Travel Medicine and Infectious Disease 48 (2022) 102324

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Prevalence of Chagas disease and strongyloidiasis among HIV-infected Latin American immigrants in Italy – The CHILI study

Paola Rodari [a,*], Francesca Tamarozzi [a], Stefano Tais [a], Monica Degani [a], Francesca Perandin [a], Dora Buonfrate [a], Emanuele Nicastri [b], Luciana Lepore [b], Maria Letizia Giancola [b], Stefania Carrara [b], Alessandro Tavelli [c], Alessandro Cozzi-Lepri [d], Antonella D'Arminio Monforte [e], Ronaldo Silva [a], Andrea Angheben [a]

[a] Department of Infectious – Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, 37024, Via Don A Sempreboni 5, Negrar di Valpolicella, Verona, Italy
[b] National Institute for Infectious Disease, IRCCS "Lazzaro Spallanzani", Via Portuense 292, 00149, Rome, Italy
[c] ICONA Foundation, Via Guido D'Arezzo 15, 20145, Milan, Italy
[d] Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME) Institute for Global Health UCL, Rowland Hill St London NW3 2PF, UK
[e] Department of Health Sciences, Clinic of Infectious Diseases, ASST Santi Paolo e Carlo, University of Milan, Via Rudinì 8, 20142, Milan, Italy

ARTICLE INFO

Keywords:
Chagas disease
Trypanosoma cruzi
Strongyloides stercoralis
HIV/AIDS
Migrants
Opportunistic infection

ABSTRACT

Introduction: Screening HIV-positive migrants for neglected tropical diseases having potential for life-threatening reactivation, such as Chagas disease and strongyloidiasis is not widely implemented. We evaluated the prevalence of these infections among a large cohort of HIV-infected migrants from Latin America living in Italy.
Method: Cross-sectional study evaluating the prevalence of *Trypanosoma cruzi* and *Strongyloides stercoralis* infections in HIV-infected migrants from Latin America enrolled in the Italian Cohort of Antiretroviral-Naïve patients (ICONA) between 1997 and 2018, based on serology performed on sera stored in the ICONA Foundation biobank. Screening for Chagas disease was performed using two commercial ELISA complemented by commercial Immunoblot and CLIA if discordant. Strongyloidiasis was evaluated using a commercial ELISA.
Results: 389 patients were analysed. Fifteen (3.86%) had at least one positive Chagas ELISA test. Prevalence of Chagas disease was 0.5% or 1.29% depending on the confirmatory technique. Serology for strongyloidiasis was positive in 16 (4.11%) patients. Only Nadir $CD4^+$ T cell count was associated with discordant serology for Chagas disease ($p = 0.046$).
Conclusions: The accuracy of seroassays for Chagas disease and strongyloidiasis in HIV-positive patients is unclear. To avoid missing potentially life-threatening infections, we suggest implementing additional diagnostic strategies in at-risk patients with inconclusive serology results.

1. Introduction

Screening for latent infections that may reactivate during immunosuppression, such as tuberculosis or toxoplasmosis, is a well-established practice in people newly diagnosed with HIV [1]. However, migrant patients may harbour a range of other infections, including Neglected Tropical Diseases (NTDs), that can reactivate in case of severe immunodeficiency, often endemic in their area of origin but poorly known in the host countries. Among NTDs, Chagas disease and *Strongyloides stercoralis* infection are both particularly relevant for people with HIV, because of the potential harm posed to the immunosuppressed host.

Chagas disease is a zoonosis caused by the protozoan *Trypanosoma cruzi,* affecting around 6–7 million people worldwide [2]. The infection is endemic in 21 Latin American countries, with the highest prevalence reported in Bolivia (6.1%) [2]. Due to migration, Chagas disease is increasingly diagnosed also in non-endemic countries; a recent meta-analysis estimated a pooled prevalence of 4.2% in migrants from Latin America living in Europe, with figures exceeding 18% in Bolivians [3]. It was estimated that 68,000–123,000 people living in Europe are infected with *T.cruzi*, but only <4% of them are actually diagnosed [4]. *T.cruzi* infection is acquired mainly from Triatomine bugs in endemic countries, and by vertical transmission or through blood transfusions or

* Corresponding author. Via Don A Sempreboni 5 Negrar di Valpolicella, Verona, 37024, Italy.
E-mail address: paola.rodari@sacrocuore.it (P. Rodari).

https://doi.org/10.1016/j.tmaid.2022.102324
Received 10 August 2021; Received in revised form 15 March 2022; Accepted 29 March 2022
Available online 1 April 2022

transplants elsewhere. After infection, untreated subjects become chronically infected, and approximately 10–30% of them may develop cardiomyopathy and/or digestive tract disease after 2-3 decades [5]. Co-infection with *T.cruzi* has been reported in 1.3%–4.2% of HIV-positive patients in Argentina [6,7] and 5% in Brazil [8]. In HIV-positive patients, *T.cruzi* infection behaves as an opportunistic infection, with reactivation during severe immunodeficiency ($CD4^+$ T cell count <200 cells/mm^3). In Brazil, infection reactivation has been listed among AIDS-defining conditions since 2004 [9] and is included in current Argentinian guidelines among the diseases for which HIV-positive patients should be screened [10]. Infection reactivation in patients with HIV/AIDS mainly involves the central nervous system (CNS) and less frequently, the heart [5,11,12]. Irrespective of the organ involved, average mortality is about 70%, reaching virtually 100% in case of CNS involvement [11].

S.stercoralis is a soil-transmitted nematode mainly diffused in tropical and subtropical regions, with estimated 614 million cases worldwide [13]. In most Latin American countries, areas of high prevalence (>20%) have been documented in Argentina, Brazil, Ecuador, Peru, and Venezuela [14]. *S.stercoralis* has the unique ability to maintain an auto-infective cycle within the host, leading to life-long but often barely symptomatic infections. Immunosuppressed individuals, however, may develop hyperinfection or disseminated strongyloidiasis, which are potentially fatal even if promptly treated [15]. Corticosteroid therapy and human T-lymphotropic virus type 1 (HTLV-1) infection are well-known triggers for severe strongyloidiasis, but disseminated strongyloidiasis may occur also in association with cancer, transplants, and HIV/AIDS [16–18]. In addition, cases of HIV-associated immune reconstitution inflammatory syndrome (IRIS) due to *S.stercoralis* infection have been reported [19–22].

Chagas disease and strongyloidiasis share several features: i) they are chronic infections which may be asymptomatic for a long time; ii) they may have potentially life-threatening consequences in immunosuppressed/immunodeficient patients; iii) they are highly prevalent in Latin American countries, often as co-infections [23]. Data on prevalence of these parasitoses in migrants with HIV living in Europe are scarce and derive from limited hospital cohorts [24–31]. This study aimed to evaluate prevalence of *T.cruzi* and *S.stercoralis* infection in a large cohort of HIV-infected migrants from Latin America living in Italy.

2. Material and methods

This is a cross-sectional study evaluating prevalence of *T.cruzi* and *S. stercoralis* infections in HIV-infected migrants from Latin America, based on serology performed on sera and data stored in the Italian Cohort of Antiretroviral-Naïve patients (ICONA) Foundation biobank and associated database, located in the National Institute for Infectious Disease (INMI), IRCCS "Lazzaro Spallanzani", Rome, Italy. The study was approved by the Ethics Committee of Verona and Rovigo Provinces (n. 2020–05 of 12/02/2020). ICONA has been approved by the Ethics Committees of all participating centres; all patients provide a written informed consent before enrolment. All analyses were conducted on anonymized samples and retrospective, recorded patient data.

2.1. Study population and data collection

Patients were selected from the ICONA Foundation cohort (https://www.fondazioneicona.org/_new2/pages/publicArea/ICONAcohort/). ICONA is a multicentre observational longitudinal study of treatment-naïve HIV-infected patients attended in 54 infectious disease clinics throughout Italy. Since enrolment started in 1997, demographic, clinical and laboratory data from >18.500 patients were included in the ICONA electronic database. For the purpose of this study, all patients older than 18 years of age, born in Latin American countries (excluding the Caribbean, where Chagas disease is not endemic), and enrolled in ICONA between January 1997 and November 2018 were eligible. Data extracted included demographic information (sex; age at enrolment in ICONA; country of origin; year of arrival in Italy), clinical data (date of HIV diagnosis; most probable way of HIV transmission; date of AIDS diagnosis; date of start of the first course of antiretroviral therapy (ART); cardiovascular co-morbidities), and laboratory data (date and value of $CD4^+$ T cell count at enrolment in ICONA and at the time of sampling of tested serum; nadir $CD4^+$ T cell count; HIV-RNA load at enrolment in ICONA and at the time of sampling of the tested serum; zenith HIV-RNA load).

2.2. Serodiagnosis of Chagas disease and strongyloidiasis

The seroprevalence study was conducted on the population of all available sera from eligible individuals stored in the ICONA biobank. For each patient, the earliest available time point of blood sampling for which serum was available was used. Sera were tested at the Department of Infectious-Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar (Verona), Italy.

Screening for Chagas disease was performed using two commercial ELISA seroassays: one based on recombinant antigens (BioELISA Chagas, Biokit, Lliça d'Almunt, Spain), and one on *T.cruzi* lysate antigenic preparation (BioELISA Chagas III, BiosChile, Santiago, Chile). In compliance with the World Health Organization (WHO) recommendations [32], infection diagnosis was based on concordant tests positivity. In case of discordance, an immunoblotting assay based on *T. cruzi* extract (CHAGAS Western Blot IgG, LDBio Diagnostic, Lyon, France) was performed. Sera with discordant results in ELISA tests were also further analysed with Chagas VirClia IgG + IgM Monotest (Vircell, Grenada, Spain), a commercial chemiluminescence assay (CLIA) based on *T.cruzi* excretory-secretory antigens, made available after the performance of the ELISA. For the serodiagnosis of strongyloidiasis, one commercial ELISA assay was used (*S. rattii* ELISA, Bordier Affinity Products SA, Crissier, Switzerland). All tests were performed as per manufacturer's instructions.

2.3. Statistical analysis

Binary variables were summarized as percentages and groups compared using Fisher's Exact test or Chi-square test, as appropriate. Since continuous variables were not normally distributed, as assessed by D'Agostino-Pearson normality test, data were described using medians, ranges, and inter-quartile ranges (IQR), and groups compared using the Mann Whitney *U* test. Possible confounding variables were evaluated using logistic regression analysis including selected covariates. All tests were two-sided. A p-value ≤ 0.05 was considered significant. All analyses were performed in Prism version 8.3.0 (San Diego, CA, USA).

3. Results

Data analysed in the study are available in Supplementary file 1.

3.1. Description of the study cohort

Of all patients registered in the ICONA database, 864 fulfilled the eligibility criteria and 389 were included in the study based on serum samples availability. The majority of patients were from Brazil (n = 154; 39.6%), followed by Peru (n = 86; 22.1%), Ecuador (n = 53; 13.6%), Argentina (n = 24; 6.17%), Colombia (n = 23; 5.9%), El Salvador (n = 16; 4.1%), Venezuela (n = 13; 3.3%), Uruguay (n = 5; 1.3%), Paraguay (n = 4; 1%), Panama (n = 3; 0.8%), Guatemala, Honduras and Mexico (each n = 2; 0.5%), and Bolivia and Chile (each n = 1; 0.3%). Three hundred seventeen (81.5%) patients were males. Median age at enrolment in ICONA was 33 years (range 19–67; IQR 28–40); 32 years (range 19–62; IQR 28–39) for males and 36 years (range 19–67; IQR 28.7–44) for females. The date of arrival in Italy was available only for 67 (17.2%) patients; all but 2 of these were first diagnosed with HIV infection after

arrival in Italy, after a median of 4 years from arrival (range 0–26; IQR 1–10). The most likely mode of HIV infection was unprotected male homosexual intercourse (n = 257, 66.1% of the whole cohort, 81.1% of the male cohort), unprotected heterosexual intercourse (n = 108, 27.8% of the whole cohort; n = 41, 12.9% of the male cohort; n = 67, 94.4% of the female cohort), intravenous drug use (n = 7; 1.8% of the whole cohort), and other/unknown (n = 17; 4.4% of the whole cohort). All patients had started antiretroviral therapy (ART) immediately after enrolment in ICONA (range 0–23 years before sampling; IQR 0–3); AIDS was diagnosed in 66 (16.97%) patients. Twenty-six (6.68%) patients had cardiovascular co-morbidities, including dyslipidemias, diabetes mellitus, coronary artery stenosis, internal carotids stenosis, myocardial infarction, arterial hypertension, ictus, and myocarditis.

At enrolment in ICONA, the median $CD4^+$ T cell count was 373 cells/μl (range 2–1530; IQR 232–608) and the median viral load was 8405 copies/ml (range 0–34 × 10^6; IQR 51–77,480). Median nadir $CD4^+$ T cell count was 289 cells/μl (range 0–991; IQR 116–440), while median zenith viral load was $\log_{10}$ 4.82 copies/ml (range $\log_{10}$ 1.28 - $\log_{10}$ 7.53; IQR $\log_{10}$ 4.16 - $\log_{10}$ 5.37).

3.2. Serology for Chagas disease and strongyloidiasis

Fifteen (3.86%) patients had at least one positive Chagas ELISA test: 12 (3.08%) patients in the recombinant antigen-based ELISA and 5 (1.29%) patients in the lysate antigen-based ELISA. Only two (0.51%) patients were positive by both ELISA tests; in all other cases, the two ELISA tests were discordant and no further cases were confirmed by immunoblotting. However, three of these sera, discordant in the ELISA test, were positive to the CLIA assay. If we consider as positive for Chagas disease also those patients with one ELISA and CLIA concordantly positive, a total of 5 (1.29%) patients would have been diagnosed with Chagas disease. Results are summarized in Table 1. Serology for strongyloidiasis was positive in 16 (4.11%) patients; no patient was positive for both strongyloidasis and Chagas disease (even when considering patients with only one positive Chagas disease seroassay).

3.3. Association between discordant Chagas disease serology and clinical factors

To further explore the factors associated with discordant results of Chagas ELISA serology, we evaluated the association between this laboratory result and clinical parameters. Results of the univariable analysis are detailed in Table 2. The only variable significantly associated with a discordant result in Chagas disease serology was $CD4^+$ T cell count at nadir (p = 0.046). Selected variables sex, age, time from HIV diagnosis to sampling, viral load, and having started ART before sampling did not confound this association (data not shown). No association between *S. stercoralis* serology result and nadir $CD4^+$ T cell count was found (p = 0.72).

Table 1
Results of serology assays for Chagas disease.

Tests performed on whole cohort (n = 389)	Concordant positive N (%)	Concordant negative N (%)	Discordant N (%)
recELISA + lysELISA*	2 (0.51%)	374 (96.14%)	13 (3.34%)
	Positive N (%)	Negative N (%)	
recELISA	12 (3.08%)	377 (96.92%)	
lysELISA	5 (1.29%)	384 (98.71%)	
Test performed on samples discordant on ELISAs (n = 13)	Positive N (%)	Negative N (%)	Positive on whole cohort n = 389 N (%)
Immunoblot	0 (0.00%)	13 (100%)	0 (0.00%)
CLIA§	3 (23.08%)	10 (76.92%)	3 (0.77%)
Final classification of patients (n = 389)	Positive N (%)	Negative N (%)	
recELISA + lysELISA + IB	2 (0.51%)	387 (99.49%)	
recELISA + lysELISA + CLIA	3 (0.77%)	386 (99.23%)	
Total	5 (1.29%)	384 (98.71%)	

N = number of patients. ELISA = Enzyme Linked Immunosorbent Assay. IB=Immunoblot. CLIA=Chemo-Luminescent Immunoassay *recELISA = recombinant-antigen based ELISA; lysELISA = lysate based-ELISA. § all CLIA-positive sera were also recELISA-positive.

Table 2
Association between clinical variables and discordant serology results of the two ELISA tests for Chagas disease.

Variable	Chagas discordant ELISA serology [N = 13] ^	Chagas concordant negative serology [N = 374] ^	p-value*
Sex [N (%)]	11 (84.62%)	305 (81.55%)	p > 0.999
Male	2 (15.38%)	69 (18.45%)	
Female			
Transmission of HIV [N (%)]	11 (84.62%)	245 (65.51%)	p = 0.520°
	2 (15.38%)	105 (28.07%)	
MSM	0	7 (1.87%)	
Heterosexual	0	17 (4.55%)	
IDU			
Other/unknown			
Diagnosis of AIDS [N (%)]	4 (30.77%)	62 (16.58%)	p = 0.249
Yes	9 (69.23%)	312 (83.42%)	
No			
Diagnosis of AIDS before sampling in patients with AIDS diagnosis [N (%)]	[N = 4]	[N = 62]	p > 0.999
	4 (100%)	50 (80.65%)	
	0	12 (19.35%)	
Yes			
No			
ART started before sampling [N (%)]	7 (53.85%)	140 (37.43%)	p = 0.254
	6 (46.15%)	234 (62.57%)	
Yes			
No			
$CD4^+$ T cell count nadir before sampling [N (%)]	7 (53.85%)	181 (48.40%)	p = 0.782
	6 (46.15%)	193 (51.60%)	
Yes			
No			
Age at enrolment in ICONA [median (IQR)]	33 (26–37)	33 (28–40)	p = 0.443
Time (days) from HIV diagnosis to sampling [median (IQR)]	156 (55–1013)	145 (30–740)	p = 0.505
Time (days) from starting ART to sampling in patients with ART started before sampling [median (IQR)]	[N = 7]	[N = 138]	p = 0.795
	347 (64–754)	148 (63–648)	
$CD4^+$ T cell count nadir [median (IQR)]	132 (69–173)	295 (116–443)	**p = 0.046**
$CD4^+$ T cell count nadir in patients with $CD4^+$ cell count nadir before sampling [median (IQR)]	[N = 7]	[N = 177]	p = 0.303
	132 (94–211)	267 (93–437)	
Time (days) from $CD4^+$ T cell count nadir to sampling in patients with $CD4^+$ cell count nadir before sampling [median (IQR)]	[N = 7]	[N = 177]	p = 0.804
	146 (26–603)	138 (53–283)	
$CD4^+$ T cell count at sampling timepoint [median (IQR)]	267 (173–418)	381 (235–613)	p = 0.2804

^In case of subset analysis, N of patients is indicated for each variable. *Fisher's Exact test or Mann Whitney *U* test for binary and continuous data, respectively. °Chi-square test. MSM = men who have sex with men. IDU = intravenous drug use. ART = anti-retroviral therapy. IQR = interquartile range.

4. Discussion

Migrant populations are offered very heterogeneous screenings for infectious diseases across Europe [33]. Screening for NTDs is not

included in current European guidelines for the management of patients with HIV [1], although they represent a substantial health problem among migrants [26]. We aimed to determine the prevalence of *T.cruzi* and *S.stercoralis* infection, potentially life-threatening in immunodeficient patients, among a large cohort of HIV-infected migrants from Latin America living in Italy.

In our cohort, the 0.5% prevalence of Chagas disease, calculated according to WHO recommendations for Chagas disease diagnosis [32] based on seropositivity in two ELISA seroassays, or 1.29% if considering positivity in one ELISA confirmed by CLIA, was lower than reported in other similar studies, where it ranged between 1.9% and 10.5% [25,28,30]. This discrepant result might be due to the fact that we applied the WHO definition of Chagas disease, which includes positivity in at least two seroassays, whereas, in several previous reports, Chagas disease was defined also in the presence of single positive serology results. Interestingly, a Chagas disease seroprevalence comparable with what reported in the literature would have been found if a single-positive serology test was considered diagnostic for infection also in our study.

The problem of discordant serology results in the diagnosis of Chagas disease is well known, accounting for up to 3% of all serology results [34,35]. This has been attributed to cross-reactions (especially with *Leishmania* spp or exposure to *Trypanosoma rangeli* [36]) or to the variable predominance of cell-mediate over humoral immunity in some individuals [37,38]. Discordant results are generally addressed by the repetition of serology over time or the application of a third test [32,39,40]. However, no formal algorithm on what type of test (in terms of antigenic preparation and format) and temporal sequence of their application is available [39], and the exclusion of Chagas disease in people with discordant serology results has been questioned [41].

In patients with HIV infection, 19% of parasitologically confirmed *T. cruzi* co-infected patients were reported to have a discordant serology result [6,10,42]. When we explored variables potentially associated with discordant serology, we found that nadir $CD4^+$ T cell count was associated with this result. Unexpectedly, this was not replicated when considering the subset of patients with nadir $CD4^+$ T cell count occurring before serum sampling, but the sample size was extremely reduced. In any case, $CD4^+$ T cell counts both at nadir and at the time of serum sampling were higher in patients with concordant-negative compared to those with discordant Chagas serology results. This suggests that negative serology was most likely a true result, and that discordant serology might reflect *T.cruzi* infection. To our knowledge, no study so far compared the performance of seroassays in patients with confirmed Chagas disease co-infected or not with HIV.

The seroprevalence of strongylodiasis in our cohort (4.1%) was comparable or slightly lower than that (4.6%–8%) reported in other cohorts of Latin American HIV-positive migrants in Europe [24,27,31]. In agreement with previous results [24], we found no association between *S.stercoralis* serology results and nadir $CD4^+$ T cell count. However, Mascarello et al. [27] found that 27% of HIV-positive *S.stercoralis* infected patients diagnosed by parasitological techniques had negative serology. Furthermore, mean $CD4^+$ T cell counts of *S.stercoralis* serology-positive patients were higher than those with serology-negative results, raising the question whether seroassays for *S. stercoralis* may be affected by HIV infection status, similar to what observed for leishmaniasis or toxoplasmosis [27]. Unfortunately, no formal study so far compared the results of serology in patients with confirmed strongyloidiasis between HIV-positive and HIV-negative subjects. Recently, Requena-Mendez et al. [43] published evidence-based guidelines for the screening of strongyloidiasis in non-endemic countries suggesting that "in immunosuppressed patients, a combination of serological and parasitological methods is mandatory, and screening should be performed before immunosuppression".

In our study, no cases of coinfection with *T.cruzi* and *S.stercoralis* was found. This is not consistent with the cohort described by Puerta-Alcalde et al. [23] which was mainly composed by Bolivians. Who show a high prevalence of Chagas disease [3] and a discrete proportion of *S. stercoralis* coinfection [23,30]. The different representation of nationalities in our cohort and the low prevalence of both infections can explain these results.

This study has several limitations, including the use of archived samples and the heterogeneity of the cohort in terms of clinical characteristics and serum availability at different time points after enrolment in ICONA. Furthermore, no information was available regarding *S.stercoralis* infection and other potentially cross-reactive helminthiases assessed using parasitological techniques. Due to the unavailability of fecal samples, we could not carry out further tests for *S.stercoralis,* such as real-time PCR or agar plate culture, which have higher specificity than serology. Moreover, blood samples were not available for further molecular testing for *T.cruzi* in patients with discordant serology results (although a negative PCR would not exclude *T.cruzi* infection) not for testing for HTLV-1. Finally, relevant epidemiological variables such as having lived in rural or urban setting, were unavailable. Rural residents are at higher risk for both Chagas disease and strongyloidiasis whereas urban people are more vulnerable to HIV infection [44]. On the other hand, to our knowledge, this is the first study formally exploring the relation between clinical and laboratory parameters and serology results for Chagas disease in HIV-positive patients.

5. Conclusions

To conclude, in the absence of solid data on the accuracy of seroassays for Chagas disease in patients with HIV, we suggest that the diagnosis of *T.cruzi* infection should not be rejected in HIV-positive patients with risk factors if only one seroassay results positive, and that follow-up serology and/or parasitological tests (microscopy/PCR on blood) should be performed, together with accurate clinical and epidemiological history and other noninvasive tests such as ECG. Equally, in the absence of information on the accuracy of seroassays for *S. stercoralis* infection in HIV-positive patients, we suggest performing both serology and specific parasitological examination (stool culture or larvae concentration techniques) in this population.

Funding

This work has been funded by Ricerca Corrente on Emerging Infections and by EULACH16/T020108 _ Pers_CHAGAS by Italian Ministry of Health (to National Institute for Infectious Disease, IRCCS, Lazzaro Spallanzani, Rome, Italy) and by Ricerca Corrente on Emerging Blood Protozoa in the Immunocompromised population: novel strategies for screening, diagnosis, monitoring and clinical management (L3P3) by Italian Ministry of Health (to IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Italy). The funders had no role in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declaration of competing interests

The authors have no conflicts of interests to declare.

CRediT authorship contribution statement

Paola Rodari: Conceptualization, Methodology, Writing – original draft, Data curation, Writing – review & editing, Project administration. **Francesca Tamarozzi:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Data curation, Writing – review & editing. **Stefano Tais:** Investigation. **Monica Degani:** Investigation. **Francesca Perandin:** Investigation, Supervision, Writing – review & editing. **Dora Buonfrate:** Supervision, Writing – review & editing. **Emanuele Nicastri:** Conceptualization, Writing – review & editing. **Luciana Lepore:** Writing – review & editing. **Maria Letizia Giancola:** Writing – review & editing. **Stefania Carrara:** Resources, Writing – review & editing. **Alessandro Tavelli:** Conceptualization, Resources, Writing – review &

editing. **Alessandro Cozzi-Lepri:** Methodology, Formal analysis, Writing – review & editing. **Antonella D'Arminio Monforte:** Conceptualization, Resources, Writing – review & editing. **Ronaldo Silva:** Methodology, Formal analysis, Writing – review & editing. **Andrea Angheben:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2022.102324.

References

[1] Ryom L, Boesecke C, Bracchi M, Ambrosioni J, Pozniak A, Arribas J, et al. Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0. HIV Med 2018;19(5):309–15. https://doi.org/10.1111/hiv.12600.

[2] Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec 2015;90(6):33–43. https://www.who.int/wer/2015/wer9006.pdf?ua=1.

[3] Requena-Mendez A, Aldasoro E, de Lazzari E, Sicuri E, Brown M, Moore DAJ, et al. Prevalence of Chagas disease in Latin-American migrants living in Europe: a systematic review and meta-analysis. PLoS Neglected Trop Dis 2015;9(2):e0003540. https://doi.org/10.1371/journal.pntd.0003540.

[4] Basile L, Jansa JM, Carlier Y, Salamanca DD, Angheben A, Bartoloni A, et al. Chagas disease in European countries: the challenge of a surveillance system. Euro Surveill 2011;16(37):19968. https://doi.org/10.2807/ese.16.37.19968-en.

[5] Perez-Molina JA, Molina I. Chagas disease. Lancet 2018;391(10115):82–94. https://doi.org/10.1016/S0140-6736(17)31612-4.

[6] Almeida EA, Lima JN, Lages-Silva E, Guariento ME, Aoki FH, Torres-Morales AE, et al. Chagas' disease and HIV co-infection in patients without effective antiretroviral therapy: prevalence, clinical presentation and natural history. Trans R Soc Trop Med Hyg 2010;104(7):447–52. https://doi.org/10.1016/j.trstmh.2010.02.004.

[7] Dolcini G, Ambrosioni J, Andreani G, Pando MA, Martinez Peralta L, Benetucci J. Prevalence of human immunodeficiency virus (HIV)-Trypanosoma cruzi co-infection and injectable-drugs abuse in a Buenos Aires health center. Rev Argent Mocrobiol. J 2008;40(3):164–6.

[8] Stauffert D, Silveira MF, Mesenburg MA, Brod Manta A, da Silva Dutra A, de Oliveira Bicca GL, et al. Prevalence of Trypanosoma cruzi/HIV coinfection in southern Brazil. Braz J Infect Dis 2017;21(2):180–4. https://doi.org/10.1016/j.bjid.2016.10.006.

[9] Almeida EA, Ramos Junior AN, Correia D, Shikanai-Yasuda MA. Brazilian Network of attention and studies on Trypanosoma cruzi/HIV co-infection and others immunossupression conditions. Rev Soc Bras Med Trop 2009;42(5):605–8. https://doi.org/10.1590/S0037-86822009000500025.

[10] Benchetrit AG, Fernandez M, Bava AJ, Corti M, Porteiro N, Martinez Peralta L. Clinical and epidemiological features of chronic Trypanosoma cruzi infection in patients with HIV/AIDS in Buenos Aires, Argentina. Int J Infect Dis 2018;67:118–21. https://doi.org/10.1016/j.ijid.2017.11.027.

[11] Almeida EA, Ramos Junior AN, Correia D, Shikanai-Yasuda MA. Co-infection Trypanosoma cruzi/HIV: systematic review (1980-2010). Rev Soc Bras Med Trop 2011;44(6):762–70. https://doi.org/10.1590/S0037-86822011000600021.

[12] Sartori AM, Ibrahim KY, Nunes Westphalen EV, Braz LMA, Oliveira Jr OC, Gakiya E, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. Ann Trop Med Parasitol 2007;101(1):31–50. https://doi.org/10.1179/136485907X154629.

[13] Buonfrate D, Bisanzio D, Giorli G, Odermatt P, Furst T, Greenway C, et al. The global prevalence of Strongyloides stercoralis infection. Pathogens 2020;9(6):468. https://doi.org/10.3390/pathogens9060468.

[14] Buonfrate D, Mena MA, Angheben A, Raquena-Mendez A, Munoz J, Gobbi F, et al. Prevalence of strongyloidiasis in Latin America: a systematic review of the literature. Epidemiol Infect 2015;143(3):452–60. https://doi.org/10.1017/S0950268814001563.

[15] Marcos LA, Terashima A, Canales M, Gotuzzo E. Update on strongyloidiasis in the immunocompromised host. Curr Infect Dis Rep 2011;13(1):35–46. https://doi.org/10.1007/s11908-010-0150-z.

[16] Buonfrate D, Requena-Mendez A, Angheben A, Munoz J, Gobbi F, Van Den Ende J, et al. Severe strongyloidiasis: a systematic review of case reports. BMC Infect Dis 2013;13:78. https://doi.org/10.1186/1471-2334-13-78.

[17] Keiser PB, Nutman TB. Strongyloides stercoralis in the immunocompromised population. Clim Microbiol Rev 2004;17(1):208–17. https://doi.org/10.1128/CMR.17.1.208-217.2004.

[18] Le Pogam A, Lopinto J, Pecriaux A, Fartoukh M, Guitard J, Voiriot G. Strongyloides stercoralis disseminated infection in an HIV-infected adult. PLoS Neglected Trop Dis 2020;14(11):e0008766. https://doi.org/10.1371/journal.pntd.0008766.

[19] Brown M, Cartledge JD, Miller RF. Dissemination of Strongyloides stercoralis as an immune restoration phenomenon in an HIV-1-infected man on antiretroviral therapy. Int J STD AIDS 2006;17(8):560–1. https://doi.org/10.1258/095646206778145712.

[20] Kim AC, Lupatkin HC. Strongyloides stercoralis infection as a manifestation of immune restoration syndrome. Clin Infecd Dis 2004;39(3):439–40. https://doi.org/10.1086/422522.

[21] Lanzafame M, Faggian F, Lattuada E, Antolini D, Vento S. Strongyloidiasis in an HIV-1-infected patient after highly active antiretroviral therapy-induced immune restoration. J Infect Dis 2005;191(6):1027. https://doi.org/10.1086/428099.

[22] Taylor CL, Subbarao V, Gayed S, Ustianowski AP. Immune reconstitution syndrome to Strongyloides stercoralis infection. AIDS 2007;21(5):649–50. https://doi.org/10.1097/QAD.0b013e3280117f94.

[23] Puerta-Alcalde P, Gomez-Junyent J, Requena-Mendez A, Pinazo MJ, Alvarez-Martinez MJ, Rodriguez M, et al. High prevalence of S. Stercoralis infection among patients with Chagas disease: a retrospective case-control study. PLoS Neglected Trop Dis 2018;12(1):e0006199. https://doi.org/10.1371/journal.pntd.0006199.

[24] Llenas-Garcia J, Fiorante S, Salto E, Rodriguez V, Matarranz M, Hernando A, et al. Should we look for Strongyloides stercoralis in foreign-born HIV-infected persons? J Immigr Minority Health 2013;15(4):796–802. https://doi.org/10.1007/s10903-012-9756-6.

[25] Llenas-Garcia J, Hernando A, Fiorante S, Matarranz M, Salto E, Rubio R, et al. Chagas disease screening among HIV-positive Latin American immigrants: an emerging problem. Eur J Clin Microbiol Infect Dis 2012;31(8):1991–7. https://doi.org/10.1007/s10096-011-1531-4.

[26] Martelli G, Di Girolamo C, Zammarchi L, Angheben A, Morandi M, Tais S, et al. Seroprevalence of five neglected parasitic diseases among immigrants accessing five infectious and tropical diseases units in Italy: a cross-sectional study. Clin Microbiol Infect 2017;23(5):335.e1–5. https://doi.org/10.1016/j.cmi.2017.02.024.

[27] Mascarello M, Gobbi F, Angheben A, Gobbo M, Gaiera G, Pegoraro M, et al. Prevalence of Strongyloides stercoralis infection among HIV-positive immigrants attending two Italian hospitals, from 2000 to 2009. Ann Trop Med Parasitol 2011;105(8):617–23. https://doi.org/10.1179/2047773211Y.0000000006.

[28] Rodriguez-Guardado A, Asensi Alvarez V, Rodriguez Perez M, Mejuto Alvarez P, Flores-Chavez M, Alonso Gonzalez P, et al. Screening for Chagas' disease in HIV-positive immigrants from endemic areas. Epidemiol Infect 2011;139(4):539–43. https://doi.org/10.1017/S0950268810001305.

[29] Sadlier CM, Brown A, Lambert JS, Sheehan G, Mallon PW. Seroprevalence of Schistosomiasis and Strongyloides infection in HIV-infected patients from endemic areas attending a European infectious diseases clinic. AIDS Res Ther 2013;10(1):23. https://doi.org/10.1186/1742-6405-10-23.

[30] Salvador F, Molina I, Sulleiro E, Burgos J, Curran A, Van den Eynde E, et al. Tropical diseases screening in immigrant patients with human immunodeficiency virus infection in Spain. Am J Trop Med Hyg 2013;88(6):1196–202. https://doi.org/10.4269/ajtmh.12-0714.

[31] Theunissen C, Bottieau E, Van Esbroeck M, Tsoumanis A, Florence E. Should we screen HIV-positive migrants for strongyloidiasis? Pathogens 2020;9(5):388. https://doi.org/10.3390/pathogens9050388.

[32] WHO Expert Committee. Control of Chagas disease. World Health Organ Tech Rep Ser 2002;905. i-vi, 1-109, back cover, https://apps.who.int/iris/handle/10665/42443.

[33] Karki T, Napoli C, Riccardo F, Fabiani M, Dente MG, Carballo M, et al. Screening for infectious diseases among newly arrived migrants in EU/EEA countries–varying practices but consensus on the utility of screening. Int J Environ Health Public Health 2014;11(10):11004–14. https://doi.org/10.3390/ijerph111011004.

[34] Moure Z, Angheben A, Molina I, Gobbi F, Espasa M, Anselmi M, et al. Serodiscordance in chronic Chagas disease diagnosis: a real problem in non-endemic countries. Clin Microbiol Infect 2016;22(9):788–92. https://doi.org/10.1016/j.cmi.2016.06.001.

[35] Pane S, Giancola ML, Piselli P, Corpolongo A, Repetto E, Bellagamba R, et al. Serological evaluation for Chagas disease in migrants from Latin American countries resident in Rome, Italy. BMC Infect Dis 2018;18(1):212. https://doi.org/10.1186/s12879-018-3118-5.

[36] Ferreira-Silva MM, Pereira GA, Rodrigues-Junior V, Meira WS, Basques FV, Langhi-Junior DM, et al. Chagas disease: performance analysis of immunodiagnostic tests anti-Trypanosoma cruzi in blood donors with inconclusive screening results. Hematol Transfus Cell Ther 2020;S2531–1379(20):30118. https://doi.org/10.1016/j.htct.2020.06.016. 8.

[37] Castro Eiro MD, Alvarez MG, Cooley G, Viotti RJ, Bertocchi GL, Lococo B, et al. The Significance of discordant serology in Chagas disease: enhanced T-cell immunity to Trypanosoma cruzi in serodiscordant subjects. Front Immunol 2017;8:1141. https://doi.org/10.3389/fimmu.2017.01141.

[38] Olivera GC, Albareda MC, Alvarez MG, De Rissio AM, Fichera LE, Cooley G, et al. Trypanosoma cruzi-specific immune responses in subjects from endemic areas of Chagas disease of Argentina. Microb Infect 2010;12(5):359–63. https://doi.org/10.1016/j.micinf.2010.01.011.

[39] Lapa JS, Saraiva RM, Hasslocher-Moreno AM, Georg I, Souza AS, Xavier SS, et al. Dealing with initial inconclusive serological results for chronic Chagas disease in clinical practice. Eur J Clin Microbiol Infect Dis 2012;31(6):965–74. https://doi.org/10.1007/s10096-011-1393-9.

[40] Moure Z, Sulleiro E, Iniesta L, Guillen C, Molina I, Alcover MM, et al. The challenge of discordant serology in Chagas disease: the role of two confirmatory techniques in inconclusive cases. Acta Trop 2018;185:144–8. https://doi.org/10.1016/j.actatropica.2018.05.010.

[41] Levy MZ, Bowman NM, Kawai V, Plotkin JB, Waller LA, Cabrera L, et al. Spatial patterns in discordant diagnostic test results for Chagas disease: links to transmission hotspots. Clin Infect Dis 2009;48(8):1104–6. https://doi.org/10.1086/597464.

[42] Cordova E, Boschi A, Ambrosioni J, Cudos C, Corti M. Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992-2007. Int J Infect Dis 2008;12(6):587–92. https://doi.org/10.1016/j.ijid.2007.12.007.

[43] Requena-Mendez A, Buonfrate D, Gomez-Junyent J, Zammarchi L, Bisoffi Z, Munoz J. Evidence-based guidelines for screening and management of Sstrongyloidiasis in non-endemic countries. Am J Trop Med Hyg 2017;97(3):645–52. https://doi.org/10.4269/ajtmh.16-0923.

[44] Magadi MA. Understanding the urban-rural disparity in HIV and poverty nexus: the case of Kenya. J Public Health 2017;39(3):e63–72. https://doi.org/10.1093/pubmed/fdw065.