Parasitic disease screening among HIV patients from endemic countries in a Toronto clinic

Cecilia T Costiniuk MD FRCPC, Curtis L Cooper MD FRCPC1,2, Steve Doucette MSc, Colin M Kovacs MD FRCPC3

BACKGROUND: Many North American-based HIV patients originate from parasitic disease-endemic regions. Strongyloidiasis, schistosomiasis and filariasis are important due to their wide distribution and potential for severe morbidity.

OBJECTIVES: To determine the prevalence, as determined by serological screening, of strongyloidiasis, schistosomiasis and filariasis among patients in an HIV-focused, primary care practice in Toronto, Ontario. A secondary objective was to determine factors associated with positive serological screens.

METHODS: A retrospective review of electronic patient records was conducted. Results of serological screens for parasites and relevant laboratory data were collected.

RESULTS: Ninety-seven patients were identified. The patients’ mean CD4+ count was 0.45×10^9/L, median viral load was undetectable and 68% were on highly active antiretroviral therapy (HAART). Most originated from Africa (37%) and South America (35%). Of the 97 patients, 10.4% and 8.3% had positive or equivocal screening results for strongyloidiasis, respectively, 7.4% and 4.2% had positive or equivocal screening results for schistosomiasis and 5.5% and 6.8% had positive or equivocal screening results for filariasis. Persons with positive parasitic serologies were more often female (28% versus 9%, P=0.03), younger in age (36 versus 43 years of age, P<0.01), had been in Canada for a shorter duration (5 versus 12 years, P<0.0001) and had a higher viral load (10,990 copies/mL versus <50 copies/mL, P<0.001). All patients were asymptomatic. Eosinophilia was not associated with positive screening results.

CONCLUSIONS: Using symptoms and eosinophilia to identify parasitic infection was not reliable. Screening for strongyloidiasis and schistosomiasis among patients with HIV from parasite-endemic countries is simple and benign, and may prevent future complications. The clinical benefits of screening for filariasis require further elucidation, but this practice appears to be the least warranted.

Key Words: Filariasis; HIV; Parasitic diseases; Schistosomiasis; Strongyloidiasis

As of 2001, greater than 40% of Toronto’s (Ontario) population was composed of foreign-born people, with the majority arising from parasite-endemic areas (1-3). Many of these individuals also originate from HIV-endemic regions (3), suggesting that HIV and parasitic co-infection is not uncommon. Among the parasitic diseases, strongyloidiasis, schistosomiasis and filariasis are of greatest concern due to their wide distribution and potential for severe morbidity and, occasionally, mortality, especially in immunosuppressed persons (4-16).

A number of gastrointestinal, dermatological and respiratory symptoms may occur as a consequence of these parasitic infections. A hyperinfection syndrome with larval dissemination is a well-documented, severe complication of Strongyloides infection (5-11). Also concerning is the interaction between parasitic diseases and HIV (17-25). There is some in vitro evidence demonstrating a trend toward enhanced replicative capacity of HIV in peripheral blood mononuclear cells from patients with untreated lymphatic filariasis and enhanced susceptibility of these cells to HIV infection (17). Patients are often asymptomatic when worm burdens are low, and as a result, infections may go unrecognized (5,26). Furthermore, practitioners in developed countries may lack familiarity with these conditions (27,28). Delays in diagnosis and in treatment may have detrimental consequences (9,27,28).

Due to the potential for significant negative sequelae attributable to parasitic infection in immunosuppressed populations, in addition to...
its potential impact on the natural history of HIV infection, all HIV patients in one of the clinics at The Maple Leaf Medical Clinic in Toronto, Ontario, are routinely screened for parasitic diseases. This practice began in 2006 with screening for strongyloidiasis and schistosomiasis occurring as part of the baseline health work-up shortly after patients join this HIV-focused primary care practice. In 2009, this screening practice expanded to include filariasis, based on the suggestion from a colleague. A retrospective chart review was conducted to evaluate the frequency of positive results, predictors of positivity and the utility of these screening practices.

METHODS
All patients with HIV infection in the physician’s clinic originating from a parasite-endemic country before emigration to Canada were identified by an electronic database search. Patient approval for use of anonymous laboratory data was obtained before data collection. Use of anonymous laboratory data extracted from the clinic database for research purposes had previous approval from the research ethics committee at the clinic. Progress notes before and at the time of parasite screening were reviewed, with attention devoted to gastrointestinal complaints. Baseline laboratory data collected at the time of parasite screening included eosinophil count, CD4+ count and viral load (VL). Baseline laboratory data were reviewed, with attention devoted to gastrointestinal complaints. Baseline laboratory data collected at the time of parasite screening included eosinophil count, CD4+ count and viral load (VL). Highly active antiretroviral therapy (HAART) use at the time of screening was noted.

Patients with positive strongyloidiasis and schistosomiasis serology results received either ivermectin and/or praziquantel. Patients with equivocal serologies underwent repeat serological testing. Patients with any positive parasitic screens were asked to provide a stool sample for ova and parasite testing, and those with positive schistosomiasis screens were asked to provide a urine specimen in addition. Obtaining urine specimens for schistosomiasis was not specifically restricted to individuals from regions endemic for Schistosoma haematobium. Individuals with repeat positive strongyloidiasis serological screens were retreated with the same medication. An eosinophil count six months after final treatment was performed. Patients with positive filarial screens were referred to a tropical medicine specialist who suggested they not be treated due to their lack of symptoms. An eosinophil count six months after serological screening for filariasis was also performed.

All serological, stool and urine screening was performed by the National Reference Centre for Parasitology (NRCP) at McGill University in Montreal, Quebec. As a screening test, the NRCP uses an immunoglobulin (Ig) G-ELISA with antigens extracted from Strongyloides stercoralis filarial larvae from an individual who is heavily infected. This test has a sensitivity of 100% and specificity of 88%. This assay may cross-react with hookworm, filariae, Paragonimus or Echinococcus. Positive samples are confirmed using an IgG4-based ELISA. This confirmatory assay has a sensitivity of 93% and specificity of 92%.

Sensitivity and specificity are 91% and 94%, respectively. Cross-reactions may occur in infections due to Schistosoma, Strongyloides or Echinococcus (29).

Baseline characteristics were summarized as means and SDs for continuous variables, and as frequencies and percentages for categorical variables. Logistic regression analysis was used to determine the odds of having eosinophilia based on positive serological screens for strongyloidiasis, schistosomiasis and filariasis. χ² tests were used to assess differences in patient demographics with regard to screening results.

RESULTS
Ninety-seven patients were identified (Figure 1). The majority of patients originated from areas throughout Africa (36.5%) and South America (35.4%). The average patient age was 41.9 years (range 24 to 58 years of age). The majority of patients were male (87.6%). The average number of years during which patients resided in Canada was 10.8 (range one to 47 years), and the average duration of HIV infection was 8.9 years (range one to 28 years).

Screening results are shown in Table 1. Ninety-six patients were screened for strongyloidiasis. Ten (10.4%) and eight (8.3%) patients had positive or equivocal screening results, respectively. Of the 95 patients who were screened for schistosomiasis, seven (7.4%) and four (4.2%) had positive or equivocal screens, respectively. With respect to filariasis screens, these were performed in 73 patients and yielded positive screens in four (5.5%) and equivocal screens in five (6.8%) of the individuals tested. Three people had positive or equivocal screens for both strongyloidiasis and schistosomiasis, and two people had positive screens for both strongyloidiasis and filariasis. All of the patients were entirely asymptomatic from a gastrointestinal perspective at screening. Information regarding the presence of cutaneous complaints was not extracted. No patients developed any clinical sequelae of chronic infection.

The mean CD4+ count at the time of screening for strongyloidiasis and schistosomiasis was 0.45×10⁹/L. The median VL was below the lower limit of detection (49 copies/mL, range 49 copies/mL to 194,693 copies/mL). At the time of screening for strongyloidiasis and schistosomiasis, 68.1% of persons were on antiretroviral medication.

The mean total white blood cell and eosinophil counts at the time of screening for patients with positive or equivocal strongyloidiasis and schistosomiasis were 5.4×10⁹/L (range 2.4×10⁹/L to 9.2×10⁹/L, normal range 3.0×10⁹/L to 10.5×10⁹/L) and 0.28×10⁹/L (range 0.47×10⁹/L to 1.4×10⁹/L, normal range 0.0×10⁹/L to 0.5×10⁹/L), respectively. For persons with positive or equivocal filariasis screens, these measures were 5.4×10⁹/L (range 2.6×10⁹/L to 7.3×10⁹/L and 0.12×10⁹/L (range 0.0×10⁹/L to 0.5×10⁹/L, respectively. Twelve persons had eosinophilia (>0.5×10⁹/L). The odds of having eosinophilia with a positive serological screen was 4.93 for strongyloidiasis (95% CI 0.64 to 38.0), 12.8 for schistosomiasis (95% CI 1.53 to 107.8) and 3.13 for filariasis (95% CI 0.29 to 33.7).

Patients with positive or equivocal screening serologies for strongyloidiasis were more likely to be female (27.78% versus 8.86%.

**Table 1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients tested, n</th>
<th>Positive, n (%)</th>
<th>Equivocal, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongyloidiasis serology</td>
<td>96</td>
<td>10 (10.4)</td>
<td>8 (8.3)</td>
</tr>
<tr>
<td>Schistosomiasis serology</td>
<td>95</td>
<td>7 (7.4)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Filariasis serology</td>
<td>73</td>
<td>4 (5.5)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Stool for ova and parasites</td>
<td>5</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Urine for schistosomiasis eggs</td>
<td>4</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A Not applicable
P=0.03), of younger age (36.44 versus 43.15 years of age, P<0.01), and to have been living in Canada for a shorter duration of time (five versus 12.21 years, P=0.0001); these patients were also more likely to have a higher VL (10,990 copies/mL versus <50 copies/mL, P<0.001). There were no associations between CD4+ count, HAART use and serological status. With regard to schistosomiasis and filariasis, there were no associations between positive screening results and sex, age, duration of time living in Canada, CD4+ count, VL and being on HAART. There was no significant increase or decrease in eosinophil count six months after treatment.

Repeat serological testing was requested for any person with a positive/equivocal strongyloidiasis screen. This was performed approximately six months after treatment. Repeat serology was positive in one of the 18 persons with a positive/equivocal strongyloidiasis screen (results were not available for two persons). Patients with positive repeat strongyloidiasis screens were retreated.

A stool sample was requested from persons with a positive or equivocal screening serology (n=38). Only four people returned stool specimens, of which all were negative for ova or parasites. A urine sample was requested from persons with positive or equivocal schistosomiasis serology screens (n=11). Five people returned urine specimens, of which all were negative for schistosoma eggs.

**DISCUSSION**

*Strongyloides* are unique among parasites because they can transform from rhabditiform to filariform larvae in the body, rather than exiting the body and forming a free-living stage (3,8-11). Due to its unique ability for autoinfection, the *Strongyloides* helminth burden can increase dramatically in a process known as the hyperinfection syndrome, which has been reported to occur in up to 2.5% of all cases (14). Dissemination may result in severe rash, gastroenteritis, meningitis and acute respiratory failure (8-10,13,27,30). The principal risk factor for *Strongyloides* hyperinfection syndrome is actually immunocaualative therapy and not HIV infection (3,27). Although cases of immune reconstitution inflammatory syndrome due to *Strongyloides* stercoralis have been reported, it is unclear if this arises due to triggering of immune responses to pre-existing disseminated infection or whether immune recovery facilitates dissemination of strongyloidiasis (18). The fatality rate with disseminated strongyloidiasis is up to 80% (15,18).

At the other end of the spectrum of strongyloidiasis is asymptomatic infection. Although chronic carriers often remain asymptomatic, there is a report of a person living in Canada for more than 50 years before developing symptoms (3). Chronic infection may present with symptoms such as intermittent gastrointestinal complaints, recurrent asthma symptoms and pruritis ani, and dermatological manifestations such as urticaria, and larva currens rashes. Sometimes fatigue will be the predominant symptom (4,5,13,26,30).

Schistosomiasis has an epidemiology similar to strongyloidiasis. Schistosomes typically have a limited lifespan of 10 to 15 years due to the absence of autoinfection (26). However, they can persist in the human host for longer periods, and it is possible for immigrants from endemic areas to remain infected for 30 to 40 years (31-33). Morbidity is dependent on the *Schistosoma* species, the intensity of infection and the host’s immune response (19-21,31-33). Egg antigens promote inflammation, hyperplasia, ulceration and microabscess formation within a variety of tissues. Granuloma formation is mediated by major histocompatibility complex class II-restricted CD4+ helper lymphocytes in response to egg antigens (33,34). In HIV infection, T-helper cell (Th) 2 lymphocytes are depleted, shifting the usual Th2-mediated helminth response to a Th1-like response, which has been shown to be associated with severe hepatosplenic disease (33,35,36). Furthermore, patients with advanced HIV are less likely to form granulomas, which are believed to be protective by sequestering egg toxins, preventing the triggering of Th1-like response in liver cells (33,37).

In women, genital schistosomiasis occurs in approximately 60% of those infected with *S haematobium* (21). Breakdown in epithelial integrity is typical in genital schistosomiasis and is believed to be associated with HIV transmission (11,19-21,38). It is known that egg-induced inflammation recruits activated immune cells expressing the CD4 and chemokine receptor CCR5 into the epithelium, which may facilitate HIV transmission. Furthermore, increased amounts of interferon-gamma, interleukin-2 and tumour necrosis factor-alpha induced by new granuloma formation may further assist HIV transmission (19). It has also been suggested that genital schistosomiasis in males may provoke chronic inflammation of the genitals and potentially increased viral shedding of HIV in semen (21).

In its fulminant form, filariasis can cause three main forms of infection, although not commonly seen in Canada. These include lymphatic filariasis, subcutaneous filariasis and serous cavity filariasis. Although data from human subjects has been limited, in vitro studies have suggested that HIV replication may be increased in patients with untreated filariasis, and that peripheral blood mononuclear cells appear to have enhanced susceptibility to HIV infection in vitro (17,21). The clinical importance of identifying occult asymptomatic filariasis infection is less clear than for strongyloidiasis and schistosomiasis because patients with filarial infection who leave the area of endemicity do not appear to be at high risk for adverse consequences (4,38). Some tropical medicine experts will treat only persons with clearly diagnosed infection due to *Loa loa*, Oncercerca volvulus or lymphatic filariasis, and disregard other infections that are asymptomatic (4).

In the present retrospective chart review, we demonstrated seroprevalence rates of 10%, 7% and 4% for strongyloidiasis, schistosomiasis and filariasis, respectively, in our HIV patients. These results are consistent with those of United Kingdom screening studies in HIV patients from Africa (6,39). All of our patients were asymptomatic. Seropositivity for strongyloidiasis was associated with female sex, younger age, fewer years living in Canada and higher VL. Fewer years living in Canada suggests more recent potential exposures in the endemic locale. The finding of higher VL in individuals with positive strongyloidiasis screens is difficult to interpret. Although there is some evidence to suggest that parasitic disease, at least filariasis, may be associated with increased HIV replication in vitro, we cannot draw firm conclusions based on our results due to the small sample size and the retrospective nature of our study.

In our experience, many clinicians rely on eosinophilia as an indicator of parasitic infection. In our evaluation, eosinophilia was not useful for this purpose, which is consistent with other screening studies (4,6). This absence of association may be indicative of aberrant immune function because eosinophilia and low IgE levels are associated with high mortality (13,16,40). In our judgment, lack of eosinophilia should not preclude consideration of parasitic infection in the differential diagnosis in the context of HIV (8,26).

In addition to patients from endemic countries, it has been suggested that any persons with risk factors for parasitic disease who may receive steroids in the future be screened for strongyloidiasis and schistosomiasis (26,27,41). This recommendation is based on the fact that steroids can have catastrophic effects in the setting of strongyloidiasis due to the propensity of steroids to increase output of infective larvae from female worms. These groups may include asthmatic patients, persons with rheumatological conditions and HIV patients who may require steroids as part of the treatment for pneumocystis pneumonia or lymphoma. Furthermore, other persons who may benefit from screening are those with poor responses to HAART due to the potential of parasitic diseases to affect antiretroviral absorption in the gastrointestinal tract (27,42). This, however, may be useful after more common causes of treatment failure have been excluded.

Treatment for strongyloidiasis consists of oral ivermectin 200 μg/kg for one to two days. There is the option to repeat this treatment two weeks later to increase the chance of eradication. Oral albendazole 400 mg twice daily for seven days is an alternative treatment for strongyloidiasis and may be effective against some filariae. Schistosomiasis is treated with praziquantel for one day. The dosing of praziquantel is dependent on the species, and is either 40 μg/kg/day.
taken orally two or three times daily or 60 mg/kg/day taken orally two or three times daily. In a study from Zimbabwe, Kallestrup et al (22) demonstrated that treatment of schistosomiasis reduced the rate of viral replication and increased the CD4+ count in infected individuals. In another African-based study, HIV viral levels were higher in individuals with various helminth infection compared with those without helminth infection, but HIV viral levels decreased after antiparasitic treatment (21,43). In nonendemic regions, a presumptive treatment strategy has been shown to be cost effective when the prevalence of strongyloidiasis exceeds 2% (44,45).

Repeat serological testing for strongyloidiasis can be performed six months after treatment to help determine whether a person has been cured (46). Some may advocate for testing nine to 12 months posttherapy, so as not to overlook persistent infection. However, serorevelations may remain elevated in persons from endemic countries even many years after immigration to nonendemic countries. A challenge in the management of strongyloidiasis is the difficulty in determining whether the parasite has been successfully treated (46). With schistosomiasis and filariasis, persistence of antibodies after parasitologic cure is expected; therefore, there is no purpose in following titres that are unlikely to decline. Similarly, there is no rationale for treating asymptomatic individuals whose serologies remain positive.

In addition to its retrospective nature, there are several limitations to our study. Serological screening and specimen collection performed with such a small sample size may not enable us to draw valid conclusions. Because this study relied on serology as an indication of previous parasitic infection, limitations of serological testing, such as cross-reactivity between organisms, apply (29). The utility of these assays is also greatest for those who have some form of symptomatology. Sensitivity and specificity for these tests may also vary between laboratories. Furthermore, patients with advanced HIV may have impaired antibody formation, which may limit the utility of these tests in these individuals.

The low provision of stool and/or urine samples in the present evaluation was likely due to inconvenience and the fact that patients were asymptomatic. Stool examination is also limited due to variable shedding of eggs in asymptomatic individuals. Urine testing for schistosomiasis may be more useful when performed on persons from regions endemic for S haematobium. Furthermore, we did not extract data regarding cutaneous symptoms from the charts. Given that the mean CD4+ count was 0.45x10^9/L, it is possible that some individuals did experience cutaneous symptoms that we did not capture in this review.

Nonetheless, these limitations should be balanced with the merits of the present study, which include the fact that our study examined screening results for patients from a variety of geographical locales, as opposed to other studies that focused on patients of African origin (6,7,39). Furthermore, while similar studies have evaluated parasitic disease seroprevalence, the majority were not in HIV patients. To our knowledge, this is the first parasitic screening study involving HIV patients from various endemic countries now residing in North America. The present study also provided us with the opportunity to determine that mass filarial screening in the absence of symptoms does not appear to be particularly useful, especially when performed before stool examinations where organisms such as Ascaris or hookworms may be more likely to be found and may result in false positives. As such, we have abandoned filarial screening in the clinic in asymptomatic individuals.

SUMMARY
Individuals with HIV from countries endemic for parasitic disease are at high risk for chronic parasitic diseases. Because they are often asymptomatic and lack eosinophilia, they may not be screened for these infections. Our analysis suggests that these criteria for screening are not reliable. Failure to identify chronic parasitic infection in HIV could have detrimental effects in the future. As demonstrated in our analysis, screening and treatment for strongyloidiasis and schistosomiasis is simple, relatively benign and inexpensive. Therefore, we advocate for both of these measures. Evidence for filariasis is less clear. As such, additional evaluation is warranted.


