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Immunological Responses to Helminths and HIV-1 Co-Infections

Elton Chavura, MSc
Swansea University, Faculty of Medicine,
Health and Life Science, Wales, United Kingdom
Prof. Wales Singini
Russel Chidya, PhD
Mzuzu University, Faculty of Environmental Science, Mzuzu, Malawi
Balwani Chingatichifwe Mbakaya, Associate. Prof.
University of Livingstonia, Department of Public Health, Malawi

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Abstract

Aim: Helminth infections result from poor sanitation. We evaluated the effect of helminth infections on HIV disease progression through the monitoring of 2 outcomes: (1) plasma HIV-1 RNA Viral load (V/L) and (2) Cluster of Differentiation (CD4+) T-lymphocyte count amongst helminth-HIV-1 co-infected persons. We hypothesized that (1) concurrent helminth infections compromise immune control, resulting in rising VL and reduced CD4+ T-lymphocyte count (2) and that, subject to successful treatment, a decrease in plasma VL could slow down disease progression. Methods: We reviewed 2032 citations, evaluated 432 abstracts, and included 10 articles according to the PRISMA diagram. The methodologies were appraised using a Mixed Method Appraisal Tool (MMAT). Results: At enrolment, plasma VL was significantly higher in individuals with helminths (5.01 log10 vs. 3.41 log10, $p < 0.001$). The effective range was 5.28 log10 copies/mL at baseline and 4.67 log10 copies/mL, ($p < 0.05$) after treatment and a trend for 0.61 log10 lower VL. Significant interactions were seen in the successfully treated groups ($p < 0.001$). CD4+ T-lymphocyte count values were not significantly different in the co-infection groups relative to those with HIV infection alone.

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Conclusion: Helminths and HIV-1 co-infections are associated with an increase in HIV-1 RNA levels that accelerate the progression of the sub-clinical disease to symptomatic AIDS.

Keywords: Helminths, WaSH, HIV/AIDS, CD4+ count, HIV-1 RNA, Viral load, disease progression

Introduction

Helminth infections result from either ingestion or contact with contaminated fecal matter. To date, there is insufficient evidence as to whether helminths have an influence on HIV-1-specific immune responses as literature results are indeterminate. Improved WaSH practices reduce the spread of neglected tropical diseases (NTDs) such as helminths infections (Campbell et al., 2018). Their efficient treatment during pregnancy may reduce the risk of Mother-Child Transmission (MTCT) of HIV, by a mechanism in which parasite antigens activate lymphocytes in the utero (Li et al., 2015). Some studies (Downs, 2017) suggest that NTDs accelerate HIV-1 infection in poor-resource settings due to their profound effects on the host immune system, which make those infected more susceptible to HIV-1 infection and less able to cope with it. Concurrent infections with NTDs such as helminths and HIV-1 are common among persons who have poor access to improved sanitation. The type 1/ type 2 model of immune responses to infection suggests a detrimental effect of helminths infection since the balance in favor of type 2 cytokines at the expense of type 1 cytokines encourages HIV-1 disease progression (Ipp et al., 2014).

Epidemiology of Helminths infections

The Global Burden of Disease Study 2010 reports an increase of 111,000 deaths globally attributable to neglected tropical diseases (NTDs) (including leishmaniasis, trypanosomiasis, schistosomiasis, cysticercosis, echinococcosis, malaria, dengue, ascariasis, and other forms of helminths) also collectively referred to as 'infectious diseases of poverty' (IDoPs) with Sub-Saharan Africa bearing the worst outcomes from their impact (Sartorius et al., 2020; Azoh, 2014; Lozano et al., 2012; WHO, 2011). While neglected, infectious tropical diseases, are much alive and primarily concentrated in poor settings of Sub-Saharan Africa, Asia, and Latin America, with geographic overlap resulting in high levels of co-infection (Engels and Zhou, 2020, Bangert et al., 2017; Bhutta, et al., 2014; Alsan et al., 2012). The global pattern of helminths infestation and the geographical distribution within the Sub-Saharan region is shown in Table 1 and figure 1 respectively.

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Table 1. Global Distribution and Prevalence of Different Helminths

Helminth Type	**Regional Distribution**
Ascariasis lumbricoides (roundworm)	Asia, Africa and Latin America
Trichuris trichiura (whipworm)	Asia, Africa and Latin America
Ancylostoma duodenale (Hookworm)	Asia, Africa and Latin America
Strongyloides stercoralis (threadworm)	Asia, Africa and Latin America
LF Wuchereria bancrofti; Brugia malayi	India, Southeast Asia, Sub-Saharan Africa
Onchocerciasis (river blindness)	Sub-Saharan Africa
Loiasis Loa loa	Sub-Saharan Africa
Dracunculiasis (guinea worm)	Sub-Saharan Africa
Schistosomiasis Schistosoma haematobium	Sub-Saharan Africa
Schistosoma mansoni	Sub-Saharan Africa and Eastern Brazil
Schistosoma japonicum (blood flukes)	China and Southeast Asia
Clonorchis sinensis (liver fluke)	Developing regions of East Asia
Opisthorchis viverrini (liver fluke)	Developing regions of East Asia
Paragonimus spp. (lung flukes)	Developing regions of East Asia
Fasciolopsis buski (intestinal fluke)	Developing regions of East Asia
Fasciola hepatica (intestinal fluke)	Developing regions of East Asia
Cysticercosis Taenia solium (pork tapeworm)	Sub-Saharan Africa

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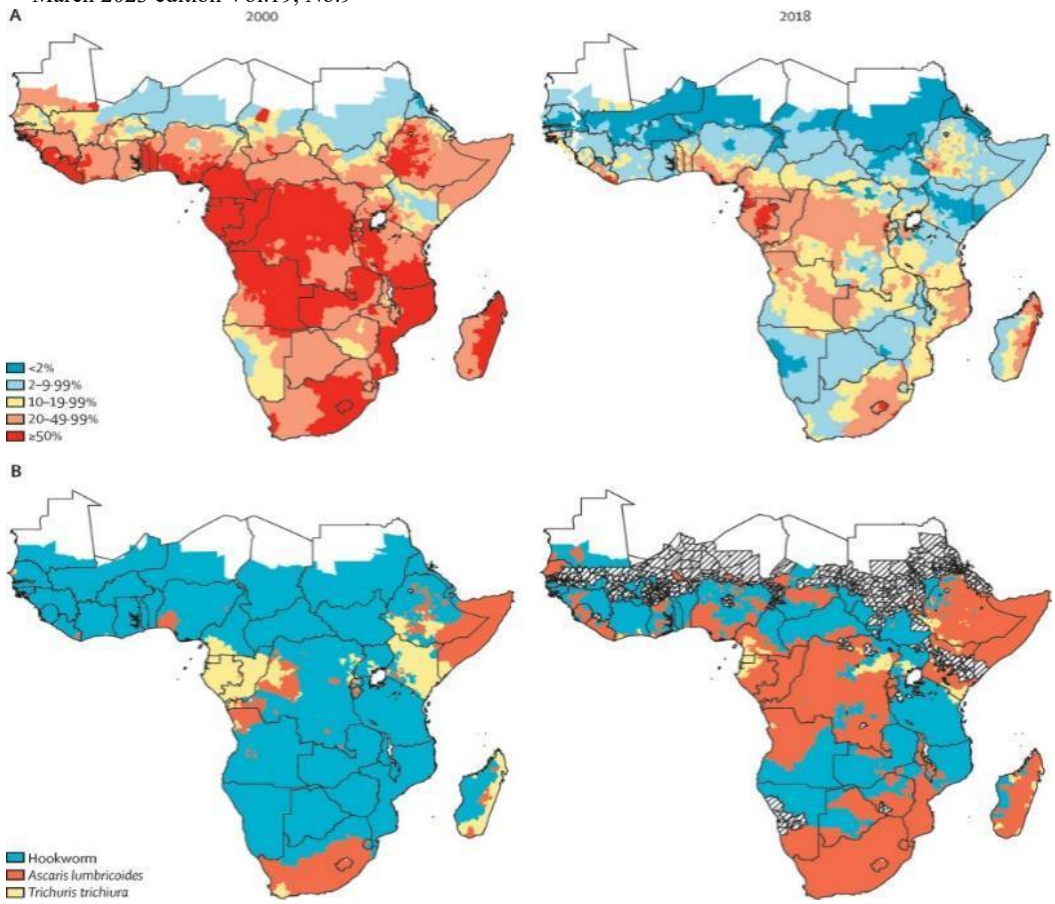

Figure 1. Illustrative distribution of helminths in Sub-Saharan Africa (Sartorius et al., 2020)

Intersections between HIV-1, and helminths

During an acute phase of infection, HIV reproduces in large amounts and destroys CD4+ cells and levels typically fall quickly at first (Richmond et al., 2021; Mpairwe et al., 2014; Elliott et al., 2014). As the immune system responds, viral load begins to fall and the CD4+ levels start to rise again but they may not return to pre-infection levels. Helminths have been implicated in increased systemic immune activation, which is linked to an increase in HIV-1 susceptibility (Hernández-Bello et al., 2012; Stillwagon, 2005). Through complex molecular mechanisms, both HIV-1 and helminth infections can lead to depletions in CD4+ T-lymphocyte cells, (Blackwell et al., 2016), and treatment of helminths has been associated with delays HIV-1 progression and improvements in CD4+ counts and reductions in HIV-1 RNA (viral load) (Means et al., 2016). HIV-1 RNA (viral load) and CD4+ T lymphocyte cell (CD4+) count are surrogate markers of antiretroviral treatment responses and HIV disease progression that have been used for decades to monitor HIV infection (WHO, 2013; Mermin et al., 2011). CD4 count is the best predictor

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for immune function, hence useful in the identification of advanced HIV disease (WHO, 2013; Mermin et al., 2011; Woodburn et al., 2009).

The primary outcome of the study was plasma HIV-1 RNA Viral load (V/L) amongst helminth-HIV-1 co-infected persons while secondary outcomes were (1) Cluster of Differentiation (CD4+) T-lymphocyte count, (2) maternal HIV-1 transmission (MTCT) and (3) mortality and other adverse events. The current method used for staging HIV infection in settings with limited resources is the sole measurement of CD4+ T cells (CD4 count test). WHO recommends a cut-off value of 200–350 CD4+ T cells/μl for adults; patients with values below this should be initiated on antiretroviral treatment (WHO, 2003b). Viral load test result might be reported as "<20", "<50", "<200", "undetectable", "not detected" (ND), "target not detected" (TND), "below the limit of detection" or "zero". A normal viral load means less than 20 to 75 copies of the human immunodeficiency virus (HIV) per milliliter of blood. We hypothesized that pre-existing helminths infections may result in rising HIV-1 viral loads and reduced levels of CD4+ T-lymphocyte count and a higher likelihood of vertical HIV-1 transmission.

Methods

Inclusion criteria

We considered all studies regardless of their design: studies involving helminth co-infection among HIV-1 infected persons. All of the included studies were from Africa and involved HIV-1 infected persons who were recently treated for helminthiasis, or had a laboratory confirmed diagnosis of helminthiasis.

Exclusion criteria

All systematic reviews, communications, perspectives, and articles from non-African countries were automatically excluded.

Information source /search strategy

Research articles were retrieved from DOAJ, PubMed, PsycINFO, CINAHL, Google Scholar, AMED, and EMBASE databases using appropriate keywords to search and retrieve articles. The search period was set from the period starting from January 2000 to December 2022, covering a period of 22 years. The following search terms were used; helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression. An effort was made to manually extract both published and unpublished interventional studies and hand search key journals.

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Risk of bias

Our review authors independently assessed the risk of bias in the included studies by considering the following characteristics: Four authors independently assessed the risk of bias in the included studies. The Mixed Methods Appraisal Tool (MMAT) was used to appraise the selected studies. MMAT is a validated checklist used to appraise the quality of studies included in any systematic review with a quantitative, qualitative, and mixed methods approach. We also specified our hypotheses before conducting the analysis.

Table 1. Search strategy

Database	Search	Search word/terms	Results
PubMed	.Title abstract and full article	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	0
EMBASE	Title, abstract and full article	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	0
PsycINFO	Title, abstract and full article	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	0
AMED	Title and abstract	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	0
CINAHL	Title and abstract	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	0
DOAJ	Title, abstract and full article	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	0
Google Scholar	Title, abstract and full article	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	10

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Reference search from other sources	Title, abstract and full article	helminths AND/OR Water, Sanitation and Hygiene AND/OR WaSH AND/OR HIV/AIDS AND/OR CD4+ count AND/OR HIV-1 RNA AND/OR Viral load AND/OR HIV disease progression	0
		Total Result Search	**10**

Selection of studies

Identified articles were imported to Mendeley desktop window before they could be reviewed against the set inclusion criteria.

Data collection process

Titles and/or abstracts of studies were retrieved using the search strategy to identify studies that potentially met the inclusion criteria stated above. A standardized form was be used to extract data from the included studies for quality and.evidence synthesis. The details will include: Author, year of study, type of participants, age, setting, country, sample size, study design, and methods, study purpose and objectives, study outcome measures. Four review authors extracted data independently; discrepancies were tabled for discussion and were fully resolved before proceeding.

Search outcome

An initial database search located 2032 articles. A total of 432 articles were left after the removal of duplicates. The remaining articles were further filtered, and 427 articles were excluded because of age bracket (256), inappropriate outcome measures (299), and studies from non-African countries (123). The remaining 10 articles were selected for the final review (see Figure 2).

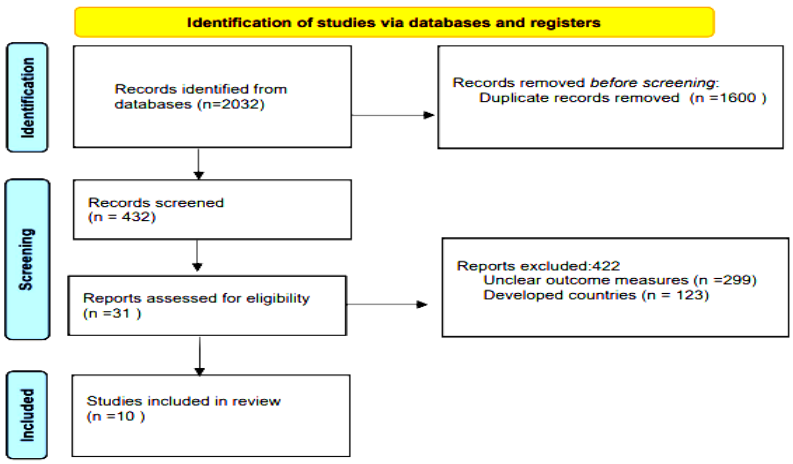

Figure 2. The PRISMA Flow Diagram

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We reviewed studies that reported the effect of helminths on HIV disease progression, focusing on CD4+ T lymphocyte count and viral load amongst PLWHA. A total of ten studies were selected and are summarized in Table 2 below.

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Table 2. Summary of studies

Author & year	Population			Country	Sample size	Study design & methods	Study purpose/ Objective	Results	
	Participant	Age	Setting					Outcome (VL)	Outcome (CD4+)
Kallestrup et al., 2005	Helminths and HIV-1 co-infected persons (130)	Adult	Hospital/ Facility-based	Zimbabwe	287	RCT	To determine the effect of helminths and their treatment on VL and CD4 count	● Coinfected patients, who received early treatment had a significantly lower increase in plasma HIV-1 RNA load than did those who received delayed treatment ($p<0.05$); ● The present study suggests that treatment of schistosomiasis can reduce the rate of viral replication	● Those who received early treatment had an increase in CD4 cell count, whereas those who received delayed treatment did not ($p<0.05$); ● The present study suggests that treatment of schistosomiasis can increase CD4 cell count in the coinfected host.
Wolday,et al., 2002	Helminths and HIV-1 co-infected persons (31)	Adult	Hospital/ Facility-based	Ethiopia	56	RCT	To study the effect of antihelminthic treatment on HIV plasma viral load (VL) in HIV- and helminth-infected individuals living in Ethiopia.	● The successful treatment of helminthic infection was accompanied by a mean decrease in HIV plasma $\log_{10}$VL of −0.36 (±0.83) that was not correlated to CD4 levels. ● Individuals infected with multiple helminth species had greater egg excretion in stools and a higher mean HIV plasma VL than those infected with a single helminth species (5.28 ± 0.35 versus 4.30 ± 1.13 $\log_{10}$ RNA copies/mL,	● No significant changes in CD4 T-lymphocyte counts between baseline and the 6-month visit for all groups.

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								respectively; p = 0.16). No correlation was found between egg excretion and either WHO staging or CD4 counts.	
Walson et al., 2010	Helminths and HIV-1 co-infected persons (298)	Adult	Hospital/ Facility-based	Kenya	1541	RCT	To determine prevalence and correlates of helminth infection among HIV-1 infected adults attending ten geographically distinct HIV Care and Treatment Clinics. To determine factors associated with STH clearance and persistence/re-infection among individuals who received albendazole as part of the clinical trial	Plasma log10 HIV RNA levels were similar between helminth species in the subset of individuals with available HIV-1 RNA levels (p = 0.10)	There were no differences in the median CD4 counts of individuals infected with different helminth species (p = 0.27)
Adeleke et al., 2015	Helminths and HIV-1 co-infected persons (57)	Adult	Hospital/ Facility-based	South Africa	252	Cross-sectional	To investigate the prevalence of intestinal helminth infestation amongst adults	Although the participants with helminth infection had a slightly higher mean viral load than those with no infection, there was no statistically significant differences in the	Although the participants with helminth infection had a slightly lower mean CD4 count than those with no infection, there was no statistically significant

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							living with HIV or AIDS at Mthatha General Hospital.	mean viral load (p = 0.98) in both groups.	differences in the mean CD4+ cell count (p = 0.79) in both groups. However, low CD4 count (< 200 cells/µL) was associated with intestinal helminthic infection. This was statistically significant (p = 0.05)
Downs et al., 2017	Helminths and HIV-1 co-infected persons Helminths un-infected and HIV-1 un-infected persons Helminths infected and HIV-1 un-infected persons	Adult	Hospital/ Facility-based	Tanzania	3146	Case-control study	To determine whether schistosome infection affects susceptibility to HIV-1 acquisition and HIV-1 viral load at the time of HIV-1 seroconversion	Schistosomiasis at the time of HIV-1 infection led to a 0.7 log_{10} increase in viral load at the time of HIV-1 seroconversion. A sustained 0.7 log_{10} HIV-1 viral load increase equates with an approximate doubling in infectivity among HIV-1-schistosome co-infected individuals and would be expected to accelerate time to symptomatic AIDS Schistosome infection increases the susceptibility of women to HIV-1 acquisition and increases the HIV-1 viral load at HIV-1 seroconversion in those who become HIV-1-infected. This study suggests that interactions exist between HIV-1 and schistosomiasis that may play a critical role in HIV-1 transmission and disease progression	No data

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Walson et al., 2008	Helminths and HIV-1 co-infected persons (299)	Adults	Hospital/ Facility-based	Kenya	1,551	RCT	To determine if treatment of helminth co-infection in HIV-1 infected adults impacted markers of HIV-1 disease progression	Mean plasma viral load was 4.75 log10 copies/mL at enrolment. Albendazole therapy resulted in a trend for 0.54 log_{10} lower HIV-1 RNA levels (p=0.09). These effects were not seen with treatment of other species of soil-transmitted helminths	Treatment of A. lumbricoides with albendazole in HIV-1 co-infected adults resulted in significantly increased CD4 counts during 3-month follow-up Mean CD4 count was 557 cells/mm3 at enrolment. Albendazole therapy resulted in significantly higher CD4 counts among individuals with Ascaris lumbricoides infection after 12 weeks of follow up (+109 cells/mm3 ; 95% CI +38.9 to +179.0, p=0.003) These effects were not seen with treatment of other species of soil-transmitted helminths
Brown et al., 2001	Helminths and HIV-1 co-infected persons (299)	Adults	Hospital/ Facility-based	Uganda	663	Prospective cohort study	To assess the relationship between helminths and HIV disease progression	At the time of enrollment into the study, the mean viral load was 4.83 log_{10} copies/mL (SD, 0.88 log_{10} copies/mL). A higher viral load was associated with a lower CD4+ cell count (p<.001) and more-advanced clinical stage (p<.001)	At the time of enrollment into the study, 38% of subjects had a CD4+ cell count <200 cells/mm3 , and 36% were in WHO clinical stages 3 or 4. At the time of enrollment into the study, the overall median CD4+ cell count was 263 cells/mm3 (interquartile range, 129–474 cells/mm3).

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								After treatment, the mean viral load was 4.76 log_{10} copies/mL at the time of enrollment and was 4.71 log_{10} copies/mL at follow-up (p= .22 , paired t test). Changes in viral load according to infection status at follow up did not differ statistically excerpt among Mansonella perstans–infected subjects, in whom the persistence of infection at follow-up was associated with a decrease in viral load (from 4.86 to 4.67 log_{10} copies/mL). p= .009.	The CD4+ cell count decreased between enrollment and the 6-month follow up in subjects with and those without helminths at enrollment, as is expected in HIV progression (no helminths, ;p<.0001 hookworm, ; p= .002 Schistosoma mansoni, p< .0001; Strongyloides stercoralis, p= .0008; and Mansonella perstans, p=.02). The mean decrease for all subjects was 45.7 cells/mm^3 . (SD, 129.7 cells/mm^3). In conclusion: There was lack of association between helminth status and lower CD4+ cell count
Mulu et al., 2013	Helminths and HIV-1 co-infected persons (87)	Adults	Hospital/ Facility-based	Ethiopia	220	prospective observational study	To define the impact of helminthic infestations and their treatment on viral load and T cell subsets in chronic HIV-1-infected patients	Helminths were found to be associated with an increased HIV RNA level. Successful treatment of intestinal helminths reduced plasma HIV RNA levels in chronic HIV-1 subtype C infection At baseline, plasma viral load was significantly higher in individuals with helminths than	Twelve weeks after antihelminthic treatment, helminth infestations and their treatment had no significant effect on CD4+ T cell counts. However, helminth-infested individuals had a higher level of CD8+ T cells at baseline (p < 0.001), which was significantly reduced (p <

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								those without helminthic infestation (5.01 log10 vs. 3.41 log10, $p < 0.001$). Twelve weeks after antihelminthic treatment, plasma HIV RNA levels were reduced in the successfully treated group ($p < 0.001$).	0.01) at 12 weeks after antihelminthic treatment.
Webb etal., 2012	Helminths and HIV-1 co-infected pregnant women	Adults	Hospital/ Facility-based	Uganda	264	RCT	To investigate the effect of helminth infections and their treatment during pregnancy on HIV load	Hookworm and Trichuris infections were associated with higher mean viral load at enrolment (adjusted mean difference 0.24log_{10} copies/ml, 95% confidence interval (CI): 0.01 to 0.47, p=0.03 and 0.37log_{10} copies/ml, 95%CI: 0.00 to 0.74, p=0.05, respectively). There were no associations between viral load and other helminth species. There was some evidence that albendazole reduced viral load at six weeks post-treatment (adjusted mean difference −0.17, 95% CI: −0.36 to 0.01, p=0.07) Infection with STH is associated with increased HIV load in pregnancy.	No data

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								Treatment with albendazole causes a small decrease in HIV load, but not reflective of a direct effect of worm removal.	
Rabiu et al., 2021	Helminths and HIV-1 co-infected pregnant women	Adults	Hospital/ Facility-based	Nigeria	197	Cross-sectional survey	To assess the effect of malaria and helminths on CD4 count, hematocrit values and viral load among HIV-infected pregnant women	The mean viral load and hematocrit values were not significantly different in the co-infection groups relative to those with HIV-infection only.	Those with co-infection of helminth and HIV had a lower CD4 count but this was not significant relative to those with HIV only. Likewise, the proportion of those with low CD4 count and low hematocrit values among those with co-infection relative to HIV only was not significant

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Data synthesis

The authors provide a narrative synthesis of the findings from the included studies with a particular focus on plasma HIV-1 RNA Viral load (V/L) amongst helminth-HIV-1 co-infected persons. A narrative synthesis was conducted based on the methodology and results of the included studies.

Results

Quality appraisal

The methodological quality of included studies was critically appraised using the Mixed Method Appraisal Tool (MMAT). Ten (10) high quality studies fulfilled the core criteria for their specific study design. No study was rated below the minimum threshold of 90%. With an average score of 96% across the included articles, the studies are categorized as very high quality and fit for synthesis. Therefore, the findings from this study can be considered credible and upon which policy, practice, and research can be based.

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Table 3. Mixed Method Appraisal Tool (MMAT)

Name of study/ author	Type of study	Methodological quality criteria	Y/N	Comment	Score
Kallestrup et al., 2005 Schistosomiasis and HIV-1 Infection in Rural Zimbabwe: Effect of Treatment of Schistosomiasis on CD4 Cell Count and Plasma HIV-1 RNA Load	Randomized controlled trial	2.1. Randomization appropriate? 2.2. Group comparability at baseline 2.3. Completeness (outcome data) 2.4. Blinding of intervention 2.5 Adherence to the intervention	Y Y Y Y Y		100%
Wolday et al., 2002 Treatment of Intestinal Worms Is Associated With Decreased HIV Plasma Viral Load	Randomized controlled trial	2.1. Randomization appropriate? 2.2. Group comparability at baseline 2.3. Completeness (outcome data) 2.4. Blinding of intervention 2.5 Adherence to the intervention	Y Y Y Y Y		100%
Walson et al 2010 Prevalence and Correlates of Helminth Co-infection in Kenyan HIV-1 Infected Adults	Randomized controlled trial	2.1. Randomization appropriate? 2.2. Group comparability at baseline 2.3. Completeness (outcome data) 2.4. Blinding of intervention 2.5 Adherence to the intervention	Y Y Y Y Y		100%
Adeleke et al., 2015 Intestinal helminth infections amongst HIV-infected adults in Mthatha General Hospital, South Africa	Cross-sectional	3.1. Sample representativeness 3.2. Measurements (outcome/intervention) 3.3. Completeness (outcome data) 3.4. Accounting for confounders 3.5. Timing of the intervention	Y Y Y Y Y		100%
Downs et al 2017	Case control	2.1. Randomization appropriate? 2.2. Group comparability at baseline	Y Y		80%

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Effects of schistosomiasis on susceptibility to HIV-1 infection and HIV-1 viral load at HIV-1 seroconversion: A nested case-control study		2.3. Completeness (outcome data) 2.4. Blinding of intervention 2.5 Adherence to the intervention	Y Y N	
Walson et al., 2008 Albendazole treatment of HIV-1 and helminth co-infection: A randomized, double blind, placebo-controlled trial	Randomized controlled trial	2.1. Randomization appropriate? 2.2. Group comparability at baseline 2.3. Completeness (outcome data) 2.4. Blinding of intervention 2.5 Adherence to the intervention	Y Y Y Y Y	100%
Brown et al., 2001 Helminth Infection Is Not Associated with Faster Progression of HIV Disease in Coinfected Adults in Uganda	Prospective cohort study	3.1. Sample representativeness 3.2. Measurements (outcome/intervention) 3.3. Completeness (outcome data) 3.4. Accounting for confounders 3.5. Timing of the intervention	Y Y Y Y Y	100%
Mulu et al., 2013 Deworming of intestinal helminths reduces HIV-1 subtype C viremia in chronically co-infected individuals	Prospective observational	3.1. Sample representativeness 3.2. Measurements (outcome/intervention) 3.3. Completeness (outcome data) 3.4. Accounting for confounders 3.5. Timing of the intervention	Y Y Y Y Y	100%

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Webb et al.,2012 The effect of anthelminthic treatment during pregnancy on HIV plasma viral load; results from a randomised, double blinded, placebo-controlled trial in Uganda	Randomized controlled trial	2.1. Randomization appropriate? 2.2. Group comparability at baseline 2.3. Completeness (outcome data) 2.4. Blinding of intervention 2.5 Adherence to the intervention	Y Y N Y Y	80%
Rabiu et al.,2021 Malaria, Helminth Infections and Clinical Status Among HIV-Infected Pregnant Women	Cross-sectional	3.1. Sample representativeness 3.2. Measurements (outcome/intervention) 3.3. Completeness (outcome data) 3.4. Accounting for confounders 3.5. Timing of the intervention	Y Y Y Y Y	100%

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Study characteristics

Ten studies fulfilled the eligibility criteria. These studies were conducted in Ethiopia, South Africa, Tanzania, Uganda, Nigeria, Zimbabwe and Kenya (See Table 2). Five studies were RCT (Webb et al., 2012; Walson et al., 2010; Walson et al., 2008; Kallestrup et al., 2005; Wolday,et al., 2002). Two studies were cross sectional (Rabiu et al., 2021; Adeleke et al., 2015). The other two were prospective observational studies (Mulu et al., 2013; Brown et al., 2001) and the last one was a case control study (Downs et al., 2017). The studies had the following sample sizes: 287 (RCT), 56 (RCT), 1,541 (RCT), 252 (C/Sectional), 3,146 (C/Control), 1,551 (RCT), 663 (P/Observational), 220 (P/Observational), 264 (RCT), 197 (C/Sectional). Participants' characteristics were as follows: helminths and HIV-1 co-infected persons, and/ or helminths un-infected and HIV-1 un-infected persons, and/ or helminths infected and HIV-1 un-infected persons. All studies were hospital/facility-based and involved adult participants.

Summary of the findings

Studies included in this review were analyzed based on the following outcomes: The primary outcome of the study was plasma HIV-1 RNA Viral load (V/L) amongst helminth-HIV-1 co-infected persons. Secondary outcomes were:

i. Cluster of Differentiation (CD4+) T-lymphocyte count
ii. maternal HIV-1 transmission (MTCT)
iii. mortality and other adverse events

The current method used for staging HIV infection in settings with limited resources is the sole measurement of CD4+ T cells (CD4 count test). WHO recommends a cut-off value of 200–350 CD4+ T cells/μl for adults; patients with values below this should be initiated on antiretroviral treatment (WHO, 2003b).

Viral load test result might be reported as "<20", "<50", "<200", "undetectable", "not detected" (ND), "target not detected" (TND), "below the limit of detection" or "zero". A normal viral load means less than 20 to 75 copies of the human immunodeficiency virus (HIV) per milliliter of blood. A normal viral load may indicate: Low risk of HIV infection. Zero risk of transmitting infection.

Different sample sizes were used in the studies, ranging from 56 to 3146. All the articles managed to statistically present the findings and clearly indicated whether the results were statistically significant or not using either p-values or confidence intervals.

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HIV-1 RNA Viral load (V/L)

Coinfected patients, who received early treatment had a significantly lower increase in plasma HIV-1 RNA load than did those who received delayed treatment ($p < 0.05$). Successful treatment led to a significant decline in HIV plasma $\log_{10}$VL of −0.36 (±0.83). Individuals who were infected with more than one helminth species experienced a higher mean plasma HIV-1 RNA Viral load than their countreparts who had just a single type of helminths (Kallestrup et al., 2005). Schistosomiasis led to a 0.7 $\log_{10}$ increase in viral load at the time of HIV-1 seroconversion thereby increasing the susceptibility of women to HIV-1 infection and viral load, suggesting a critical role of the infection in transmission and disease progression particularly among women (Downs et al., 2017). Hookworm and Trichuris infections were associated with higher mean viral load at enrolment (adjusted mean difference 0.24$\log_{10}$ copies/ml, 95% confidence interval (CI): 0.01 to 0.47, $p = 0.03$ and 0.37$\log_{10}$ copies/ml, 95%CI: 0.00 to 0.74, $p = 0.05$, respectively). Infection with STH was associated with increased HIV load in pregnancy (Webb etal., 2012) and a higher viral load was associated with a lower CD4+ cell count ($p<.001$) and more-advanced clinical stage ($p < 0.001$), (Brown et al., 2001). There was some evidence (though not very strong) that treatment with albendazole reduced viral load at six weeks post-treatment (adjusted mean difference −0.17, 95% CI: −0.36 to 0.01, $p = 0.07$), (Webb et al., 2012)

In conclusion, HIV-1 RNA levels were significantly higher at enrolment, in individuals with helminths than those without helminthic infestation (5.01 $\log_{10}$ vs. 3.41 $\log_{10}$, $p < 0.001$). The magnitude of effect was variable, ranging from 5.28 $\log_{10}$ copies/mL at baseline and 4.67 $\log_{10}$ copies/mL, ($p < 0.05$) after successful treatment and a trend for 0.61 $\log_{10}$ lower HIV-1 RNA levels. All but one RCT reported decline in plasma HIV-1 RNA levels and significant interactions were seen in the successfully treated groups ($p < 0.001$). Although some variations existed, this study suggests that interactions exist between HIV-1 and helminths infestation that may play a critical role in disease progression.

Cluster of Differentiation (CD4+) T-lymphocyte Count

Early treatment of schistosomiasis led to an increase in CD4+ cell count, whereas late treatment did not ($p < 0.05$), suggesting that treatment of schistosomiasis can boost CD4+ cell count in co-infected hosts if timely commenced (Kallestrup et al., 2005). Treatment with Albendazole resulted in significantly higher CD4+ counts among individuals with Ascaris lumbricoides infestation (+109 cells/mm3; 95% CI +38.9 to +179.0, p=0.003), (Walson et al., 2008). Low CD4+ count (< 200 cells/μL) was significantly associated with intestinal helminths infecstation ($p = 0.05$) ($p = 0.05$) (Adeleke, 2015) but there were no significant differences in the median CD4+

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counts of persons who were infected with different helminth species (p = 0.27), (Walson et al., 2010). Two studies (Downs et al., 2017; Webb etal., 2012) did not provide data on this outcome. All other studies reported statistically insignificant differences in the mean CD4+ cell count (p = 0.79) in both groups (Adeleke et al., 2015); inconsistent results (Walson et al., 2010; Brown et al., 2001); insignificant differences relative to those with HIV only, (Robiu et al., 2021). Similarly, other studies (Mulu et al., 2013; Wolday et al., 2002) did not find any significant effect of helminths on CD4+ count.

In conclusion, there were inconsistent results on the effect of helminths on CD4+ T-lymphocyte count as values were not significantly different in the co-infection groups relative to those with HIV-infection alone. We determined the quantity and quality of evidence from studies examining MTCT and mortality as poor owing to the limited number of studies that reported the two as outcomes. We did not find suitable studies that estimated mother to child transmission rates in HIV-1 infected women (vertical transmission). Similarly no study reported about any adverse events as an outcome.

Discussion

Evidence about the effect of helminths infections on HIV disease progression among PLWHA remains mixed and inconclusive as studies have implicated helminths in increasing systemic immune activation, which is linked to an increase in HIV-1 susceptibility and faster progression to AIDS; yet some have reported no association. Mixed opinions have always resulted from contextual factors, or study settings, sampling framework, methodological limitations, characteristics of the study population, and in some cases failure to limit bias on the part of researchers and variations in error tolerance thresholds. In this systematic review, we systematically synthesized evaluated, and summarized the findings of all relevant individual studies in an attempt to resolve the research question. We critically appraised and summarized the published evidence on the effect of helminths infections on HIV disease progression among PLWHA. All the included studies reported plasma HIV-1 RNA Viral load (V/L) and Cluster of Differentiation (CD4+) T-lymphocyte count amongst helminth-HIV-1 co-infected persons as study outcomes and must have been explicitly defined within the abstract. We also reviewed studies that reported the efficacy of antihelminthic treatment on HIV prognostic markers.

Early treatment resulted in significantly higher CD4+ counts among individuals with Ascaris lumbricoides infestation (Walson et al., 2008) and lower viral loads. (Downs et al., 2017; Adeleke et al., 2015; Webb et al., 2012; Kallestrup et al., 2005). Specifically, a 1·0 log10 copies per mL drop in plasma viral load translate to a 2-year delay in the development of an AIDS-defining condition. The same amount of plasma HIV-1 RNA decline takes

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away half of HIV-1 transmission risk. Our analysis showed a viral-load decline of at least 0·6 log10 copies per mL from the included studies. This evidence supports that even small declines can lead to the slowing down of HIV progression and could positively contribute towards lowering HIV transmission risk amongst the larger population (Modjarrad et al., 2010). Treatment of co-infections prevalent among PLWHA might therefore result in suppression of plasma HIV-1 RNA concentrations, delay time to an AIDS-defining event and substantial public-health risk reduction.

No statistically significant difference was seen between the co-infection groups relative to those with HIV-infection alone. The lack of association between CD4+ count and helminth infection in the present study could be attributable to the small sample sizes that were used in the primary studies (see study characteristics) and the ultimate number of studies that made it to the final selection for this systematic review, some of which were not designed specifically to address this hypothesis. Declining CD4+ counts have been closely linked with higher burdens and severe forms of strongyloides, ascaris and hookworms infestation (Bava et al., 2009). Significant decline in the prevalence of helminths have been reported among persons who are adherent to antiretroviral therapy (ART), suggesting that immune recovery may result in protection against some forms of helminth infestation (Tran et al., 2019; Walson et al., 2010; Bava et al., 2009; Bachur et al., 2008). This can well be extended to the reason of a lack of mortality in helminths–infested subjects in the current study suggesting that CD4+ cells mirrors a real immune advantage in HIV-infected subjects.

The lack of association between helminth infections status and lower CD4+ cell count argues against the second part of our hypothesis and sharply contradicts the results of other previous studies [Brown et al., 2021; Adeleke et al., 2015; Borkow et al., 2000]. We hypothesized that concurrent helminths infections may lead to impaired immune control of HIV-1, resulting in escalating HIV-1 viral loads and reduced levels of CD4+ T-lymphocyte count. Subject to successful treatment, we further hypothesized a decrease in plasma HIV-1 RNA load and slowing down of HIV-1 disease progression. In this study, we have demonstrated that helminths are associated with an increase in HIV-1 RNA levels that accelerate the progression of sub-clinical disease to symptomatic AIDS. In the same way, successful treatment of helminths reduced plasma viral load among co-infected persons. There were inconsistent results on the effect of helminths on CD4+ T-lymphocyte count as values were not significantly different in the co-infection groups relative to those with HIV-infection alone. Plasma human immunodeficiency virus type 1 (HIV-1) viral load and CD4+ cell count are used to predict the likely outcome or course of disease amongst persons infected with HIV.

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Limitation of the study

Most studies were not included due to inadequate reporting of some essential data elements. Owing to fewer studies on the concurrent infections with helminths and HIV-1 among persons living in poor resource settings, there is an urgent need for well controlled and double-blinded large scale studies to fully resolve this question.

Implications of the study findings for practice, research, and policy

The World Health Assembly estimates that two billion people are infected by helminths worldwide and that an estimated 160 million still harbor at least one of the following: Wuchereria bancrofti, Brugia malayi, Loa loa, and Onchocerca volvulus among the pathogenic phyla (Vanhamme et al., 2020); cestode (tapeworms) and the trematode (flukes) among the Platyhelminthes class (Deoletal., 2019). Attributable causes of helminths infestation remain poor WaSH and bad living conditions among HIV-1 co-infected persons in poor resource settings. PLWHA, children and pregnant women are highly susceptible to complications associated with helminths infestation (Blackwell et al., 2016). While preventive chemotherapy can be attained more cheaply through external donor support, and administered safely to reduce helminthiasis, routine mass campaigns have focused on children. Secondly such campaigns have lost an opportunity to mainstream WaSH as a long-term preventive and sustainable strategy for the control of helminths infestations in the face of potential threats such as drug resistance and donor fatigue. Through an integrated WaSH/HIV approach, substantial behavioral change in handwashing, use of latrines and appropriate food handling practices need to be reinforced. There is need for modelling of WaSH in high HIV sentinel sites to enhance robustness, understandability and validation of a set of WaSH/HIV indicators and outcomes. Geophagy and pica (the craving and purposive consumption of substances not culturally defined as food eg soil/earth by some pregnant women from other tribes) must be discouraged through effective behavior change and health promotion programs that target pregnant women living with HIV.

"The Global strategy on WaSH to combat Neglected Tropical diseases- 2021-2030" aligns with the Sustainable Development Goal targets 6.1 and 6.2 on drinking water and sanitation. Potable water supply and basic sanitation are key towards the attainment of the other SDG targets including good health and well-being (SDG 3), economic growth (SDG 8), and reduced inequalities (SDG 10).

Conclusion

We have demonstrated that WaSH is critical for PLWHA's health. Evidence from this systematic review suggests that helminths and HIV-1 co-

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infections are associated with an increase in HIV-1 RNA levels that accelerate progression of sub-clinical disease to symptomatic AIDS. At the same time, the study found no association between CD4+ count and helminth infection. It follows therefore that efforts to reduce fecal contamination of the environment through WaSH interventions could be essential for the long-term, sustainable control of helminthiasis. This study proposes preventive chemotherapy as a potential preventive HIV service package for PLWHA. This evidence supports that WaSH and HIV/AIDS co-programming could be beneficial for the prevention and control of helminths, suppression of HIV load. Large scale trials are suggested to yield strong evidence.

Conflict of interes: The authors declare no competing interests.

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