections, also are highly prevalent. There are biologically plausible reasons for possible effects of helminth infection in HIV-1-infected individuals, and findings from multiple studies suggest that helminth infection may adversely affect HIV-1 progression. Since initial publication of this review (Walson 2007), additional data from randomized controlled trials (RCTs) has become available. We sought to evaluate all currently available evidence to determine if treatment of helminth infection in HIV-1 co-infected individuals impacts HIV-1 progression.

Objectives—To determine if treating helminth infection in individuals with HIV-1 can reduce the progression of HIV-1 as determined by changes in CD4 count, viral load, or clinical disease progression.

Search strategy—In this 2008 update, we searched online for published and unpublished studies in *The Cochrane Library*, MEDLINE, EMBASE, CENTRAL, and AIDSEARCH. We also searched databases listing conference abstracts, scanned reference lists of articles, and contacted authors of included studies.

Selection criteria—We searched for RCTs and quasi-RCTs that compared HIV-1 progression as measured by changes in CD4 count, viral load, or clinical disease progression in HIV-1 infected individuals receiving anti-helminthic therapy.

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CONTRIBUTIONS OF AUTHORS

JW, BH, and GJS all contributed to the protocol design of this updated review. JW and BH screened the identified abstracts and manuscripts; JW, BG, and GJS all assisted in the analysis of the findings and preparation of the final manuscript.

DECLARATIONS OF INTEREST

None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

N/A

*Indicates the major publication for the study

SOURCES OF SUPPORT

Internal sources

- University of Washington, Center for AIDS Research (CFAR), USA.

External sources

- NIH Office of AIDS Research (OAR) for Prevention Science Initiative (PSI), USA.

Data collection and analysis—Data regarding changes in CD4 count, HIV-1 RNA levels, and/or clinical staging after treatment of helminth co-infection were extracted from identified studies.

Main results—Of 7,019 abstracts identified (6,384 from original searches plus 635 from updated searches), 17 abstracts were identified as meeting criteria for potential inclusion (15 from previous review plus an additional two RCTs). After restricting inclusion to RCTs, a total of three studies were eligible for inclusion in this updated review.

All three trials showed individual beneficial effects of helminth eradication on markers of HIV-1 disease progression (HIV-1 RNA and/or CD4 counts). When data from these trials were pooled, the analysis demonstrated significant benefit of deworming on both plasma HIV-1 RNA and CD4 counts.

Authors' conclusions—To date, three RCTs have evaluated the effects of deworming on markers of HIV-1 disease progression in helminth and HIV-1 co-infected individuals. All trials demonstrate benefit in attenuating or reducing plasma viral load and/or increasing CD4 counts. When taken together, there is evidence of benefit for deworming HIV-1 co-infected adults. Given that these studies evaluated different helminth species and different interventions, further trials are warranted to evaluate species-specific effects and to document long-term clinical outcomes following deworming.

INDEX TERMS

Medical Subject Headings (MeSH); *Health Resources; *HIV-1 [genetics]; CD4 Lymphocyte Count; Disease Progression; Helminthiasis [complications; *drug therapy]; HIV Infections [*complications; parasitology; virology]; Poverty Areas; RNA; Viral [analysis]; Schistosomiasis [drug therapy]; Viral Load; MeSH check words; Humans

PLAIN LANGUAGE SUMMARY

Deworming helminth co-infected individuals for delaying HIV disease progression

Persons in resource-constrained settings are often disproportionately affected by both HIV-1 and other infectious diseases, such as helminth infections. Helminths are parasitic organisms that live within the human body. Over one-third of the world's population is infected with at least one species of helminth. Findings from some observational studies have suggested that treating helminth infections may slow the progression of HIV-1 disease. If treatment of helminth infections can reduce morbidity and mortality or delay the need for antiretroviral drugs among HIV-1-infected persons, the clinical, programmatic, and public health benefits of these effects are likely to be substantial. The results of this systematic review suggest that eradication of helminths appears to impart significant benefit to HIV-1 and helminth co-infected individuals. Further studies are warranted to determine the long-term impact of deworming and to evaluate the relative benefit of eradicating individual helminth species.

BACKGROUND

Many individuals living in areas of the world hardest hit by the HIV-1 epidemic are also infected with other common pathogens. These infections may have detrimental effects on the host's ability to control the HIV-1 virus (Lawn 2001; Actor 1993). In 2007, we published a systematic review of the literature in the Cochrane library including data from a single randomized clinical trial and several observational studies (Walson 2007). The review suggested that treatment of helminth infection may result in delayed progression of HIV-1 disease as measured by changes in CD4 counts and plasma viral load but it acknowledged that available data were limited by issues of study design, sample size, and follow-up duration. Since the publication of our review, data from additional RCTs have become available. We

updated this review with the intent to summarize the findings of all available evidence from randomized trials evaluating the impact of deworming on markers of HIV disease progression.

Studies have estimated that as many as half of the 22.5 million people infected with HIV-1 in sub-Saharan Africa may be co-infected with helminths (Fincham 2003; UNAIDS 2007). Helminth infection leads to significant stimulation of the host immune response, as these infections are often characterized by the daily production of millions of eggs, excretory products, and secretions. Helminth-infected individuals display increased levels of eosinophilia, increased immunoglobulin (Ig)E levels, and a strong Th2 immune bias (Bentwich 1996; Kassu 2003). Most helminth infections also induce strong immunoregulatory responses driven by regulatory T cells, which are potentially capable of contributing to HIV pathogenesis by suppressing HIV-1-specific immune responses, as recently shown in vitro (Kinter 2007). In addition, chronic helminth infections have also been shown to be associated with antigen-specific anergy and hypo-responsiveness, which may also down-regulate control of HIV-1 replication (Borkow 2006). Immune activation may also result in increased cellular susceptibility to HIV-1 infection (Shapira-Nahor 1998). Several clinical studies have suggested that helminth co-infection in HIV-1-infected individuals may result in increased plasma levels of HIV-1 RNA and possibly in more rapid disease progression (Kallestrup 2005; Wolday 2002). These and other recent findings substantiate the previously suggested hypothesis that helminth infection may play an important role in the pathogenesis of HIV-1 in Africa (Bentwich 1995).

In a study of HIV-1-infected and uninfected individuals in Ethiopia, helminth co-infection was associated with increased T-cell activation, and subsequent anti-helminthic treatment appeared to reduce the degree of T-cell activation. In addition, treatment of helminth infection resulted in a significant increase in absolute CD4 counts (192 versus 279 cells/mm³, $p=0.002$) (Kassu 2003). Another study, also conducted in Ethiopia, noted an association between stool helminth burden and plasma HIV-1 RNA levels among individuals with helminth co-infection ($p<0.001$). Successful treatment of helminth co-infection (clearance of helminth eggs in stool) led to a significant decrease in HIV-1 plasma viral load ($-0.36 \log_{10}$) in these patients (Wolday 2002). However, several subsequent observational studies have shown conflicting results regarding the impact of anti-helminth therapy on CD4 count, HIV-1 viral load, and clinical disease progression (Brown 2004; Elliott 2003; Modjarrad 2005). A systematic review of observational and randomized trial data conducted in 2007 suggested that deworming could have a likely benefit on plasma HIV viral load and unclear effects on CD4 counts (Walson 2007).

As HIV-1 treatment programs are expanded in areas in which both HIV-1 and helminth infections are prevalent, it is important to determine whether treating helminth infection can slow HIV-1 disease progression. Relatively modest increases in viral load ($0.3-0.5 \log_{10}$ copies/mL) may increase the annual risk of progression to an AIDS-defining illness or death by as much as 25%–44% (Modjarrad 2008). Mathematical modeling of potential HIV-1 vaccine efficacy suggests that a reduction in set-point HIV-1 RNA levels of $0.5 \log_{10}$ copies/mL could slow the onset of AIDS by 3.5 years and could delay the need for antiretroviral medications by almost a full year (Gupta 2007).

Deworming is a simple, practical, and inexpensive intervention that could be easily implemented in resource-constrained settings where helminth co-infections are common. In contrast with antiretroviral therapy, the cost of deworming is minimal, having been estimated to be as low as US\$0.25 per treatment including delivery costs (Bundy 2009; Partnership for Child Development 1998). In addition, deworming is practical and logistically simple, as a single course of treatment is only required every six to 12 months. If anti-helminthic therapy enables HIV-1-infected individuals to delay initiation of antiretroviral therapy or reduces

morbidity and mortality, the public health significance of de-worming HIV-1-infected individuals may be substantial.

In this Cochrane review, we evaluated data from RCTs evaluating the impact of treating helminth co-infection in HIV-1 infected individuals on markers of HIV-1 progression, including changes in HIV-1 RNA, CD4 counts, and clinical indicators of AIDS.

OBJECTIVES

To determine if treating helminth infection in individuals with HIV-1 is associated with decreased progression of HIV-1 as measured by CD4 count, HIV-1 viral load, or clinical disease progression.

METHODS

Criteria for considering studies for this review

Types of studies—RCTs or quasi-RCTs. Given the lack of randomized trials at the time of the initial review, data from observational studies were also considered, following the policy of the HIV-1/AIDS Cochrane Review Group (HIV-1 CRG). At the time of the 2008 update, it was determined that sufficient RCTs were identified for inclusion and observational studies were excluded.

Studies performed in general or specific populations and in both hospitals and/or clinics were included. Studies performed in any country and published in any language were included. Studies that relied on historical controls and ecological studies were excluded, as these provide unreliable data for determining causation and/or association.

Types of participants—All HIV-1 infected individuals with and without documented helminth co-infection included in studies assessing the association between helminth co-infection and HIV-1 disease progression. Helminths included were schistosomes, *Strongyloides*, microfilaria, hookworm, whipworm, *Ascaris*, and *Trichostrongylus*. Included studies documented helminth infection by direct stool microscopy, concentration techniques, other microscopic methods (e.g. Kato-Katz), culture of stool samples, antigen-testing methods (e.g. ELISA kits), modified Knott's concentration methods for microfilaria, or other immunochromatographic testing methods.

Types of interventions

Interventions: Anti-helminthic therapy, defined as any pharmaceutical intervention or interventions approved for use in the eradication of helminth infection in humans. Interventions included the benzimidazoles, ivermectin, praziquantel, diethylcarbamazine, bithionol, oxfamiquine, pyrantel, and nitazoxanide.

Controls: Another anti-helminthic drug, placebo, or no treatment.

Types of outcome measures

The outcome measures evaluated

1. Levels of HIV-1 RNA
2. Absolute CD4 count
3. Clinical disease progression, including mortality

4. Adverse events associated with anti-helminthic therapy were recorded if reported in the studies

Search methods for identification of studies

See: HIV-1/AIDS Group methods used in reviews.

See: Cochrane Review Group search strategy.

1. Electronic searching

- a. Initially, MEDLINE online (1980–2006) was searched in July 2006 using the strategy documented in the table titled: Initial Search Strategy for MEDLINE (Table 1). This initial search yielded 937 abstracts and identified only one randomized trial. In November 2006, the search strategy was modified to include observational studies, and this search yielded 3,329 abstracts.

When updated in August 2008, the initial search strategy was updated (see table titled: Revised Search Strategy for MEDLINE) (Table 2) and yielded an additional 153 abstracts.

- b. Initially, EMBASE online (1980–2006) was searched in August 2006 using the strategy documented in the table titled: Initial Search Strategy for EMBASE (Table 3). This initial search yielded 91 abstracts. In November 2006, the search strategy was modified to include observational studies, and this search yielded 2830 abstracts.

When updated in August 2008, the initial search strategy was updated (see table titled: Revised Search Strategy for EMBASE) (Table 4) and yielded an additional 67 abstracts.

- c. Initially, CENTRAL online (1980–2006) was searched in August 2006 using the strategy documented in the table titled: Initial Search Strategy for CENTRAL (Table 5). This initial search yielded 69 abstracts. When updated in August 2008, the initial search strategy was updated (see table titled: Revised Search Strategy for CENTRAL) (Table 6) and yielded an additional 87 abstracts.

- d. Initially, AIDSEARCH online (1980–2006) was searched in August 2006 using the strategy documented in the table titled: Initial Search Strategy for AIDSEARCH (Table 7). This initial search yielded 156 abstracts. When updated in August 2008, the initial search strategy was updated (see table titled: Revised Search Strategy for AIDSEARCH) (Table 8) and yielded an additional 243 abstracts.

2. Reference lists—Reference lists of all the studies that were included in the pool of retrieved studies, including those of other reviews, were examined to identify any further studies.

3. Personal contact—We contacted authors of studies initially selected for inclusion in the pool of retrieved studies to identify any further studies. Data on CD4 count and HIV-1 RNA levels were requested from authors when they were not presented in the published manuscripts.

Data collection and analysis

The development of the search strategy was performed with the assistance of the Cochrane HIV/AIDS Group (HIV-1 CRG). The titles, abstracts, and descriptor terms of all downloaded material from the electronic searches were read by at least two of the investigators independently (BH, JW, and/or GJS) and irrelevant reports were discarded. All citations identified were then independently evaluated by at least two of the investigators independently (BH, JW, and/or GJS) to establish relevance of the article according to the pre-specified criteria. When there was uncertainty as to the relevance of the study, the full article was obtained.

1. Selection of studies—JW and BH independently applied the inclusion criteria for this update. There were no differences requiring a third reviewer to resolve. Studies were reviewed for relevance based on study design, types of participants, exposures, and outcome measures. We sought further information from the authors where papers contained insufficient information to make a decision about eligibility.

2. Data extraction—Data utilized in this update were independently extracted by JW and BH. Standardized data extraction forms for randomized trials were used.

The following characteristics were extracted from each included study:

Administrative details: Identification; author(s); published or unpublished; year of publication; year in which study was conducted
 Details of study: Study design; type; duration; completeness of follow-up; 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; socioeconomic status; HIV-1 clinical staging (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

3. Quality assessment—Quality assessment was performed using standardized quality assessment forms. The methodologic quality of the included clinical trials were evaluated independently by two authors (JW, BH, and/or GJS), according to a validity checklist for clinical trials (<http://www.igh.org/Cochrane>). Studies were evaluated for adequacy of allocation concealment. Selection bias was assessed by evaluating the method of generation of allocation sequence and adequacy of allocation concealment. Performance and detection biases were assessed by checking whether participants, investigators, or assessors were blinded. Attrition bias was assessed by the adequacy of follow-up and intention-to-treat analysis. Trials with loss to follow-up less than or equal to 20% were rated as adequate and were rated as inadequate if loss to follow-up was unclear or above 20%.

4. Data synthesis—Incomplete data: Where data were incomplete, attempts were made to contact the authors for clarification of relevant information.

Outcome measures: A narrative synthesis was performed. CD4 and viral load outcomes included in this review were continuous. All outcomes were assessed using mean difference (MD) and 95% confidence interval. Results from three randomized clinical trials were statistically pooled using a random-effects method (DerSimonian 1986) given the heterogeneity of the interventions and underlying helminth infection for meta-analysis. Given that all outcomes were reported using similar scales of measurement (CD4 counts in cells/mm³ and viral load as log₁₀ copies/mL), all outcomes were assessed with a mean difference (MD) and 95% confidence interval.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified three RCTs that met criteria for inclusion in this review.

Studies included in this review: Kallestrup 2005; Nielsen 2007; Walson 2008.

Details of each study are noted below and given in the table titled: Characteristics of included studies.

Kallestrup 2005: A randomized clinical trial evaluating the effect of treatment of schistosomiasis on markers of HIV-1 progression was conducted in rural Zimbabwe. The primary objective of the trial was to determine whether treatment of schistosomiasis has an effect on the course of HIV-1 infection, as measured by changes in HIV-1 RNA and CD4 count. Individuals with documented schistosomiasis and with or without HIV-1 were randomized to receive praziquantel therapy at inclusion or after a three-month delay. In this trial, 287 individuals were enrolled, of whom 130 HIV-1 and schistosomiasis co-infected individuals were included. Of these 130 individuals, 64 received early treatment and 66 received delayed therapy. Participants were assessed by clinical examination as well as laboratory determination of CD4 count, plasma HIV-1 RNA, and CDC clinical stage at enrollment and three months after inclusion. Actual changes in CD4 counts and HIV-1 RNA viral loads for the HIV-infected group were not included in the published manuscript, but were provided by the author upon request for inclusion in this review.

Nielsen 2007: A randomized double-blind placebo-controlled cross-over trial of treatment of lymphatic filariasis to evaluate the effect on HIV-1 was conducted in rural Tanzania. The primary objective of the trial was to determine whether treatment of filarial infection has an effect on the course of HIV-1 infection, as measured by changes in HIV-1 RNA, CD4 percentage, and CD4/CD8 ratio. Individuals with documented HIV-1 and with or without *Wuchereria bancrofti* infection (without obvious clinical manifestations) were randomized to receive diethylcarbamazine (DEC) therapy or placebo at the beginning of the study, and the opposite treatment was given 12 weeks later. In this trial, 34 individuals were enrolled and 18 HIV-1 and filarial co-infected individuals were included. Of these 18 individuals, 10 received early treatment and seven received delayed therapy; one was lost to follow-up. Participants were assessed by laboratory determination of plasma HIV-1 RNA, CD4 percentage, and CD4/CD8 ratio at enrollment and three months after inclusion. Actual changes in CD4 percentage and HIV-1 RNA viral loads were not included in the published manuscript, but were provided by the author upon request for inclusion in this review.

Walson 2008: A randomized double-blind placebo-controlled trial of treatment of soil-transmitted helminth infection to evaluate the effect on HIV-1 was conducted in urban and rural Kenya. The primary objective of the trial was to determine whether treatment of soil-transmitted helminth co-infection in HIV-1-infected adults impacted markers of HIV-1 disease progression, as measured by changes in HIV-1 RNA and CD4 count. Individuals attending HIV-1 care clinics and with evidence of helminth infection were randomized to receive albendazole therapy or placebo at inclusion. At 12 weeks of follow-up, all participants with evidence of helminth infection were treated regardless of randomization arm. In this trial, 234 individuals were enrolled, of whom 208 HIV-1 and soil-transmitted helminth co-infected individuals were included in the final intent-to-treat analysis. Of these 208 individuals, 108 received early treatment and 100 received placebo. Participants were assessed by clinical examination as well as laboratory determination of CD4 count and plasma HIV-1 RNA at enrollment and three months after inclusion. Actual changes in CD4 counts and HIV-1 RNA viral loads were not included in the published manuscript, but were available for inclusion in this review.

Risk of bias in included studies

Three randomized trials of treatment of helminth co-infection in HIV-1 infected individuals were identified (Kallestrup 2005; Nielsen 2007; Walson 2008). Treatment allocation was

concealed from both participants and investigators in two of the studies (Nielsen 2007; Walson 2008), but was not concealed from participants or investigators in one study (Kallestrup 2005). An intent-to-treat analysis was performed and reported in two studies (Kallestrup 2005; Walson 2008). Outcome comparisons were made only for patients for whom follow-up data were available in the remaining study (Nielsen 2007).

Selection bias is unlikely to have occurred in any of the included studies where randomization occurred at enrollment; however, only two of the studies (Nielsen 2007; Walson 2008) detailed the method of randomization. Reported baseline characteristics between randomization groups appeared similar in all trials.

Performance bias (misclassification of exposure) is unlikely to have occurred in any of the included studies where documentation of helminth infection was performed at enrollment.

Detection bias is unlikely to have occurred in any of the included studies where outcome measurements were standardized for all participants.

Attrition bias may have been an issue in the study by Nielsen 2007 where there appeared to be differential loss to follow-up between the HIV infected/CFA+ participants in each group (four in one group, two in the other group). Loss to follow-up rates appeared similar among the HIV-1-infected comparator groups in the remaining two trials. In addition, one study (Kallestrup 2005) reported that 79% of the established patient cohort were followed-up, although the study reported that reasons for study drop-out were evenly distributed, with the exception of a single group which had a higher number of losses to follow-up due to migration.

Assessment of the quality of the included studies is provided in the table titled: Assessment of Quality of Included Randomized Studies (Table 9).

Effects of interventions

In this 2008 update we identified 635 abstracts in addition to the 6,384 identified in the original search (Walson 2007). The additional abstracts included 243 from AIDSEARCH, 87 from CENTRAL, 67 from Embase, 153 from Medline, and 85 from GATEWAY. Of the 635 abstracts identified, two additional abstracts met criteria for potential inclusion (Nielsen 2007; Walson 2008). One RCT identified in the original search also met criteria for inclusion, making a total of three studies eligible for inclusion (Kallestrup 2005; Nielsen 2007; Walson 2008) (Figure 1). Given the availability of three randomized trials, the observational studies included in the original study were determined to be ineligible for this review. The characteristics of the included studies are presented in the table titled: Characteristics of included studies.

All of the included studies were conducted in Africa and included HIV-1-infected individuals who were treated for different helminth infections using different pharmaceutical interventions. All three included studies included antiretroviral-naïve individuals. Unpublished data were requested from the authors of all three of the included studies and were used in the analysis (Kallestrup 2005; Nielsen 2007; Walson 2008).

Fourteen studies were excluded and are presented along with the rationale for exclusion in the table titled: Characteristics of excluded studies. Reasons for exclusion included inadequate study design (not randomized) in all 14 studies (Brown 2004; Brown 2005; Elliott 2003; Gallagher 2005; Ganley-Leal 2006; Hosseinipour 2007; Kallestrup 2006; Kassu 2003; Kelly 1996; Lawn 2000; McElroy 2005; Modjarrad 2005; Mwanakasale 2003; Wolday 2002). Additional reasons for exclusion included inadequate reporting or collection of outcome data (Brown 2005; Gallagher 2005; Ganley-Leal 2006; Hosseinipour 2007; Lawn 2000; Kassu

2003; Kelly 1996; Mwanakasale 2003), lack of a control comparison group (Brown 2005; Hosseinipour 2007; Lawn 2000), failure to confirm helminth infection status (Kelly 1996), and reporting of data already presented in another included study (Kallestrup 2006). The original review did not exclude non-randomized trials (Walson 2007).

We had pre-specified in our protocol that meta-analysis would be performed if data permitted. A pooled analysis was performed of the three included randomized trials.

Markers of HIV-1 Disease Progression—The results of the study evaluating treatment of schistosomiasis co-infection demonstrated a statistically significant benefit on plasma HIV-1 RNA levels (Kallestrup 2005). Individuals in the treatment group had minimal change in plasma viral load over three months of follow-up ($-0.001 \log_{10}$ copies/mL) compared to an increase in those who did not receive treatment during this period ($0.21 \log_{10}$ copies/mL), ($p=0.03$). This trial noted a statistically significant benefit on CD4 count with treatment when both HIV-1-infected and HIV-1-uninfected individuals were included, with a non-significant trend for a difference between the two study arms when limited to HIV-1-infected individuals. Treatment resulted in a 1.7 cells/ μ L-mean decline compared to a 35.2 cells/ μ L-mean decline in the untreated group ($p=0.17$) (Unpublished data provided by author). This study also evaluated differences in CDC clinical staging between the treated and untreated groups. At the three-month visit, there were no differences with regard to the number of individuals in CDC stage A, B, or C (43:20:1 for the treatment arm compared to 44:20:2 in the untreated arm), although the study was underpowered for this assessment.

The study evaluating treatment of lymphatic filariasis co-infection also demonstrated a statistically significant benefit on plasma HIV-1 RNA levels (Nielsen 2007). The data presented in the published manuscript considered the 12-week visit as the initial visit and the 24-week visit as the final visit. Individuals treated at the initial visit with DEC were then considered as the 'placebo' arm and those who were not treated until the 12-week visit were the 'treatment' arm. For the purposes of this analysis, we considered only individuals with confirmed HIV-1 infection who were also CFA+ at the baseline visit. We considered individuals treated with DEC at the initial visit to be in the 'treatment' arm and those who did not receive treatment to be in the 'placebo' arm. We reported outcomes as reported for the 12-week visit. Given that as of the 12-week visit all participants had been treated with DEC, we did not include data from the 24-week follow-up period. There were no significant differences in viral load changes between the two groups after 12 weeks of follow-up (no change in the treatment arm vs. an increase of $0.08 \log_{10}$ copies/mL in the placebo arm, $p=0.9$). Data in this study were collected only for CD4 percentage and not for absolute CD4 count data. There were no significant differences in the change in CD4 percentage in this study, although the study did suggest a decrease in CD4 percentage of 1.3% in the treatment group compared to an increase of 3.9% in the placebo arm at 12 weeks of follow-up (difference of -5.2 [95% CI for difference = $-17.62, 7.26$], $p=0.4$).

The largest of the studies reported evaluated treatment of a variety of soil-transmitted helminths, including hookworm, *Trichuris sp.* and *Ascaris sp.* (Walson 2008). Individuals who received treatment with albendazole had a greater reduction in viral load ($-0.15 \log_{10}$ copies/mL) when compared to those in the placebo group ($-0.02 \log_{10}$ copies/mL), although the difference was not significant ($p=0.32$). However, individuals in the treatment arm experienced a significantly lower decline in CD4 count than did individuals in the placebo arm (decline of 25 cells/ μ L in the treatment arm compared to a decline of 68 cells/ μ L in the placebo arm, $p=0.04$).

Pooled Analysis of Data from All RCT's—The pooled meta-analyses of all three trials suggest statistically significant benefits associated with treatment of helminth co-infection in

HIV-1-infected adults. When data on changes in HIV-1 RNA levels were pooled for all three studies (Kallestrup 2005; Nielsen 2007; Walson 2008), a significantly lower increase in viral load among individuals treated for helminth co-infection was observed compared to those receiving placebo ($p=0.02$) (Analysis 1.1 and Figure 2). In addition, when data from the two studies that evaluated absolute CD4 counts were pooled (Kallestrup 2005; Walson 2008), a significant increase in CD4 counts following treatment of helminth co-infection was observed compared to those receiving placebo ($p=0.03$) (Analysis 2.1 and Figure 3).

Mortality and clinical staging—Mortality and clinical staging data were not consistently reported across studies and these data were not included in the pooled analysis.

Adverse events—None of the included trials reported differences in adverse events between the groups compared in this analysis.

DISCUSSION

Approximately one-third to one-half of the global population is infected with at least one species of helminth, with the vast majority of these infections occurring in resource-limited areas of the world where the HIV/AIDS pandemic is most severe. It has been suggested that deworming is unlikely to have an effect on HIV-1 progression in co-infected individuals (Hosseinipour 2007). In a previously published Cochrane Review on this subject, we determined that there were insufficient data to determine potential benefit of deworming to prevent or delay HIV-1 disease progression (Walson 2007). At the time of that review, however, only one RCT evaluating the potential benefit of treating helminth co-infection in HIV-1-infected individuals had been reported, and that trial was limited to evaluation of schistosomiasis co-infection (Kallestrup 2005). Since publication of that review, the results of two additional randomized trials have been reported (Nielsen 2007; Walson 2008). All three randomized trials show benefit in markers of HIV-1 disease progression with the treatment of helminth co-infection. A pooled analysis of all available RCT data suggests that treatment of helminth co-infection may attenuate increases in HIV-1 RNA and result in slower decline in CD4 count.

It is important to note that each of the included RCTs evaluated the effect of different interventions (praziquantel, albendazole, and DEC) and different helminth infections (schistosomiasis, soil-transmitted helminths, and *W. bancrofti*). Although the immunologic consequences of all these infections may be similar, the pooled analysis of effect is limited by the heterogeneity of these trials. There may be important differences in the effects of different helminth species and different intensities of infection on HIV-1 progression. Helminth burden has been correlated with HIV-1 RNA levels in HIV-1 co-infected individuals and may be an important factor in determining the extent to which helminths affect HIV-1 progression (Wolday 2002). In addition, helminth species differ in their level of tissue invasiveness, level of resulting host immune activation, and other factors, which may explain observed differences in the interactions between HIV-1 and various helminths seen in some studies (Walson 2008; Brown 2006).

All of the included studies were limited by a short follow-up duration. The finding of changes in HIV-1 RNA levels and CD4 counts, despite the short duration of follow-up in these studies, may not reflect a sustained change in these markers. CD4 decline appears to be related to immune activation status and changes in regulatory T cell expression and function that may transiently resolve following treatment of helminth infection (Brown 2006). In addition, short-term changes in CD4 count may reflect changes in the distribution of these cells within the body. Helminth infection may also directly suppress the Th1 response, leading to a reduction in virus-specific CD8+ cytotoxic T lymphocytes (CTLs) (Allen 1996; Maizels 2003). Plasma

HIV-1 viral load is directly related to HIV-1-specific CTL responses in humans, and a reduction in CTL response is associated with a more rapid progression of HIV-1 disease (Actor 1993; Gomez-Escobar 2000; Goodridge 2001; Pastrana 1998; van der Kleij 2002). It is plausible that the changes in immune control of HIV-1 replication could lead to transient changes in HIV-1 RNA levels following helminth infection or eradication.

The results of this systematic review suggest that treating helminth infection in HIV-1 co-infected adults appears to impart beneficial effects on both HIV-1 viral load and CD4 counts. There are limitations to the studies identified as well as to the pooled analysis, and currently available data do not support empiric anti-helminthic therapy or routine helminth screening of HIV-1 infected adults. There is a need for larger TRCTs with a longer follow-up duration to assess the impact of deworming on HIV-1 progression in populations with a high prevalence of both helminth and HIV-1 infection. In addition, studies designed to evaluate species-specific effects are needed to determine if differences exist among the many different helminths infecting and affecting humans worldwide.

AUTHORS' CONCLUSIONS

Implications for practice

Millions of HIV-1-infected individuals are currently living in helminth endemic areas of the world. Given the multiple possible mechanisms by which helminth co-infection may impact the course of HIV-1 infection, it is important to determine if deworming can reduce HIV-1 disease progression. The potential benefit of deworming on HIV-1 progression has been evaluated in a three separate randomized controlled trials. The pooled data from these trials suggest beneficial short-term effects on both CD4 counts and plasma HIV-1 RNA levels. However, the available data do not currently support empiric therapy or routine helminth screening of HIV-1 infected individuals.

Implications for research

Helminth treatment appears to result in short-term beneficial effects on CD4 counts and HIV-1 RNA levels. However, no study conducted to date has evaluated changes in clinical outcomes, CD4 counts, or adverse events over a period of time sufficient to demonstrate meaningful long-term differences. In addition, there appears to be significant variability among different species of helminths. It is important that larger RCTs with longer follow-up duration assess the impact of deworming on these outcome measures.

Acknowledgments

The authors would like to acknowledge the valuable input of Drs Zvi Bentwich, Dawit Wolday, Michael Brown, and Alison Elliott. In addition, the authors would also like to acknowledge that Per Kallestrup and Nina Nielsen provided additional unpublished data to include in this update.

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Figure 1.

Figure 2.

Forest plot of comparison: 1 Viral Load, outcome: 1.1 Change in Log10 HIV-1 RNA after antihelminthic treatment or no treatment.

Figure 3.

Forest plot of comparison: 2 CD4 count, outcome: 2.1 Change in CD4 after anti-helminthic treatment or no treatment.

Table 1

Initial Search Strategy for MEDLINE

Number	Search Terms
#1	“HIV Infections”[MeSH] OR “HIV”[MeSH] OR hiv [tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR “Sexually Transmitted Diseases, Viral”[MeSH:NoExp]
#2	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (“clinical trial” [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])
#3	HELMINTHS OR ROUNDWORM OR ROUND WORM OR ROUND-WORM OR ROUNDWORMS OR ROUND WORMS OR ROUND-WORMS OR NEMATODES OR NEMATODE OR CESTODE OR CESTODES OR TAPEWORM OR TAPE WORM OR TAPE-WORM OR TAPEWORMS OR TAPE WORMS OR TAPEWORMS OR TREMATODE OR TREMATODES OR FLUKE OR FLUKES OR WORM OR WORMS OR PARASITE OR PARASITES OR ASCARIS OR TRICHURIS OR ENTEROBIUS OR STRONGYLOIDE OR STRONGLYLOIDES OR ANCYLOSTOMA OR ANCYLOSTOMAS OR NECATOR OR NECATORS OR HYMENOLEPIS OR PARAGONIMUS OR FASCIOLA OR TAENIA OR HOOKWORM OR HOOK WORM OR HOOK-WORM OR HOOKWORMS OR HOOK WORMS OR HOOK-WORMS OR WHIPWORM OR WHIP WORM OR WHIP-WORM OR WHIPWORMS OR WHIP WORMS OR WHIP-WORMS OR SHISTOSOMIASIS OR MANSONELLA OR FILARIASIS OR MICROFILARIA OR TRICHOSTRONGYLUS
#4	BENZIMIDAZOLES OR ALBENDAZOLE OR MEBENDAZOLE OR IVERMECTIN OR PRAZIQUANTEL OR DIETHYLCARBAMAZINE OR BITHIONOL OR OXAMNIQUINE OR PYRANTEL OR NITAZOXANIDE
#5	#1 AND #2 AND #3 AND #4

Table 2

Revised Search Strategy for MEDLINE

NUMBER	SEARCH TERMS
#1	"HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv [tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect* [tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome [tw] OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp]
#2	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])
#3	HELMINTHS OR ROUNDWORM OR ROUND WORM OR ROUND-WORM OR ROUNDWORMS OR ROUND WORMS OR ROUND-WORMS OR NEMATODES OR NEMATODE OR CESTODE OR CESTODES OR TAPEWORM OR TAPE WORM OR TAPE-WORM OR TAPEWORMS OR TAPE WORMS OR TAPE-WORMS OR TREMATODE OR TREMATODES OR FLUKE OR FLUKES OR WORM OR WORMS OR PARASITE OR PARASITES OR ASCARIS OR TRICHURIS OR ENTEROBIUS OR STRONGYLOIDE OR STRONGYLOIDES OR ANCYLOSTOMA OR ANCYLOSTOMAS OR NECATOR OR NECATORS OR HYMENOLEPIS OR PARAGONIMUS OR FASCIOLA OR TAENIA OR HOOKWORM OR HOOK WORM OR HOOK-WORM OR HOOKWORMS OR HOOK WORMS OR HOOK-WORMS OR WHIPWORM OR WHIP WORM OR WHIP-WORM OR WHIPWORMS OR WHIP WORMS OR WHIP-WORMS OR SCHISTOSOMIASIS OR MANSONELLA OR FILARIASIS OR MICROFILARIA OR TRICHOSTRONGYLUS OR TRICHOSTRONGYLOSIS OR STRONGYLOIDEA OR PARAGONIMIASIS
#4	BENZIMIDAZOLES OR ALBENDAZOLE OR MEBENDAZOLE OR IVERMECTIN OR PRAZICANTEL OR DIETHYLCARBAMAZINE OR BITHIONOL OR OXAMNIQUINE OR PYRANTEL OR NITAZOXANIDE
#5	#3 OR #4
#6	#1 AND #2 AND #5
#7	#1 AND #2 AND #5 Limits: Publication Date from 2006/07/01 to 2008

Table 3

Initial Search Strategy for EMBASE

NUMBER	SEARCH TERMS
#1	('human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection') OR ('human immunodeficiency virus'/exp OR 'human immunodeficiency virus') OR (hiv:ti OR hiv:ab) OR ('hiv-1':ti OR 'hiv-1':ab) OR ('hiv-2':ti OR 'hiv-2':ab) OR ('human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab) OR ('human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab) OR ('human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab) OR ('human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab) OR ('acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab) OR ('acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab) OR ('acquired immunodeficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab)
#2	((random*:ti OR random*:ab) OR (factorial*:ti OR factorial*:ab) OR (cross?over*:ti OR cross?over*:ab OR crossover*:ti OR crossover*:ab) OR (placebo*:ti OR placebo*:ab) OR ((doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab)) OR ((singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab)) OR (assign*:ti OR assign*:ab) OR (allocat*:ti OR allocat*:ab) OR (volunteer*:ti OR volunteer*:ab) OR ('crossover procedure'/de) OR ('double-blind procedure'/de) OR ('single-blind procedure'/de) OR ('randomized controlled trial'/de))
#3	('helminths'/de OR 'helminths') OR ('roundworm'/de OR 'roundworm') OR ('round worm'/de OR 'round worm') OR ('round-worm'/de OR 'round-worm') OR roundworms OR 'round worms' OR 'round-worms' OR nematodes OR ('nematode'/de OR 'nematode') OR ('cestode'/de OR 'cestode') OR cestodes OR ('tapeworm'/de OR 'tapeworm') OR ('tape worm'/de OR 'tape worm') OR ('tape-worm'/de OR 'tape-worm') OR tapeworms OR 'tape worms' OR 'tapeworms' OR ('trematode'/de OR 'trematode') OR trematodes OR ('fluke'/de OR 'fluke') OR flukes OR ('worm'/de OR 'worm') OR worms OR ('parasite'/de OR 'parasite') OR ('parasites'/de OR 'parasites') OR ('ascaris'/de OR 'ascaris') OR ('trichuris'/de OR 'trichuris') OR ('enterobius'/de OR 'enterobius') OR strongyloide OR stronglyloides OR ('ancylostoma'/de OR 'ancylostoma') OR ancylostomas OR ('necator'/de OR 'necator') OR necators OR ('hymenolepis'/de OR 'hymenolepis') OR ('paragonimus'/de OR 'paragonimus') OR ('fasciola'/de OR 'fasciola') OR taeniia OR ('hookworm'/de OR 'hookworm') OR ('hook worm'/de OR 'hook worm') OR ('hook-worm'/de OR 'hook-worm') OR hookworms OR 'hook worms' OR 'hook-worms' OR ('whipworm'/de OR 'whipworm') OR 'whip worm' OR 'whip-worm' OR whipworms OR 'whip worms' OR 'whip-worms' OR shistosomiasis OR ('mansoniella'/de OR 'mansoniella') OR ('filariasis'/de OR 'filariasis') OR ('microfilaria'/de OR 'microfilaria') OR ('trichostrongylus'/de OR 'trichostrongylus')
#4	('benzimidazoles'/de OR 'benzimidazoles') OR ('albendazole'/de OR 'albendazole') OR ('mebendazole'/de OR 'mebendazole') OR ('ivermectin'/de OR 'ivermectin') OR ('praziquantel'/de OR 'praziquantel') OR ('diethylcarbamazine'/de OR 'diethylcarbamazine') OR ('bithionol'/de OR 'bithionol') OR ('oxamniquine'/de OR 'oxamniquine') OR ('pyrantel'/de OR 'pyrantel') OR ('nitazoxanide'/de OR 'nitazoxanide')
#5	#3 OR #4
#6	#1 AND #2 AND #5

Table 4

Revised Search Strategy for EMBASE

NUMBER	SEARCH TERMS
#1	((('human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection') OR ('human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection')) OR (('human immunodeficiency virus'/exp OR 'human immunodeficiency virus') OR ('human immunodeficiency virus'/exp OR 'human immunodeficiency virus')) OR (hiv:ti OR hiv:ab) OR ('hiv-1':ti OR 'hiv-1':ab) OR ('hiv-2':ti OR 'hiv-2':ab) OR ('human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab) OR ('human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab) OR ('human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab) OR ('human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab) OR ('acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab) OR ('acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab) OR ('acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab) AND [2006–2008]/py
#2	((random*:ti OR random*:ab) OR (factorial*:ti OR factorial*:ab) OR (cross?over*:ti OR cross?over*:ab OR crossover*:ti OR crossover*:ab) OR (placebo*:ti OR placebo*:ab) OR ((doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab)) OR ((singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab)) OR (assign*:ti OR assign*:ab) OR (allocat*:ti OR allocat*:ab) OR (volunteer*:ti OR volunteer*:ab) OR (('crossover procedure'/exp OR 'crossover procedure')) OR (('double-blind procedure'/exp OR 'double-blind procedure')) OR (('single-blind procedure'/exp OR 'single-blind procedure')) OR (('randomized controlled trial'/exp OR 'randomized controlled trial')) AND [2006–2008]/py
#3	((('helminths'/exp OR 'helminths') OR ('helminths'/exp OR 'helminths')) OR (('roundworm'/exp OR 'roundworm') OR ('roundworm'/exp OR 'roundworm')) OR (('round-worm'/exp OR 'round-worm') OR ('round-worm'/exp OR 'round-worm')) OR roundworms OR 'roundworms' OR 'round-worms' OR nematodes OR ('nematode'/exp OR 'nematode') OR ('nematode'/exp OR 'nematode')) OR (('cestode'/exp OR 'cestode') OR ('cestode'/exp OR 'cestode')) OR cestodes OR (('tapeworm'/exp OR 'tapeworm') OR ('tapeworm'/exp OR 'tapeworm')) OR (('tape-worm'/exp OR 'tape-worm') OR ('tape-worm'/exp OR 'tape-worm')) OR ('trematode'/exp OR 'trematode') OR ('trematode'/exp OR 'trematode')) OR trematodes OR (('fluke'/exp OR 'fluke') OR ('fluke'/exp OR 'fluke')) OR flukes OR (('worm'/exp OR 'worm') OR ('worm'/exp OR 'worm')) OR worms OR (('parasite'/exp OR 'parasite') OR ('parasite'/exp OR 'parasite')) OR ('ascaris'/exp OR 'ascaris') OR ('ascaris'/exp OR 'ascaris')) OR (('trichuris'/exp OR 'trichuris') OR ('trichuris'/exp OR 'trichuris')) OR ('enterobius'/exp OR 'enterobius') OR ('enterobius'/exp OR 'enterobius')) OR strongyloide OR strongyloides OR (('ancylostoma'/exp OR 'ancylostoma') OR ('ancylostoma'/exp OR 'ancylostoma')) OR ancylostomas OR (('necator'/exp OR 'necator') OR ('necator'/exp OR 'necator')) OR necators OR (('hymenolepis'/exp OR 'hymenolepis') OR ('hymenolepis'/exp OR 'hymenolepis')) OR (('paragonimus'/exp OR 'paragonimus') OR ('paragonimus'/exp OR 'paragonimus')) OR (('fasciola'/exp OR 'fasciola') OR ('fasciola'/exp OR 'fasciola')) OR ('taenia'/exp OR 'taenia') OR (('hookworm'/exp OR 'hookworm') OR ('hookworm'/exp OR 'hookworm')) OR (('hook worm'/exp OR 'hook worm') OR ('hook worm'/exp OR 'hook worm')) OR (('hook-worm'/exp OR 'hook-worm') OR ('hook-worm'/exp OR 'hook-worm')) OR hookworms OR 'hook worms' OR 'hook-worms' OR ('whipworm'/exp OR 'whipworm') OR ('whipworm'/exp OR 'whipworm')) OR 'whip worm' OR 'whip-worm' OR whipworms OR 'whip worms' OR 'whip-worms' OR shistosomiasis OR (('mansoniella'/exp OR 'mansoniella') OR ('mansoniella'/exp OR 'mansoniella')) OR (('filariasis'/exp OR 'filariasis') OR ('filariasis'/exp OR 'filariasis')) OR (('microfilaria'/exp OR 'microfilaria') OR ('microfilaria'/exp OR 'microfilaria')) OR (('trichostrongylus'/exp OR 'trichostrongylus') OR ('trichostrongylus'/exp OR 'trichostrongylus')) OR trichostrongylosis OR strongyloidea OR pargonimiasis AND [2006–2008]/py
#4	((('benzimidazoles'/exp OR 'benzimidazoles') OR ('benzimidazoles'/exp OR 'benzimidazoles')) OR (('albendazole'/exp OR 'albendazole') OR ('albendazole'/exp OR 'albendazole')) OR (('mebendazole'/exp OR 'mebendazole') OR ('mebendazole'/exp OR 'mebendazole')) OR (('ivermectin'/exp OR 'ivermectin') OR ('ivermectin'/exp OR 'ivermectin')) OR (('praziquantel'/exp OR 'praziquantel') OR ('praziquantel'/exp OR 'praziquantel')) OR (('diethylcarbamazine'/exp OR 'diethylcarbamazine') OR ('diethylcarbamazine'/exp OR 'diethylcarbamazine')) OR (('bithionol'/exp OR 'bithionol') OR ('bithionol'/exp OR 'bithionol')) OR (('oxamniquine'/exp OR 'oxamniquine') OR ('oxamniquine'/exp OR 'oxamniquine')) OR (('pyrantel'/exp OR 'pyrantel') OR ('pyrantel'/exp OR 'pyrantel')) OR (('nitazoxanide'/exp OR 'nitazoxanide') OR ('nitazoxanide'/exp OR 'nitazoxanide')) AND [2006–2008]/py
#5	#3 OR #4
#6	#1 AND #2 AND #5

Table 5

Initial Search Strategy for CENTRAL

NUMBER	SEARCH TERMS
#1	HIV-1 OR HIV-1* OR HIV-1-2* OR HIV-11 OR HIV-12 OR (HIV-1 INFECT*) OR (HUMAN IMMUN-ODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFI-CIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUN* DEFICIENCY VIRUS) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUN* DEFICIENCY SYNDROME) in All Fields in all products
#2	MeSH descriptor HIV-1 Infections explode all trees in MeSH products
#3	MeSH descriptor HIV-1 explode all trees in MeSH products
#4	(ANIMAL OR ANIMALS) AND (NOT HUMANS) in All Fields in all products
#5	HELMINTHS OR ROUNDWORM OR ROUND WORM OR ROUND-WORM OR ROUNDWORMS OR ROUND WORMS OR ROUND-WORMS OR NEMATODES OR NEMATODE OR CESTODE OR CES-TODES OR TAPEWORM OR TAPE WORM OR TAPE-WORM OR TAPEWORMS OR TAPE WORMS OR TAPE-WORMS OR TREMATODE OR TREMATODES OR FLUKE OR FLUKES OR WORM OR WORMS OR PARASITE OR PARASITES OR ASCARIS OR TRICHURIS OR ENTEROBIUS OR STRONGYLOIDE OR STRONGLYLOIDES OR ANCYLOSTOMA OR ANCYLOSTOMAS OR NECATOR OR NECATORS OR HYMENOLEPIS OR PARAGONIMUS OR FASCIOLA OR TAENIA OR HOOKWORM OR HOOK WORM OR HOOK-WORM OR HOOKWORMS OR HOOK WORMS OR HOOK-WORMS OR WHIPWORM OR WHIP WORM OR WHIP-WORM OR WHIPWORMS OR WHIP WORMS OR WHIP-WORMS OR SHISTOSOMIASIS OR MANSONELLA OR FILARIASIS OR MICROFILARIA OR TRICHOSTRONGYLUS
#6	BENZIMIDAZOLES OR ALBENDAZOLE OR MEBENDAZOLE OR IVERMECTIN OR PRAZICQUANTEL OR DIETHYLCARBAMAZINE OR BITHIONOL OR OXAMNIQUINE OR PYRANTEL OR NITAZOXANIDE
#7	#5 OR #6
#8	#1 OR #2 OR #3
#9	#7 AND #8
#10	#9 AND NOT #4 from 1980–2006

Table 6

Revised Search Strategy for CENTRAL

NUMBER	SEARCH TERMS
#1	(HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (VIRAL SEXUALLY TRANSMITTED DISEASES)
#2	HELMINTHS OR ROUNDWORM OR ROUND WORM OR ROUND-WORM OR ROUNDWORMS OR ROUND WORMS OR ROUND-WORMS OR NEMATODES OR NEMATODE OR CESTODE OR CES-TODES OR TAPEWORM OR TAPE WORM OR TAPE-WORM OR TAPEWORMS OR TAPE WORMS OR TAPE-WORMS OR TREMATODE OR TREMATODES OR FLUKE OR FLUKES OR WORM OR WORMS OR PARASITE OR PARASITES OR ASCARIS OR TRICHURIS OR ENTEROBIUS OR STRONGYLOIDE OR STRONGYLOIDES OR ANCYLOSTOMA OR ANCYLOSTOMAS OR NECATOR OR NECATORS OR HYMENOLEPIS OR PARAGONIMUS OR FASCIOLA OR TAENIA OR HOOKWORM OR HOOK WORM OR HOOK-WORM OR HOOKWORMS OR HOOK WORMS OR HOOK-WORMS OR WHIPWORM OR WHIP WORM OR WHIP-WORM OR WHIPWORMS OR WHIP WORMS OR WHIP-WORMS OR SCHISTOSOMIASIS OR MANSONELLA OR FILARIASIS OR MICROFILARIA OR TRICHOSTRONGYLUS OR TRICHOSTRONGYLOSIS OR STRONGYLOIDEA OR PARAGONIMIASIS
#3	BENZIMIDAZOLES OR ALBENDAZOLE OR MEBENDAZOLE OR IVERMECTIN OR PRAZIQUANTEL OR DIETHYLCARBAMAZINE OR BITHIONOL OR OXAMNIQUINE OR PYRANTEL OR NITAZOXANIDE
#4	#2 OR #3
#5	#1 AND #4 from 2006 to 2008

Table 7

Initial Search Strategy for AIDSEARCH

NUMBER	SEARCH TERMS
#1	PT=randomized CONTROLLED TRIAL
#2	PT=CONTROLLED CLINICAL TRIAL
#3	randomized CONTROLLED TRIALS
#4	RANDOM ALLOCATION
#5	DOUBLE BLIND METHOD
#6	SINGLE BLIND METHOD
#7	PT=CLINICAL TRIAL
#8	CLINICAL TRIALS OR CLINICAL TRIALS, PHASE I OR CLINICAL TRIALS, PHASE II OR CLINICAL TRIALS, PHASE III OR CLINICAL TRIALS, PHASE IV OR CONTROLLED CLINICAL TRIALS OR MULTICENTER STUDIES
#9	(SINGL* OR DOUBL* OR TREBL* OR TRIPL*) NEAR6 (BLIND* OR MASK*)
#10	CLIN* NEAR6 TRIAL*
#11	PLACEBO*
#12	PLACEBOS
#13	RANDOM*
#14	RESEARCH DESIGN
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	ANIMALS NOT (HUMAN AND ANIMALS)
#17	#15 NOT #16
#18	HELMINTHS OR ROUNDWORM OR ROUND WORM OR ROUND-WORM OR ROUNDWORMS OR ROUND WORMS OR ROUND-WORMS OR NEMATODES OR NEMATODE OR CESTODE OR CES-TODES OR TAPEWORM OR TAPE WORM OR TAPE-WORM OR TAPEWORMS OR TAPE WORMS OR TAPE-WORMS OR TREMATODE OR TREMATODES OR FLUKE OR FLUKES OR WORM OR WORMS OR PARASITE OR PARASITES OR ASCARIS OR TRICHURIS OR ENTEROBIUS OR STRONGYLOIDE OR STRONGLYLOIDES OR ANCYLOSTOMA OR ANCYLOSTOMAS OR NECATOR OR NECATORS OR HYMENOLEPIS OR PARAGONIMUS OR FASCIOLA OR TAENIA OR HOOKWORM OR HOOK WORM OR HOOK-WORM OR HOOKWORMS OR HOOK WORMS OR HOOK-WORMS OR WHIPWORM OR WHIP WORM OR WHIP-WORM OR WHIPWORMS OR WHIP WORMS OR WHIP-WORMS OR SHISTOSOMIASIS OR MANSONELLA OR FILARIASIS OR MICROFILARIA OR TRICHOSTRONGYLUS
#19	BENZIMIDAZOLES OR ALBENDAZOLE OR MEBENDAZOLE OR IVERMECTIN OR PRAZIQUANTEL OR DIETHYLCARBAMAZINE OR BITHIONOL OR OXAMNIQUINE OR PYRANTEL OR NITAZOXANIDE
#20	#18 OR #1921 #17 AND #20 AND PY=1980-2006

Table 8

Revised Search Strategy for AIDSEARCH

NUMBER	SEARCH TERMS
#1	(HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)
#2	((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE- BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR ("CLINICAL TRIAL") OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL* AND (MASK* OR BLIND*)) OR PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*)) NOT (ANIMALS NOT HUMAN)
#3	#1 AND #2
#4	HELMINTHS OR ROUNDWORM OR ROUND WORM OR ROUND-WORM OR ROUNDWORMS OR ROUND WORMS OR ROUND-WORMS OR NEMATODES OR NEMATODE OR CESTODE OR CES-TODES OR TAPEWORM OR TAPE WORM OR TAPE-WORM OR TAPEWORMS OR TAPE WORMS OR TAPE-WORMS OR TREMATODE OR TREMATODES OR FLUKE OR FLUKES OR WORM OR WORMS OR PARASITE OR PARASITES OR ASCARIS OR TRICHURIS OR ENTEROBIUS OR STRONGYLOIDE OR STRONGYLOIDES OR ANCYLOSTOMA OR ANCYLOSTOMAS OR NECATOR OR NECATORS
#5	HYMENOLEPIS OR PARAGONIMUS OR FASCIOLA OR TAENIA OR HOOKWORM OR HOOK WORM OR HOOK-WORM OR HOOKWORMS OR HOOK WORMS OR HOOK-WORMS OR WHIPWORM OR WHIP WORM OR WHIP-WORM OR WHIPWORMS OR WHIP WORMS OR WHIP-WORMS OR SCHISTOSOMIASIS OR MANSONELLA OR FILARIASIS OR MICROFILARIA OR TRICHOSTRONGYLUS OR TRICHOSTRONGYLOSIS OR STRONGYLOIDEA OR PARAGONIMIASIS
#6	BENZIMIDAZOLES OR ALBENDAZOLE OR MEBENDAZOLE OR IVERMECTIN OR PRAZIQUANTEL OR DIETHYLCARBAMAZINE OR BITHIONOL OR OXAMNIQUINE OR PYRANTEL OR NITAZOXANIDE
#7	#4 OR #5 OR #6
#8	#7 AND #3
#9	#8 AND PY=(2006 OR 2007 OR 2008)

Table 9

Assessment of Quality of Included Randomized Studies

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias
Description of Assessment Criteria	Was randomization employed to assess the treatment and comparison groups?	Were the recipients of care and those providing care unaware of the assigned intervention?	How were HIV-1 and helminth infection status ascertained and confirmed and were assessors of outcome measures blinded to intervention groups?	Were all groups followed for the same time frame and were at least 80% of participants in all groups included in the final analysis?
Kallestrup 2005	**	*	*	*
Nielsen 2007	**	**	**	*
Walson 2008	**	**	**	**

* unclear if study design adequate to minimize role of bias

** study design adequate to minimize role of bias