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Research Article

Coinfection of Human Filarial *Loa loa*, *Mansonnella perstans* in Human T Lymphotropic Virus Type 1 Infected Individuals in Gabon

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Abstract

A survey was conducted throughout Gabon to search simultaneously for Human T-Lymphotropic Virus type 1 (HTLV-1) using quantitative polymerase chain reaction (qPCR) and the serological method as well as filarial infection on the same sample by direct examination of 10 µL of blood and the concentration technique. 3728 samples were analyzed, showing that 8.3% (320/3728) were positive for HTLV-1, 22.3% (831/3728) exhibited *Loa loa* and 9.8% (366/3728) were positive for *Mansonnella perstans*. A total of 95 (2.5%) individuals had HTLV-1–*L. loa* coinfection and 33 (0.9%) HTLV-1–*M. perstans* coinfection. Interestingly, there were more carriers of *L. loa* microfilaria positive for HTLV-1 than *L. loa*-negative individuals (10.1% vs. 6.7%, respectively; $p=0.0004$). Regarding *Mansonnella perstans* distribution (another filarial species prevalent in Gabon), there was no significant difference between HTLV-1 / *M. perstans* carriers and non-carriers (7.4% vs. 7.9%, respectively; $p=0.77$). Furthermore, a density of *Loa loa* microfilariae over 30,000 microfilariae per milliliter influences HTLV-1 carriage ($p=0.02$). The prevalence of *L. loa*, *M. perstans* microfilaremia and HTLV-1 mono-infections and coinfections was higher in forest ecosystems than in savannah and lakeland ($p<0.001$). Correlations were also found with age and sex. These results suggest that *L. loa* and not *M. perstans* microfilariae carriage may affect the carriage of HTLV-1. A relationship between sex, age, and the forest ecosystem is suggested.

Keywords: *Loa loa*, *Mansonnella perstans*, HTLV1, microfilaremia, coinfection

Introduction

Loa loa is a filaria restricted to central Africa and some West African countries. Despite its restricted geographic environment, numerous imported cases are reported worldwide [1]. This parasite now appears to be a public health problem in many areas of the world, since it hampers the WHO strategy based on mass chemotherapy to control filarial *Onchocerca volvulus* and *Wuchereria bancrofti* in West Africa [2]. Excessive mortality has recently been reported in areas with hypermicrofilariaemia [3]. Indeed, Human T-Lymphotropic Virus type 1 (HTLV-1) is the causative agent of Adult T-cell Leukemia/Lymphoma (ATL) [4] and Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy (TSP/HAM) [5]. It has also been associated with a variety of inflammatory diseases [6]. A significant association between parasitic infections such as *Strongyloides stercoralis* and HTLV-1 infection has previously been shown in areas where HTLV-1 is endemic. Due to the immunomodulating effects of the virus and the presence of the parasite, patients with both infections could be at risk for overwhelming strongyloidiasis as well as T-lymphocyte hemopathy. The

infection of carriers of strongyloides by HTLV-1 significantly increases the number of larval parasites in stool and impairs the action of anti-helminthic agents, resulting in an immediate increase and longer-term failure of therapy [7]. Furthermore, it has also been shown that strongyloides infection stimulates the oligoclonal proliferation of HTLV-1-infected cells in HTLV-1 carriers [8], which leads to the development of ATL. Therefore, the fact that ATL arises significantly earlier and more often in individuals with combined infection is an argument in favour of the parasite's role as a leukemogenic cofactor. Parasites could be implicated as potential inducers of cancer. For example, *Schistosoma* are implicated in bladder cancer [9-11] *Fasciola can* promote cholangiocytes, leading to cell proliferation [12], and cancer of the pancreas may be induced by *Clonorchis sinensis* [13]. The aforementioned facts suggest that the association between pathogens should be studied. Many reports have shown different outcomes in the case of coinfection. The reports are generally based on exacerbation of infection and negative effects on human health [14]. The burden of coinfection, particularly involving helminths, on human health has been reported [15].

To our knowledge, there is no study on the geographic distribution of *L. loa* and HTLV-1 in Africa. Our previous study provides a map of *L. loa* and *Mansonella perstans* microfilaremia in Gabon and describes important relationships between parasitological indices and clinical manifestations [16]. On the other hand, we provided a map of HTLV in Gabon and found a high prevalence countrywide [17]. Therefore, the present study evaluates coinfection between HTLV-1, *L. loa* and *M. perstans* in a rural population of Gabon where these three infections are highly prevalent. Risk factors for coinfection need to be identified for good planning of control programs.

Materials and Methods

Area of study

The survey was conducted in rural Gabonese populations. The country is 800 km long and 20–300 km wide, bordered to the west by the Atlantic Ocean and consists of 80% rain forest. The forest zone extends from west to east, from the coastal basin with the grassland forest in the interior and northeastern forest plates band, through a wide mountainous forest band of 60–100 km parallel to the coast. The south and southeast contain isolated areas of *savannah and steppe*. A coastal and continental marine ecosystem named lakeland is located around the mouth of the Ogooué river. The population is approximately 1.5 million and there are 2048 villages located in nine provinces. Rural populations are located along roads and rivers, and few villages have more than 300 inhabitants [16].

Study population

The survey covered 212 randomly selected villages. Stratification was based on the nine provinces and the different ecosystems. Between 20 and 30 villages per province were randomly selected. Healthy volunteers older than 15 years of age that had been living in the village for more than 1 year were eligible for inclusion in the study [16,17]. All villages were geo-referenced.

Ethical considerations

The study protocol was reviewed and approved by the Gabonese Ministry of Health (Research authorization no. 00093/MSP/SG/SGAQM). The Health Director and the Governor of each province received written information. Individual written consent was required before blood sampling.

Questionnaire

The rationale for the study was explained and a one-page questionnaire was distributed to all participants. We collected demographic data (age, sex, and occupation), geographic data (name of the village, length of residence, department, and province) and medical history (eye worm, Calabar swelling, chronic arthralgia, pruritus, neurological symptoms).

Blood collection

Blood samples were usually collected in the villages' local healthcare centers between 9 AM to 2 PM. They were stored in 7 mL Vacutainer tubes containing ethylene diaminetetraacetic acid (EDTA) (VWR International, France).

Parasitological analysis

Analysis started systematically with direct examination of a wet blood film, then by a concentration technique follows: 1 ml blood was diluted with 9 ml PBS in a conical tube and 200 µl of saponin (2%) was added to lyse red blood cells. The tubes were centrifuged (10 min, 500g) and the supernatants discarded. The entire pellet was then examined under the microscope (×10 objective) and microfilariae were identified and counted. Two experienced technicians read the slides separately, and the results were verified by a parasitologist as previously reported [16]. Parasite species were identified by their size, motility and by the absence or presence of a sheath, parameters differentiating *L. loa* and *M. perstans*. *L. loa* is 230–250 µm long, has a diameter of 5–7 µm, a sheath that does not stain with Giemsa, a tapered tail with nuclei to the end and a short cephalic space, while *M. perstans* is 150–200 µm long, has a diameter of 3–5 µm, no sheath, a rounded tail with nuclei to the end and a very short cephalic space.

Determination of HTLV serological status

Two enzyme-linked immunosorbent assays (Platelia® HTLV-I New, Bio-Rad, France; Vironostika® HTLV-1/2, Bio-Merieux, France) were first used for HTLV serology. HTLV-positive or borderline-positive samples were tested by Western blotting (HTLV Blot 2.4, MP Diagnostics Suisse S.A., Switzerland) to differentiate HTLV-1 and HTLV-2 status from HTLV indeterminate serological status.

Molecular analysis and HTLV-1 proviral load

DNA was extracted from 200 µL of buffycoat with the QIAamp® DNA mini-kit (Qiagen, Courtaboeuf, France) according to the manufacturer's recommendations. Polymerase chain reaction (PCR) amplification was performed with HTLV-1-specific primers located within the long terminal repeat (LTR) or the envelope glycoprotein (env) sequence, as previously described [18].

HTLV-1/2 proviral load was measured by a multiplex real-time PCR assay involving a molecular beacon probe for simultaneous detection, differentiation and quantification of HTLV-1, -2, and -3 as well as STLV-1 and -3, as previously described [19].

Statistical analysis

Prevalence rates for *L. loa*, *M. perstans*, and HTLV-1 were estimated nationwide. The chi-squared test and Fisher's exact test were used as appropriate to identify statistical associations between *L. loa*, *M. perstans* microfilaremia and HTLV-1 prevalence rates. Univariate crude conditional maximum likelihood estimates of odds ratios (OR) and exact 95% confidence intervals (CI) were determined for each potential risk factor using STATA software version 9.0 (Stata Corporation, College Station, USA). Multivariate logistic regression models stratified by ecosystem were constructed from risk factors with a significance of ≤ 0.10 in univariate analysis, using a backward stepwise elimination procedure. All *p*-values below 0.05 were considered statistically significant.

Results

Description of the population

We conducted a large epidemiological study in Gabon on individuals aged over 15 years from 212 Gabonese villages in nine regions, representing 10% of villages in the country, for the presence of *L. loa*, *M. perstans*, and HTLV-1 infection.

In total, samples and data from 4392 individuals were collected countrywide. Of these, 4392 were tested for both filariases and 4381 for HTLV serology. Of the samples tested for HTLV serology, there were 3850 positive and negative results and 531 undetermined results, which were excluded from the analysis. Finally, after revision of the database, our analysis included 3728 individuals with sociodemographic characteristics and biological data for *L. loa*, *M. perstans* and HTLV-1 (Figure 1). This population represented 1.1% of the rural Gabonese population.

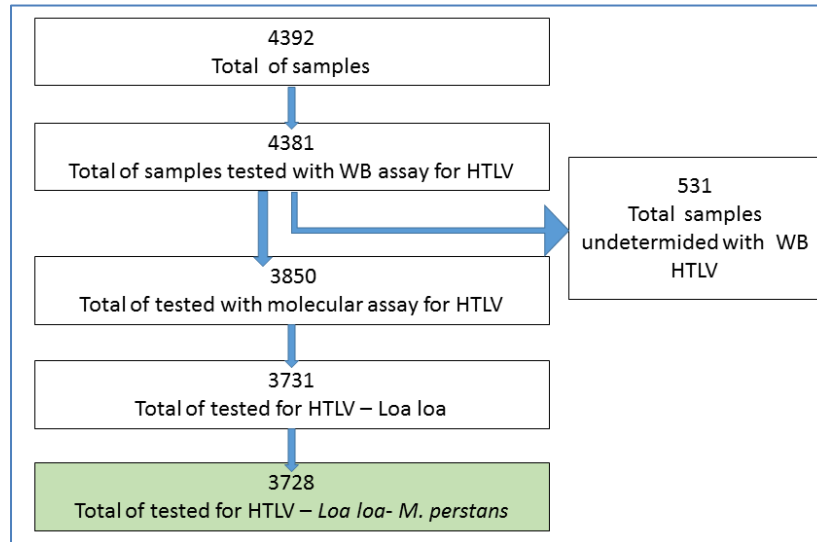


Figure 1. chart of revised data base among the study participants

The sex ratio (M/F) was 0.9 (47.1%, n=1757 for men and 52.9%, n=1971 for women); the mean age was 47 years \pm 14 and approximately 59.5% of individuals were aged over 45 years. Farmers represented 69.8% (n=2599) of the population and hunters 9.8% (367). Around 75.9% (n=2829) of the population lived in the forest ecosystem, 12.9% (n=482) in savannah, and 11.2% (n=417) in Lakeland (Table 1).

Table 1. Sociodemographic and clinical characteristics of the study population

Characteristics		Total number	Percentage%
Sex	Male	1757	47.1
	Female	1971	52.9
Age	[15–30]	551	14.8
	[30–45]	961	25.7
	[45–60]	1199	32.2
	≥ 60	1017	27.3
Occupation	Farming	2599	69.8
	Hunting	367	9.8
	Others	762	20.4
Location	Forest	2829	75.9
	Savannah	482	12.9
	Lakeland	417	11.2

Distribution of microfilariae and HTLV serologic status in the study participants

The overall prevalence rates of *L. loa*, *M. perstans* microfilariae, and HTLV-1 seropositivity were 22.3% (95% CI: 20.9–23.6), 9.8% (95% CI: 8.8–10.8), and 8.3% (95% CI: 7.4–9.2), respectively. At the same time, the prevalence of *L. loa*–HTLV-1 coinfection was 2.5%, (95% CI: 2.0–3.1), while 0.9% (95% CI: 0.6–1.2) of individuals exhibited *M. perstans*–HTLV-1 coinfection (Table 2). Furthermore, the prevalence of HTLV-1 (11.3%, 94/831) in *L. loa* microfilariae-

positive individuals was higher than in the *L. loa* negative (7.7%, 222/2897) individuals ($p < 0.001$). Similar analysis done on *M. perstans* microfilaria showed that there was no significant difference between HTLV-1/*M. perstans* carriers and non-carriers (7.4% vs. 7.9%, respectively; $p = 0.77$).

Table 2. Prevalence of *Loa loa*, *Mansonnella perstans* microfilaremia, human T-lymphotropic virus type 1 (HTLV-1) infection and coinfection in the main ecological regions of Gabon

	<i>L. loa</i>			HTLV			<i>M. perstans</i>			HTLV-1 + <i>L. loa</i>			HTLV + <i>M. perstans</i>		
	+	% [95% CI]	<i>p</i> *	+	% [95% CI]	<i>p</i> *	+	% [95% CI]	<i>p</i> *	+	% [95% CI]	<i>p</i> *	+	% [95% CI]	<i>p</i> *
All populations (N=3728)	831	22.3 [20.9–23.6]		320	8.3 [7.4–9.2]		366	9.8 [8.8–10.8]		95	2.5 [2.0–3.1]		33	0.9 [0.6–1.2]	
Ecosystems															
Lakeland (N=417)	65	15.6 [12.8–19.7]	**	17	3.8 [2.1–5.7]	**	18	4.1 [2.2–6.0]	**	2	0.5 [0–1.1]	**	0	0 [0–0]	**
Savannah (N=482)	64	13.3 [10.2–16.3]		25	5.2 [3.2–7.2]		34	7.1 [4.7–9.3]		4	0.8 [0–1.6]		1	0.2 [0.0–0.6]	
Forest (N=2829)	702	25.0 [23.4–26.6]		275	9.7 [8.2–10.9]		319	11.3 [9.2–12.7]		89	3.1 [2.5–3.8]		32	1.1 [0.7–1.5]	
Interior forest (N=1156)	290	24.9 [22.4–27.5]		114	10.0 [8.2–11.7]		126	11.1 [9.2–12.9]		37	3.2 [2.2–4.2]		16	1.4 [0.7–2.0]	
Grassland forest (N=723)	221	30.1 [27.4–34.1]		64	8.8 [6.7–10.9]		117	16.2 [13.5–18.9]		22	3.0 [1.2–4.3]		7	0.9 [0.2–1.7]	
North eastern forest (N=702)	145	20.6 [17.6–23.6]		67	9.5 [7.4–11.8]		38	5.4 [3.7–7.1]		23	3.3 [1.9–4.6]		5	0.7 [0.1–1.3]	
Mountain forest (N=248)	46	18.5 [13.6–23.3]		30	12.0 [7.9–16.1]		33	13.3 [9.0–17.5]		7	2.8 [0.8–4.9]		4	1.6 [0.1–3.2]	
p*: Kruskal–Wallis test and Pearson test for coinfection section; **: $p < 0.001$															

Geographic distribution according to the administrative regions

L. loa and *M. perstans* prevalences were higher in Estuaire at 31.9% (95% CI: 26.2–37.6) and 22.3% (95% CI: 17.2–27.4), respectively, and lowest in Ogooue Maritime at 11.1% (95% CI: 7.3–16.2) and 1.4% (95% CI: 0–3.1), respectively, while the HTLV-1 prevalence was higher in Haut Ogooue at 15.3% (95% CI: 11–19.6) and lower in Ogooue Maritime at 3.9% (95% CI: 1.2–6.6) (Table 3).

The distribution of coinfecting individuals showed a high *L. loa*–HTLV-1 prevalence in Haut -Ogooue at 5.4% (95% CI: 2.7–8.1), Ogooué-Ivindo at 5% (95% CI: 3.2–6.9), and Ogooué Lolo at 3.8% (95% CI: 1.9–5.8). High prevalences were also found for *M. perstans*–HTLV-1 coinfection in Ogooue Lolo at 2.6% (95% CI: 1–4.2), Haut -Ogooue at 1.8% (95% CI: 0.2–3.4), and Ngounie at 1.6% (95% CI: 0.2–3). By contrast, low *L. loa*–HTLV-1 and *M. perstans*–HTLV-1 prevalence rates (0%) were found in Ogooue Maritime (Table 3, Figure 2).

Finally, prevalence rates in administrative regions increased on a west–east axis, from the Atlantic coast to the border of the Republic of Congo: the lowest prevalences were found in regions located along the Atlantic Ocean (WoleuNtem, Estuaire, Ogooue Maritime, Nyanga), medium ones in central regions of the country (MoyenOgooue, Ngounie) and the highest prevalences in eastern regions (OgooueIvindo, Ogooue Lolo, Haut Ogooue) (Figure 2).

Table 3. Prevalence of *Loa loa*–human T-lymphotropic virus type 1 (HTLV-1) and *Mansonnella perstans*–HTLV-1 coinfection according to age, sex and occupation

Variables		<i>L. loa</i> –HTLV-1			<i>M. perstans</i> –HTLV-1		
		Positive/ tested	% (95% CI)	<i>p</i> value*	Positive/ tested	% (95% CI)	<i>p</i> value*
Age	[15–30]	3/551	0.5 [0.0–1.2]	<0.0001	1/551	0.2 [0.0–0.5]	0.086
	[30–45]	19/961	1.9 [1.1–2.2]		6/961	0.6 [0.1–1.1]	
	[45–60]	30/1199	2.5 [1.6–3.4]		13/1199	1.1 [0.5–1.7]	
	≥ 60	43/1017	4.2 [2.9–5.5]		43/1017	1.3 [0.6–1.9]	
Sex	Male	44/1756	2.5 [1.7–3.2]	0.874	16/1757	0.9 [0.4–1.3]	0.875
	Female	51/1972	2.6 [1.8–3.3]		17/1971	0.8 [0.4–1.3]	
Occupation	Farmer	69/2601	2.6 [2.0–3.3]	0.679	19/2601	0.7 [0.4–1.1]	0.192
	Hunter	10/366	2.7 [1.0–4.4]		6/366	1.6 [0.3–2.9]	
	Others	16/761	2.1 [1.1–3.1]		8/761	1.0 [0.3–1.8]	
All populations		95/3728	2.5 [1.9–2.9]		33/3728	0.8 [0.6–1.1]	

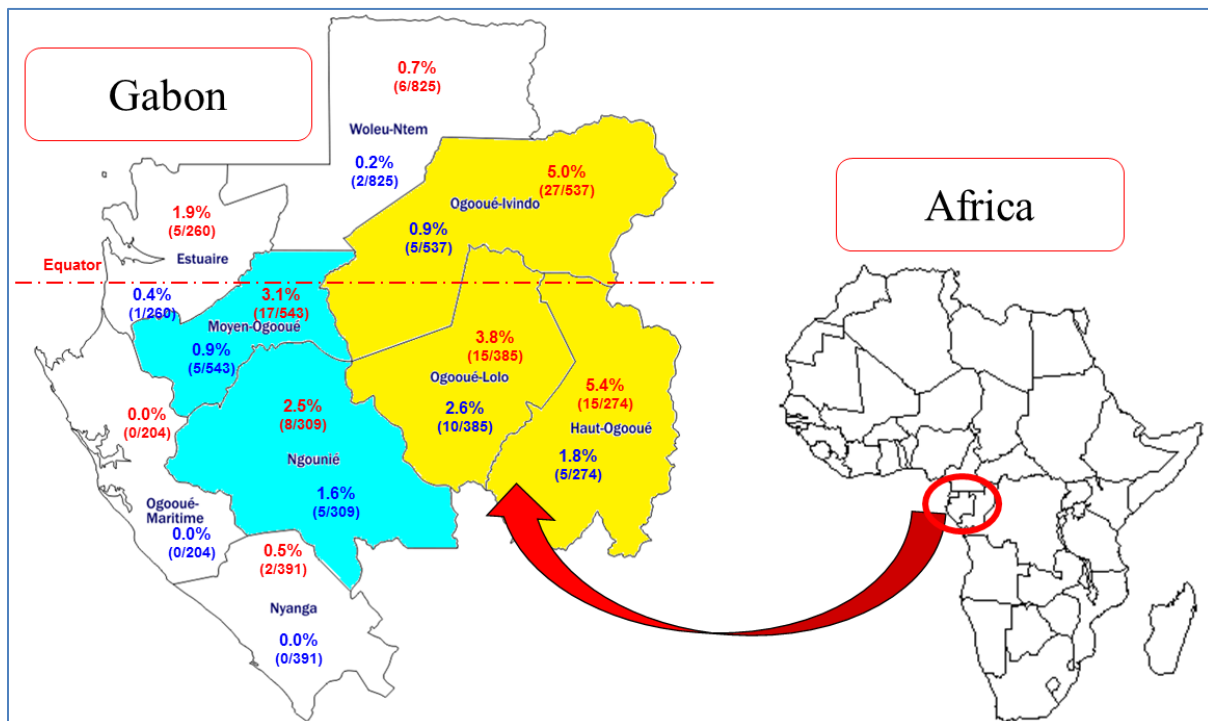


Figure 2. Prevalence of Human T-Lymphotropic Virus type 1 (HTLV-1), *Loa loa* and *Mansonnella perstans* coinfection according to the nine regions. Red, prevalences of HTLV-1-*L. loa* coinfection; blue, prevalence of HTLV-1-*M. perstans* coinfection

Prevalence of *L. loa*, *M. perstans* microfilaremia and HTLV-1 infection in the main ecological regions of Gabon

In ecological regions, the *L. loa* and *M. perstans* prevalence rates were significantly higher ($p < 0.0001$) in the forest (25% and 11.1%, respectively) compared with Lakeland (15.6% and 4.1%, respectively) and savannah (13.3% and 7.1%, respectively); the HTLV-1 prevalence rate was significantly higher ($p < 0.001$) in forest (9.7%) compared with Lakeland (3.8%) and savannah (5.2%) (Table 2).

The distribution of coinfecting individuals showed higher *L. loa*-HTLV-1 and *M. perstans*-HTLV-1 prevalence in forest regions (3.1% and 1.1%, respectively) than in savannah (0.8% and 0.2%, respectively) and Lakeland (0.5% and 0%, respectively) ($p < 0.001$). There was no difference in the forest ecosystem between grassland, mountain forest, interior and north eastern forest regions (Table 2).

Analysis of risk factors in coinfecting individuals

Univariate analysis of sociodemographic characteristics showed that the prevalence of *L. loa*-HTLV-1 coinfections increased linearly with age ($p < 0.0001$) (Figure 3), but no correlation was found in *M. perstans*-HTLV-1 coinfection. There was also no correlation with sex and occupation (Table 3).

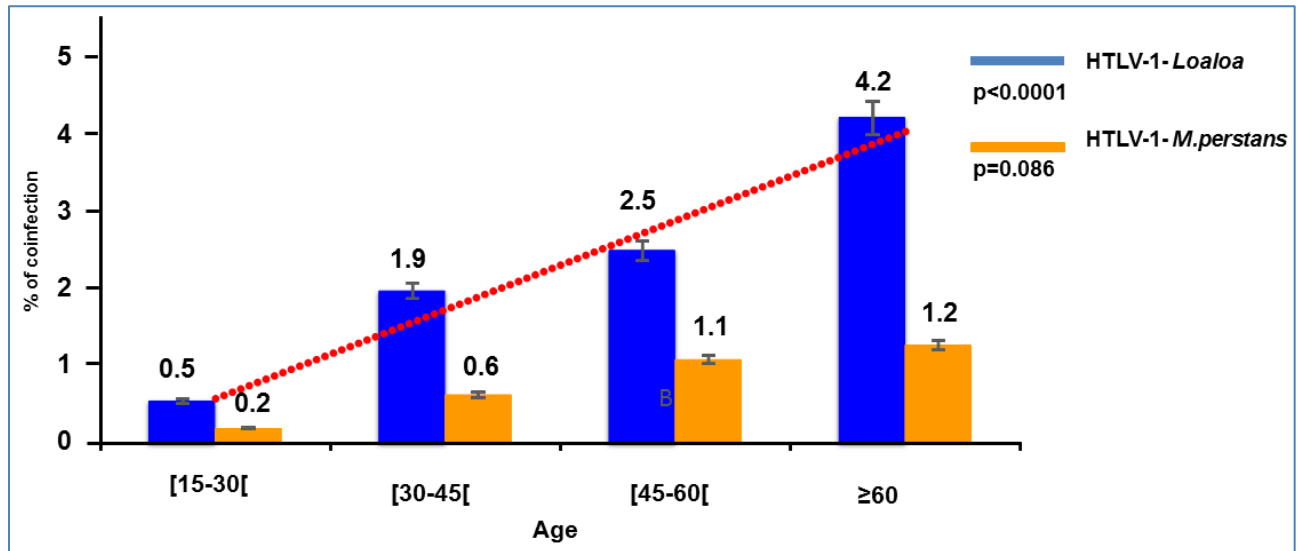


Figure 3. Prevalence of *Loa loa*-Human T-Lymphotropic Virus type 1 (HTLV-1) and *Mansonnella perstans*-HTLV-1 coinfections according to age

We also examined the relationship with clinical symptoms, i.e. the influence of amicrofilaremic individuals (defined as individuals without microfilaremia but ocular passage of adult worms or Calabar swelling or pruritus) on HTLV-1. No relationship was seen ($p = 0.26$). Furthermore, *L. loa*-HTLV-1 and *M. perstans*-HTLV-1 coinfections were associated with the forest ecosystem ($p < 0.0001$) (Table 2).

In multivariate analysis, age and sex remained significantly associated with *L. loa*-HTLV-1 and *M. perstans*-HTLV-1 coinfections in the forest ecosystem (Table 4).

Table 4. Logistic regression of positive human T-lymphotropic virus type 1 adjusted with *Loa loa* prevalence and sex, age, occupation and ecosystem

		Odds ratio	(95% CI)	p value
<i>L. loa</i>		1.57	[1.21--2.05]	0.001
Age	[15-30]	1		
	[30-45]	1.96	[1.17-3.29]	0.01
	[45-60]	2.95	[1.81-4.82]	<0.001
	≥ 60	3.64	[2.23-5.95]	<0.001
Sex	Male	0.44	[0.33-0.58]	<0.001
	Female	1		
Ecosystem	Lakeland	0.4	[0.24-0.67]	<0.001
	Savannah	0.5	[0.33-0.77]	0.002
	Forest	1		

Microfilarial density and HTLV viral load

The influence of the density of *L. loa* microfilariae was also examined, revealing that when the microfilariae density was compared with the HTLV-1 proviral load, a trend was observed toward a relationship between microfilariae density and viral load, but this did not reach statistical significance ($p=0.06$) (Figure 4). However, when individuals were split into group according to the density of microfilaremia (Table 5), it was shown that a density of microfilariae over 30,000 influences HTLV-1 carriage ($p=0.02$).

Table 5. Influence of HTLV on *Loa loa*

HTLV1	<i>Loa loa</i> microfilaremia >8000/mL			<i>Loa loa</i> microfilaremia >30000/mL		
	+	-	P*	+	-	P*
Positive	23	76	0.057	6	92	0.02
Negative	116	624		26	712	

P*: Pearson's Chi-squared test

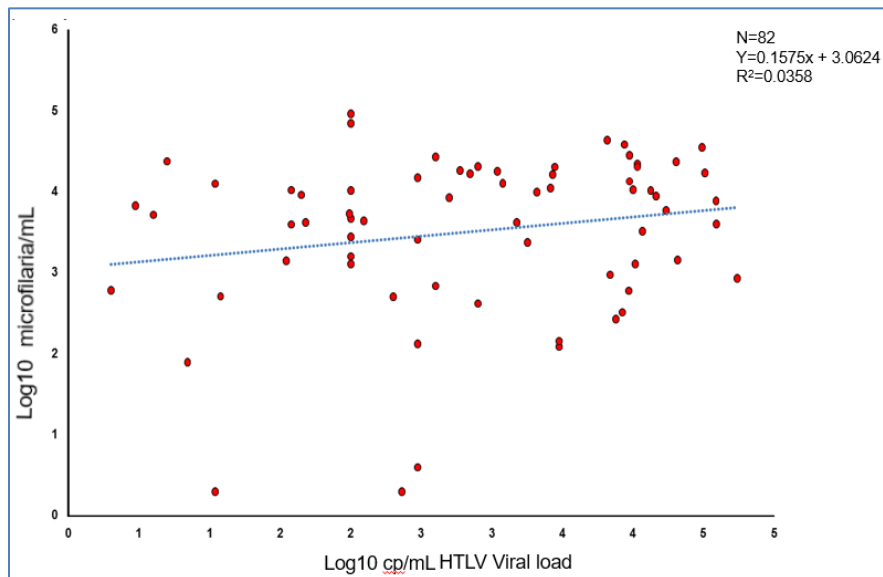


Figure 4. Correlation between *Loa loa* microfilariae density and Human T-Lymphotropic Virus type 1 viral load

Discussion

Gabon is a central African country where HTLV-1 viruses as well as the *L. loa* and *M. perstans* parasites are highly prevalent, as previously described [16,17]. The present article confirms this assertion and shows that *L. loa* microfilaremia is highly prevalent in HTLV-1-infected individuals compared with uninfected individuals. This prevalence is particularly high in the eastern forest areas of Gabon: the Ogooué-Ivindo, Haut-Ogooué and Ogooué-Lolo regions. Finally, prevalence rates in administrative regions increased on a west–east axis, from the Atlantic coast to the border of the Republic of Congo: the lowest prevalences were found in regions located along the Atlantic Ocean, medium ones in central regions of the country and the highest prevalence in eastern regions. Although coinfection with *L. loa* was not studied, the prevalence of HTLV-1 was shown by previous studies to be high in the same area [19-22]. Another previous study on the prevalence of filarial species also showed that *L. loa* was prevalent in the same area. Variation of both with age and sex, particularly in women, corroborates previous studies [16].

Coinfection between parasite and virus, in particular between helminth and HTLV-1, has been studied before. This association generally results in an exacerbation of clinical manifestation in infected individuals. An association of this kind has been shown in cases of strongyloidiasis [23]. The potential mechanism underlying this clinical expression is due to immune response modulation toward unbalanced Th1/Th2, leading to increased production of interferon gamma (IFN γ) [24], while another recent study showed an association between the HTLV-1 proviral load and clinical symptoms [25]. In the course of this study, we found a trend towards an association between hypermicrofilaremia and a high viral load. At the same time, it seems that there is no relation between amicrofilaremia and HTLV-1. Of the coinfections reported in Gabon, *Plasmodium falciparum* and parvovirus B19 result in severe clinical expression of malaria [26], others in co-infection between protozoa and intestinal helminth [27] and malaria and helminth [28]. The interaction of these pathogens, which share the same geographical ecosystem and affect the same population [27,28], may have either detrimental or beneficial effects. It is noticeable that *L. loa*, an inducer of encephalitis, and HTLV, an inducer of T-cell leukemia, as well as the appearance of TSP/HAM in the same geographic area, seems striking: whether these three clinical expressions are concomitant or associated with this coinfection is questionable.

The results presented here suggest some relationship between HTLV and *L. loa* microfilariae, a stage that is specifically designated as the cause of encephalitis and responsible for the immune dysregulation seen in most filarial infections [26]. Also, the similarities between the neurological symptoms generated by HTLV-1/ATL and those of *L. loa* raise questions as to the outcome of this coinfection. The first question regards coinfection with a high density of *L. loa* microfilariae, which would serve as a trigger. The second relates to the coinfection of HTLV-1 with *L. loa* hypermicrofilaremia, which could serve as a cofactor in the induction of leukemia or the fatality observed in regions endemic for *L. loa* during mass chemotherapy. Further studies are needed.

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Conflicts of Interest

The authors declare no conflict of interest.

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