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ERIK DA SILVA PINTO

ANÁLISE EPIDEMIOLÓGICA E ESPAÇO-TEMPORAL DA COINFECÇÃO DE LEISHMANIOSES E HIV NO ESTADO DA BAHIA

ILHÉUS – BAHIA
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Dissertação apresentada à Universidade Estadual de Santa Cruz, como parte das exigências para obtenção do título de Mestre em Ciência Animal.

Linha de pesquisa: Biodiversidade, Clínica e Sanidade Animal
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Orientadora: Profa. Dra. Anaiá da Paixão Sevá

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Dedico esta dissertação à minha mãe, Luzia, por apoiar cada etapa da minha jornada acadêmica, e aos pacientes acometidos pelas leishmanioses, que, mesmo anonimamente, tornam-se a essência deste estudo, contribuindo para o avanço do conhecimento e a busca por melhores estratégias de prevenção e tratamento.

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“Refresca teu coração. Sofre, sofre, depressa, que é para as alegrias novas poderem vir...”

Guimarães Rosa

ANÁLISE EPIDEMIOLÓGICA E ESPAÇO-TEMPORAL DA COINFECÇÃO DE LEISHMANIOSES E HIV NO ESTADO DA BAHIA

RESUMO

Os objetivos foram avaliar as características epidemiológicas e espaço-temporais da leishmaniose visceral (LV), leishmaniose tegumentar (LT) e HIV em escala espaço-temporal no estado da Bahia, Brasil. Para tanto, incluiu-se identificar e comparar o perfil dos casos isolados e coinfectados, bem como prevalência, letalidade, morbidade, faixa etária, recidivas e abandono de tratamento, além de ilustrar e analisar suas distribuições geográficas. Tratou-se de um estudo descritivo ecológico de série temporal, que analisou os casos entre 2008 e 2022. Os dados sociodemográficos e clínico-epidemiológicos foram coletados do SINAN e organizados para análises descritivas e estatísticas realizadas nos programas R Studio e Jamovi. As tendências temporais de incidência foram analisadas com modelos de regressão joinpoint. Mapas temáticos foram criados no QGIS para representar a distribuição espacial. Entre 2008 e 2022, foram notificados 8.664 casos de LV, com 57,18% confirmados, e 2,30% destes coinfectados com HIV. E no mesmo período, foram notificados 41.303 casos de LT, com 98,40% confirmados e 0,48% coinfectados com HIV. A tendência dos casos de LV foi decrescente de 2014 a 2022 (inclinação: -0,26; IC 95%: -0,32 a -0,20; valor de p: 0,002), enquanto os casos de coinfecção LV/HIV permaneceram estacionários. Os casos de LT apresentaram aumento em 2010 e 2012, mas também apresentaram tendência decrescente após 2013. A coinfecção TL/HIV também apresentou tendência decrescente no período de 2010 a 2013. A análise GLM mostrou que adultos e idosos têm maior chance de coinfecção LV/HIV do que LV isolada, quando comparados a crianças. Homens e moradores de áreas urbanas também apresentaram maior risco de coinfecção, quando comparados a mulheres e moradores de áreas rurais. Dentre os sintomas, 90% dos casos de LV apresentaram febre e 30,4% apresentaram edema, ambos mais comuns na LV isolada quando comparados à coinfecção LV/HIV. Além disso, 8,9% dos casos de coinfecção TLHIV apresentaram presença de dano de mucosa, enquanto 3,8% dos casos de LT isolada apresentaram presença de dano de mucosa. A letalidade da LV aumentou ao longo dos anos, enquanto a letalidade da AIDS diminuiu, mostrando correlação inversa (rho=-0,270, p=0,330, R^2= 0,000997). Da mesma forma, a letalidade da TL aumentou, enquanto a letalidade da coinfecção TL/HIV diminuiu (rho=-0,549, p=0,034, R^2=0,176). Os casos de LV foram mais prevalentes nas partes central e oeste do estado, os casos de TL tiveram maior incidência nas regiões sul e oeste do estado, enquanto os casos de HIV se concentraram nas partes costeiras e extremo sul. As coinfecções LV/HIV e TL/HIV ocorreram em locais focais, com a intensidade correspondendo à incidência isolada de LV e TL, respectivamente. Clinicamente, as coinfecções apresentaram maior letalidade em comparação às doenças isoladas, particularmente em populações socioeconomicamente vulneráveis. Os padrões de utilização de medicamentos também diferiram, com o antimonial pentavalente sendo amplamente usado em casos isolados, enquanto a anfotericina B foi mais frequente em coinfecções. As taxas de abandono de tratamento e recidivas foram mais elevadas entre os coinfectados. Fatores como alta temperatura, baixa umidade, urbanização e desigualdades socioeconômicas foram associados à maior incidência de LV e coinfecções LV/HIV. O estudo reforça a importância de intervenções integradas que considerem determinantes sociais, controle vetorial e ampliação do acesso ao diagnóstico e tratamento.

Palavras-chave: AIDS; *Leishmania*; leishmaniose visceral, leishmaniose tegumentar

EPIDEMIOLOGICAL AND SPACE-TIME ANALYSIS OF LEISHMANIASIS AND HIV COINFECTION IN THE STATE OF BAHIA

ABSTRACT

The objectives were to evaluate the epidemiological and spatiotemporal characteristics of visceral leishmaniasis (VL), cutaneous leishmaniasis (TL), and HIV on a spatiotemporal scale in the state of Bahia, Brazil. To this end, the study included identifying and comparing the profile of isolated and co-infected cases, as well as prevalence, lethality, morbidity, age range, relapses, and treatment abandonment, in addition to illustrating and analyzing their geographic distributions. This was an ecological descriptive time-series study, which analyzed cases between 2008 and 2022. Sociodemographic and clinical-epidemiological data were collected from SINAN and organized for descriptive and statistical analyses performed in the R Studio and Jamovi programs. Temporal trends in incidence were analyzed with joinpoint regression models. Thematic maps were created in QGIS to represent the spatial distribution. Between 2008 and 2022, 8,664 cases of VL were reported, with 57.18% confirmed, and 2.30% of these co-infected with HIV. And in the same period, 41,303 cases of LT were reported, with 98.40% confirmed and 0.48% co-infected with HIV. The trend in VL cases was decreasing from 2014 to 2022 (slope: -0.26; 95% CI: -0.32 to -0.20; p-value: 0.002), while cases of VL/HIV co-infection remained stationary. LT cases increased in 2010 and 2012, but also showed a decreasing trend after 2013. LT/HIV coinfection also showed a decreasing trend from 2010 to 2013. The GLM analysis showed that adults and the elderly have a higher chance of LV/HIV coinfection than isolated LT, when compared to children. Men and urban residents also had a higher risk of coinfection, when compared to women and rural residents. Among the symptoms, 90% of LT cases presented fever and 30.4% presented edema, both more common in isolated LT when compared to LT/HIV coinfection. In addition, 8.9% of LT/HIV coinfection cases presented mucosal damage, while 3.8% of isolated LT cases presented mucosal damage. The lethality of VL increased over the years, while the lethality of AIDS decreased, showing an inverse correlation (rho=-0.270, p=0.330, R^2= 0.000997). Similarly, the lethality of LT increased, while the lethality of LT/HIV co-infection decreased (rho=-0.549, p=0.034, R^2=0.176). VL cases were more prevalent in the central and western parts of the state, LT cases had a higher incidence in the southern and western regions of the state, while HIV cases were concentrated in the coastal parts and extreme south. LT/HIV and LT/HIV co-infections occurred in focal locations, with the intensity corresponding to the isolated incidence of VL and LT, respectively. Clinically, co-infections presented higher lethality compared to isolated diseases, particularly in socioeconomically vulnerable populations. Medication use patterns also differed, with pentavalent antimonial being widely used in isolated cases, while amphotericin B was more frequently used in co-infections. Treatment abandonment and relapse rates were higher among co-infected individuals. Factors such as high temperature, low humidity, urbanization and socioeconomic inequalities were associated with higher incidence of VL and VL/HIV co-infections. The study reinforces the importance of integrated interventions that consider social determinants, vector control and increased access to diagnosis and treatment.

Keywords: AIDS; *Leishmania*; visceral leishmaniasis, tegumentary leishmaniasis

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LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

AIDS	Acquired Immunodeficiency Syndrome
AAPC	Average Annual Percent Change
APC	Annual Percent Change
CI	Confidence Interval
DTNs	Doenças Tropicais Negligenciadas
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
IBGE	Instituto Brasileiro de Geografia e Estatística
IFAT	Indirect Fluorescent Antibody Test
IMG	Moran's Global Autocorrelation Index
ISCIII	Instituto de Salud Carlos III (Espanha)
LISA	Local Indicators of Spatial Association
LT	Leishmaniose Tegumentar
LT/HIV	Coinfecção Leishmaniose Tegumentar e HIV
LV	Leishmaniose Visceral
LV/HIV	Coinfecção Leishmaniose Visceral e HIV
MHDI	Municipal Human Development Index
NTDs	Neglected Tropical Diseases
R^2	Coefficient of Determination
SD	Standard Deviation
SESAB	Secretaria da Saúde do Estado da Bahia
SIG	Sistemas de Informação Geográfica
SINAN	Sistema de Informação de Agravos de Notificação
SUS	Sistema Único de Saúde
TARV	Terapia Antirretroviral
TL	Tegumentary Leishmaniasis
TL/HIV	Coinfection Tegumentary Leishmaniasis and HIV
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Visceral Leishmaniasis
VL/HIV	Coinfection Visceral Leishmaniasis and HIV
WHO	World Health Organization
X^2	Chi-Square Test

SUMÁRIO

1 INTRODUÇÃO

As Doenças Tropicais Negligenciadas (DTNs) afetam mais de um bilhão de pessoas em todo o mundo, impactando principalmente populações vulneráveis, sem acesso adequado a serviços de saúde e infraestrutura básica (BANGERT *et al.*, 2017; MAHESHWARI; BANDYOPADHYAY, 2020). Essas doenças representam um desafio sanitário, social e econômico significativo, sendo agravadas por fatores como mudanças climáticas, conflitos, migração e urbanização acelerada (EHRENBERG; AULT, 2005; HOTEZ, 2013).

Dentre as DTNs, as leishmanioses são infecções parasitárias causadas por protozoários do gênero *Leishmania*, transmitidos por vetores flebotomíneos. No Brasil, as duas principais formas clínicas da doença são a leishmaniose visceral (LV), que acomete órgãos internos e pode ser fatal se não tratada, e a leishmaniose tegumentar (LT), que afeta pele e mucosas, podendo causar lesões desfigurantes (WHO, 2019). O Brasil é um dos países com maior carga de leishmanioses no mundo, e a Bahia se destaca como um dos estados mais afetados, com alta incidência e ampla distribuição geográfica da doença (MACHADO *et al.*, 2021a).

A coinfecção *Leishmania*/HIV tem se tornado uma preocupação crescente, especialmente em regiões endêmicas para ambas as doenças. A imunossupressão causada pelo HIV predispõe os indivíduos à infecção por Leishmania e favorece o agravamento da doença, reduzindo a eficácia do tratamento e aumentando a letalidade dos casos (OKWOR; UZONNA, 2013). Estudos indicam que a coinfecção apresenta desafios adicionais para o diagnóstico e manejo clínico, além de exigir estratégias específicas de vigilância epidemiológica (SOUSA-GOMES; ROMERO; WERNECK, 2017).

Diante desse cenário, é fundamental compreender a distribuição epidemiológica, espacial e temporal da coinfecção *Leishmania*/HIV no estado da Bahia. O estudo dessas interações permite identificar áreas de maior risco, orientar políticas públicas e aprimorar estratégias de vigilância e controle da doença, contribuindo para ações mais eficazes em saúde pública.

2 OBJETIVO GERAL

Avaliar as características epidemiológicas e espaço-temporais da coinfecção entre leishmanioses e HIV, bem como das formas isoladas das leishmanioses, no estado da Bahia.

3 OBJETIVOS ESPECÍFICOS

- Caracterizar e comparar o perfil epidemiológico dos casos de leishmanioses isoladas e em coinfecção com HIV, considerando prevalência, letalidade, morbidade, faixa etária, recidivas e abandono de tratamento;

- Identificar a distribuição geográfica das leishmanioses isoladas e em coinfecção com HIV;

- Detectar os fatores ambientais, climáticos e socioeconômicos associados aos casos de leishmanioses isoladas e em coinfecção com HIV;

- Relacionar a ocorrência das leishmanioses isoladas e em coinfecção com HIV aos municípios de residência e de notificação dos casos.

4 REVISÃO DE LITERATURA

4.1 Leishmaniose Visceral e Leishmaniose Tegumentar Americana

As leishmanioses são ocasionadas por diversas espécies do gênero *Leishmania*, apresentando as mais variadas características clínicas, que vão desde a úlceras cutâneas até infecções em órgãos viscerais, principalmente na medula óssea, fígado e baço (STEVERDING, 2017). Clinicamente, é dividida em leishmaniose visceral (LV) e tegumentar americana (LT), sendo essa última apresentando a forma cutânea e mucocutânea (BURZA; CROFT; BOELAERT, 2019).

Mundialmente classificadas como doenças tropicais negligenciadas, as leishmanioses já infectaram mais de 12 milhões de pessoas em todo o mundo (INCEBOZ, 2019). Atrelado a essa perspectiva, Leishmania é um protozoário parasito unicelular transmitido por fêmeas de flebotomíneos do gênero Lutzomyia. Este parasito apresenta um ciclo de vida dimórfico, alternando entre a forma promastigota (móvel), presente no vetor, e a forma amastigota (intracelular e imóvel), encontrada nos hospedeiros infectados, incluindo humanos e outros mamíferos (KUMARI *et al.*, 2021; TORRES-GUERRERO *et al.*, 2017).

No Brasil, as principais espécies de *Leishmania* causadoras da LV são *L. chagasi, L. donovani* e *L. infantum*, ocorrendo de forma endêmica no País (AGUIAR; RODRIGUES, 2017). A mesma pode apresentar uma condição clínica fatal, por lesionar os órgãos viscerais do hospedeiro humano e animal. Além de sintomas inespecíficos, o principal quadro clínico é caracterizado por febre e esplenomegalia associadas ou não a hepatomegalia (LIMA *et al.*, 2019; STEVERDING, 2017).

A LT no Brasil é causada pelos agentes *Leishmania amazonensis*, *L. braziliensis* e *L. guyanensis* (INCEBOZ, 2019). Clinicamente, a doença se manifesta por lesões ou úlceras cutâneas, frequentemente localizadas em áreas da pele mais expostas, como nariz, mãos, antebraços e pernas. No entanto, em formas difusas, as lesões podem surgir em regiões não expostas à picada do vetor. Nos casos mucocutâneos, ocorrem lesões metastáticas, com inflamação dos tecidos moles da boca, nariz, laringe e faringe (THAKUR; JOSHI; KAUR, 2020).

As leishmanioses continuam sendo doenças infecciosas de extrema preocupação em diversos países endêmicos (ORGANIZAÇÃO PAN-AMERICANA DE SAÚDE, 2021).

Embora tenha havido uma redução no número de casos de LV, a doença ainda causa impacto significativo nas regiões mais desfavorecidas desses países (SASIDHARAN; SAUDAGAR, 2021).

A LV foi inicialmente registrada no início do século XX na América Latina, com ocorrência restrita a aldeias rurais. No entanto, a partir de 1981, observou-se a urbanização dessa parasitose no Brasil, com a disseminação do parasito para cidades próximas. Nas décadas seguintes, esse processo levou ao aumento do número de casos em áreas urbanas, de modo que, em determinado período, a proporção de infecções urbanas superou as rurais. Estima-se que, ao longo dos anos, a LV tenha acometido mais de cem mil habitantes em diversas cidades brasileiras (COSTA, 2008; WERNECK *et al.*, 2007).

No Brasil, a LV apresenta uma distribuição heterogênea, com maior incidência nas regiões Norte, Nordeste e Centro-Oeste (BRUHN *et al.*, 2024). Entre os estados mais afetados, a Bahia se destaca como um dos principais focos da doença, registrando alta endemicidade em diversas áreas. Ao analisar a situação no estado, constata-se uma disseminação abrangente da LV, com maior concentração de casos na região central. Além disso, essa área apresenta alta vulnerabilidade social e baixos índices de desenvolvimento humano, fatores que contribuem para a persistência e expansão da doença (ANDRADE; SOUZA; CARMO, 2022).

Dentre os casos da LV, há uma prevalência maior no sexo masculino, especialmente em crianças menores de 9 anos, em populações com menor nível de escolaridade ou que ainda não frequentaram a escola, e em residentes de áreas urbanas (MARTINS-MELO *et al.*, 2014a; REIS *et al.*, 2017). Quando analisamos as opções de tratamento disponíveis, fica claro que a LV carece de alternativas terapêuticas inovadoras. Essa falta de progresso destaca a condição da LV como uma doença tropical negligenciada, uma vez que os estudos mais avançados se baseiam no uso de compostos já aprovados para uso clínico, seja em combinação ou não com compostos "redescobertos" (SANGENITO *et al.*, 2019).

Dentre os países com casos de LT, o Brasil figura entre os dez que respondem por mais de 70% dos casos (WHO, 2020). Ela se caracteriza por ser uma doença endêmica no estado da Bahia, localizado no Nordeste do Brasil (SEVÁ *et al.*, 2023). Além disso, tem havido um aumento significativo no número de casos da forma mais grave da doença, uma redução na eficácia dos tratamentos com antimoniais e alterações na composição demográfica da população afetada (JIRMANUS *et al.*, 2012; SESAB, 2024).

A LT apresenta uma prevalência predominante em pacientes do sexo masculino e em populações pardas. Além disso, a faixa etária mais afetada no país é entre 20 e 39 anos. Em relação à escolaridade, observa-se que a maior proporção de casos ocorre entre indivíduos que possuem apenas o ensino fundamental (LOPES *et al.*, 2023).

Por fim, as leishmanioses são doenças complexas que tem sido um desafio para a humanidade ao longo dos séculos (BENCHIMOL; JOGAS JUNIOR, 2020). No entanto, existe a possibilidade de alcançar a eliminação das leishmanioses em algumas décadas, caso novas pesquisas explorando abordagens mais eficazes no tratamento da doença sejam desenvolvidas. Por fim, os esforços conjuntos da comunidade política e científica podem levar a um mundo livre do parasita *Leishmania* (SASIDHARAN; SAUDAGAR, 2021).

4.2 Vírus da Imunodeficiência Humana (HIV) e a Coinfecção com as Leishmanioses

A coinfecção entre o HIV e as leishmanioses representa um desafio significativo para a saúde pública devido à sua apresentação clínica insidiosa e ao impacto no sistema imunológico. Tanto o HIV quanto a LV/LT possuem a capacidade de estabelecer infecções assintomáticas e comprometer a resposta imunológica do hospedeiro. Além disso, a interação entre essas doenças pode potencializar a progressão da infecção por HIV, acelerando a manifestação da Síndrome da Imunodeficiência Adquirida (AIDS), ao mesmo tempo em que favorece a disseminação do parasito da leishmaniose no organismo. Como consequência, indivíduos coinfectados podem apresentar maior risco de recorrência da LV/LT e de agravamento do quadro imunológico, tornando-se potenciais reservatórios do parasita (FERREIRA *et al.*, 2018).

A infecção pelo HIV é endêmica em diversas regiões do mundo e, com a sua disseminação para áreas rurais, aliada à expansão da leishmaniose para regiões suburbanas, há uma crescente sobreposição geográfica dessas doenças. Esse fenômeno tem resultado no aumento da incidência da coinfecção por *Leishmania*/HIV. Casos de coinfecção foram registrados em 35 países, sendo que a maioria dos estudos descreve a associação entre LV e HIV, enquanto há menor número de pesquisas abordando a coinfecção entre LT e HIV (NGOUATEU *et al.*, 2012).

No que se refere ao tratamento, atualmente não há protocolos específicos e padronizados para a abordagem da coinfecção *Leishmania*/HIV. Os fármacos antileishmania, como os antimoniais pentavalentes, a anfotericina B lipossomal e a miltefosina, apresentam eficácia reduzida em indivíduos coinfectados, além de estarem associados a altas taxas de recidiva e mortalidade (LINDOSO *et al.*, 2018). Dessa forma, a recomendação atual baseia-se no uso da terapia antirretroviral (TARV) para o controle do HIV, combinada com esquemas terapêuticos individualizados para a leishmaniose, considerando fatores como resposta clínica, efeitos adversos e condições do paciente. Diante desse cenário, torna-se essencial a realização de estudos para aprimorar as estratégias terapêuticas, incluindo a avaliação de novas combinações farmacológicas e protocolos específicos para essa população vulnerável.

4.3 Geoprocessamento em Saúde

O geoprocessamento engloba diversas técnicas que abrangem obtenção, processamento, manipulação e representação de informações espaciais. As principais ferramentas utilizadas nesse contexto são o sensoriamento remoto, estatística espacial, a cartografia digital e os sistemas de informação geográfica (SIG). O SIG desempenha um papel fundamental ao possibilitar a realização de análises espaciais. Utilizando tais técnicas, é viável identificar e descrever os padrões geográficos presentes em um conjunto de dados (BRASIL, 2006).

Na área da saúde, as técnicas de análise espacial têm sido cada vez mais aplicadas para compreender a distribuição de doenças e os fatores ambientais associados. Essas análises permitem avaliar condições como poluição, desmatamento e mudanças no uso do solo, que podem influenciar a propagação de enfermidades em diferentes contextos urbanos e rurais. Além disso, aspectos socioeconômicos, como condições de moradia, acesso a serviços de saúde, emprego, superlotação e estilo de vida, também são considerados, uma vez que impactam diretamente a saúde da população. Do ponto de vista epidemiológico, essas ferramentas possibilitam a identificação de áreas de risco, a modelagem da distribuição espacial dos fatores associados a determinadas patologias e a formulação de estratégias mais eficazes para vigilância e controle. A utilização de mapas e outros recursos analíticos contribui para a visualização dos indicadores de saúde, apoiando a tomada de decisão em políticas públicas (BARBOSA *et al.*, 2014; MACHADO *et al.*, 2021a; ROQUETTE; NUNES; PAINHO, 2018).

5 ARTIGO

EPIDEMIOLOGICAL AND SPATIO-TEMPORAL ANALYSIS OF CO-INFECTION OF LEISHMANIASIS AND HIV IN BAHIA STATE, BRAZIL

(A submeter: *PLOS Neglected Tropical Diseases*)

Epidemiological and spatio-temporal analysis of co-infection of leishmaniasis and HIV in Bahia state, Brazil

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Abstract

The objectives were to evaluate the epidemiological and spatiotemporal characteristics of visceral leishmaniasis (VL), cutaneous leishmaniasis (TL), and HIV on a spatiotemporal scale in the state of Bahia, Brazil. To this end, the study included identifying and comparing the profile of isolated and co-infected cases, as well as prevalence, lethality, morbidity, age range, relapses, and treatment abandonment, in addition to illustrating and analyzing their geographic distributions. This was an ecological descriptive time-series study, which analyzed cases between 2008 and 2022. Sociodemographic and clinical-epidemiological data were collected from SINAN and organized for descriptive and statistical analyses performed in the R Studio and Jamovi programs. Temporal trends in incidence were analyzed with joinpoint regression models. Thematic maps were created in QGIS to represent the spatial distribution. Between 2008 and 2022, 8,664 cases of VL were reported, with 57.18% confirmed, and 2.30% of these co-infected with HIV. And in the same period, 41,303 cases of LT were reported, with 98.40%

confirmed and 0.48% co-infected with HIV. The trend in VL cases was decreasing from 2014 to 2022 (slope: -0.26; 95% CI: -0.32 to -0.20; p-value: 0.002), while cases of VL/HIV co-infection remained stationary. LT cases increased in 2010 and 2012, but also showed a decreasing trend after 2013. LT/HIV coinfection also showed a decreasing trend from 2010 to 2013. The GLM analysis showed that adults and the elderly have a higher chance of LV/HIV coinfection than isolated LT, when compared to children. Men and urban residents also had a higher risk of coinfection, when compared to women and rural residents. Among the symptoms, 90% of LT cases presented fever and 30.4% presented edema, both more common in isolated LT when compared to LT/HIV coinfection. In addition, 8.9% of LT/HIV coinfection cases presented mucosal damage, while 3.8% of isolated LT cases presented mucosal damage. The lethality of VL increased over the years, while the lethality of AIDS decreased, showing an inverse correlation (rho=-0.270, p=0.330, R^2= 0.000997). Similarly, the lethality of LT increased, while the lethality of LT/HIV co-infection decreased (rho=-0.549, p=0.034, R^2=0.176). VL cases were more prevalent in the central and western parts of the state, LT cases had a higher incidence in the southern and western regions of the state, while HIV cases were concentrated in the coastal parts and extreme south. LT/HIV and LT/HIV co-infections occurred in focal locations, with the intensity corresponding to the isolated incidence of VL and LT, respectively. Clinically, co-infections presented higher lethality compared to isolated diseases, particularly in socioeconomically vulnerable populations. Medication use patterns also differed, with pentavalent antimonial being widely used in isolated cases, while amphotericin B was more frequently used in co-infections. Treatment abandonment and relapse rates were higher among co-infected individuals. Factors such as high temperature, low humidity, urbanization and socioeconomic inequalities were associated with higher incidence of VL and VL/HIV co-infections. The study reinforces the importance of integrated

interventions that consider social determinants, vector control and increased access to diagnosis and treatment.

Keywords: AIDS; Leishmania; visceral leishmaniasis, tegumentary leishmaniasis

Introduction

Neglected Tropical Diseases (NTDs) affect more than one billion people worldwide, who are from the most vulnerable populations, without distinction of economic class or income (BANGERT *et al.*, 2017; MAHESHWARI; BANDYOPADHYAY, 2020) In this sense, NTDs become a challenge for the health, social, and economic development of countries, in which they are exacerbated by changes in the global scenario, such as climate change, conflicts, migration, and urbanization processes (EHRENBERG; AULT, 2005; HOTEZ, 2013)

Among one of the main NTDs, leishmaniasis stands out, with a high number of cases in several countries around the world (WHO, 2019) These are diseases that present little pharmacological alternative for clinical treatment, in addition to requiring continuous patient monitoring (SANGENITO *et al.*, 2019) It is worth noting that only a small portion of patients adhere to treatment, which requires specialized health services, located in urban centers, in addition to promoting exposure to the risks of side effects and toxicological effects, due to the long period of medication use (CHARLTON *et al.*, 2018; SANGENITO *et al.*, 2019)

Leishmaniasis is caused by protozoa of several species of *Leishmania*, presenting the most varied clinical characteristics, ranging from cutaneous and/or mucocutaneous ulcers, characterized as tegumentary leishmaniasis (TL), to lesions in visceral organs, especially bone marrow, liver, and spleen, characterized as visceral leishmaniasis (VL) (BURZA; CROFT; BOELAERT, 2019; STEVERDING, 2017).

In Brazil, the main species of *Leishmania* that causes VL is *L. infantum chagasi* (WHO, 2010) This disease generates a fatal clinical condition, especially if left untreated (MADALOSSO *et al.*, 2012; MAIA-ELKHOURY *et al.*, 2019) Epidemiologically, some

municipalities in the Northeast and North regions of the country with high relative risk for the development of VL stand out (MELO *et al.*, 2023) The state of Bahia is located in the Northeast of Brazil, and a wide spatial dispersion of VL can be seen in it. Especially in the central region of the state, with the highest incidence of VL, it is an area that concentrates high social vulnerability and low human development (ANDRADE; SOUZA; CARMO, 2022)

Studies indicate a higher prevalence of VL in males, especially in children under 9 years of age, in populations with a lower level of education or who have not yet attended school, and in residents of urban areas (MARTINS-MELO *et al.*, 2014a; REIS *et al.*, 2017)

Regarding TL in Brazil, the causative species are *L. amazonensis*, *L. braziliensis*, and *L. mexicana* (BRASIL, 2023) Such as cause clinical lesions such as prominent ulcers in the areas of the skin (such as nose, hands, forearms, legs) where the insect vector bite occurred. However, mucocutaneous cases may occur, with metastatic lesions, with inflammation of the soft tissues of the mouth, nose, larynx and pharynx (THAKUR; JOSHI; KAUR, 2020)

It is worth considering that Brazil is among the ten countries that account for more than 70% of TL cases, and in the state of Bahia it is an endemic disease (WHO, 2020) In addition, there has been a significant case series of the most severe form and a reduction in the efficacy of antimonial treatments (JIRMANUS *et al.*, 2012)

TL has a predominant incidence in male patients and in brown populations. In addition, the most affected age group in the country is between 20 and 39 years old. Regarding education, it is observed that the highest proportion of cases occurs among individuals who have only elementary education (LOPES *et al.*, 2023)

Regarding the severity of leishmaniasis, co-infection with the human immunodeficiency virus (HIV) stands out. HIV infection is an important public health problem worldwide (UNAIDS, 2023) With the immunosuppressive effect of HIV, people affected by *Leishmania* are also predisposed to the worsening of the parasitological disease (OKWOR; UZONNA,

2013) Thus, several studies have observed that the lethality of VL/HIV co-infection is higher when compared to isolated parasite infection, emphasizing the importance of integrated approaches in the diagnosis and treatment of these infections (MACHADO *et al.*, 2021a; SOUSA-GOMES; ROMERO; WERNECK, 2017) In addition, the coexistence of HIV and VL presents a significant risk due to asymptomatic infection that goes unnoticed. Both HIV and VL share similar characteristics, such as the ability to cause asymptomatic infection and suppress the immune system (FERREIRA *et al.*, 2018)

Regarding co-infection between TL and HIV, changes in the size of ulcers are reported, in addition to therapeutic failures and recurrences of the disease, modifying the clinical and therapeutic course of TL (GUERRA *et al.*, 2011). However, there are no studies in the literature describing the lethality rates of TL/HIV, emphasizing the need to know these epidemiological indicators.

In Brazil, the current spatial behavior of VL demonstrates an increase in the number of priority municipalities, concentrated in the states of Tocantins, Maranhão, Piauí, and Mato Grosso do Sul, as well as areas of Pará, Ceará, Piauí, Alagoas, Pernambuco, Bahia, São Paulo, Minas Gerais, and Roraima (MELO *et al.*, 2023) Regarding TL, it presents a scenario of concentration of cases in the North region, with the state of Acre leading the incidence, in addition to Mato Grosso, Maranhão and Bahia (BELO *et al.*, 2023) However, there is a lack of studies that are specifically dedicated to the analysis of the spatial patterns of co-infection between leishmaniasis and HIV in Bahia.

There are several epidemiological studies on leishmaniasis that have used spatial analysis to identify regions at higher risk for the disease (MACHADO *et al.*, 2020a; NUNES *et al.*, 2020; SEVÁ *et al.*, 2017) Thus, the use of Geographic Information Systems (GIS) in epidemiology plays a crucial role in understanding the health-disease process. This allows for the strategic allocation of resources, the implementation of monitoring, and the adoption of

127 effective preventive and control measures for various parasitic diseases, including leishmaniasis
128 (MARTINS-MELO *et al.*, 2014b; SOUZA *et al.*, 2018)

129 Therefore, the present study aims to know the epidemiological situation of VL and TL
130 co-infection with HIV, and to compare it with both when isolated in the state of Bahia. In
131 addition, we intend to map the geographic distribution of diseases in isolation and in co-
132 infection, identify environmental, climatic and socioeconomic risk factors associated with these
133 cases, analyze and compare the epidemiological profile, including prevalence, lethality,
134 morbidity, age group, recurrences and treatment abandonment, and relate the occurrence of
135 isolated and concomitant infections to the municipalities of residence and notification.

136

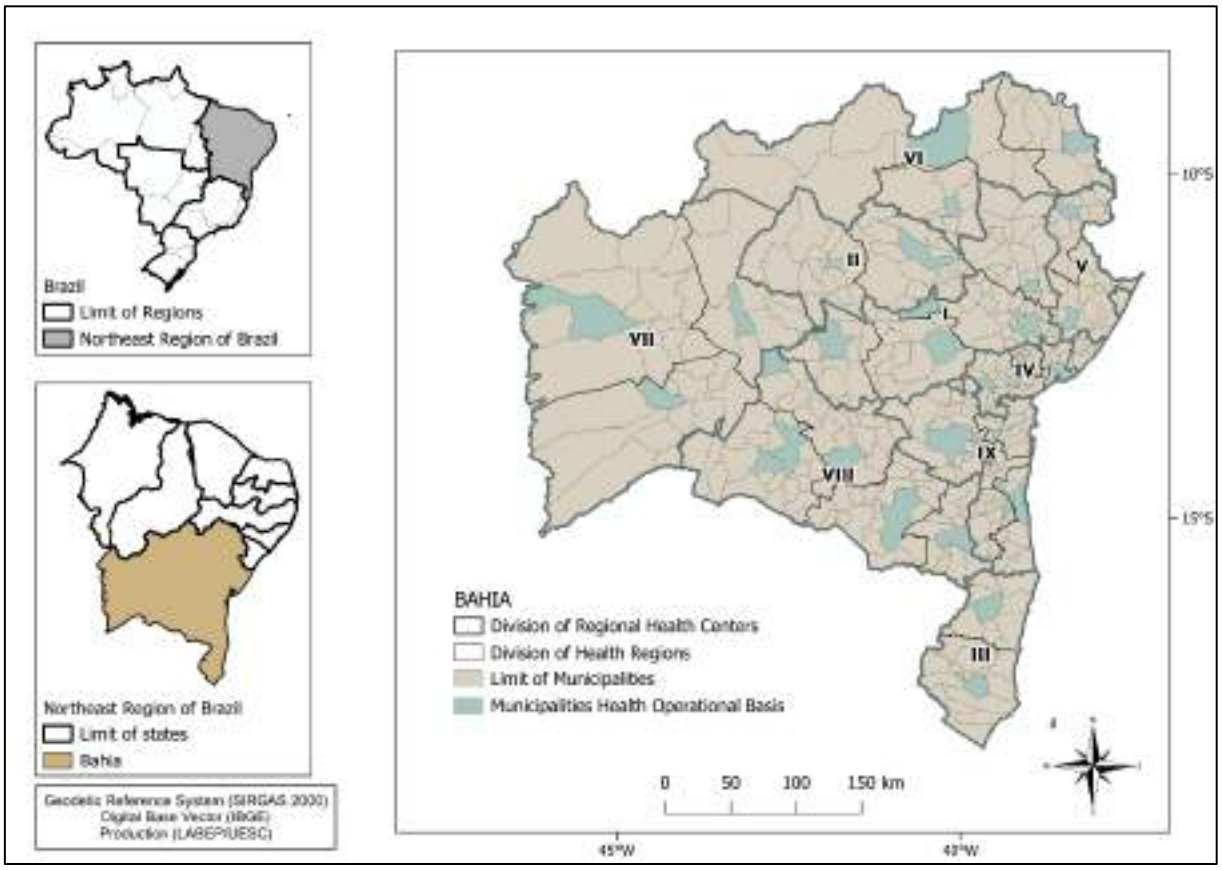
137 **Material and Methods**

138 This is an ecological time-series study, regarding cases of visceral leishmaniasis (VL),
139 tegumentary leishmaniasis (TL) and human immunodeficiency virus (HIV), isolated and in co-
140 infection (VL/HIV and TL/HIV), of Bahia state in Brazil. That cases are obtained and analyzed
141 at the aggregate level, by municipality, from 2008 until 2022.

142 ***1. Study area***

143 The study was carried out in the state of Bahia, located in the Northeast Region of Brazil,
144 with an area of 564,760.429 km² and having the largest population in the Region, with
145 14,136,417 inhabitants. The 417 municipalities are grouped into nine Regional Health Center
146 (RHC), subdivided in Regional Health Bases (RHB), that are represented by specific
147 municipalities, considered as Health Operational Basis (HOB) (SESAB, 2023) (Figure 1).

Figure 1. Division of the Health Region and their Regional Health Centers, of Bahia state, in the Northeast Region of Brazil.



Legend 1. Regional Health Centers (RHC). I. Central-East, II. Center-North, III. Extreme South, IV. East, V. Northeast, VI. North, VII. West, VIII. Southwest, and IX. South.

2. Data description

There was obtained human cases of VL and TL with and without co-infection with HIV, in addition to isolated cases of HIV, per year from 2008 to 2022. They were previously provided by the Health Department of the State of Bahia (SESAB) and available in the Notifiable Diseases Information System (SINAN).

The data VL and TL cases refer to the fillable fields of the investigation forms for each disease cases in SINAN, which is composed by sociodemographic (race/color, age group, sex, education, pregnant status and zone) and clinical-epidemiological questions (signs and symptoms, co-infection with HIV, type of diagnosis and case classification, type of treatment

and the evolution of the case). There were also record the municipalities of residence, notification and probable location of infection (PLI). In case of PLI field is not filled in or ignored, the place of infection was considered to be the municipality of residence of the patients for the analyses, due to the chronic nature of the diseases, representing a higher probability of being infected in the site with the highest frequency.

Cases of HIV infection are composed by sociodemographic (age group, sex, race, and municipality of residence) and clinical-epidemiological questions (kind of transmission, such as sexual, through the use of drugs, blood transfusion, blood transfusion for hemophilia and accident with biological material, in addition to the type of diagnostic test and evolution of the case).

To calculate the incidence of cases, the population of each municipality was obtained from the IBGE, available at the SINAN. They were specific of the census of 2010 and for the other years they are estimated.

3. Data analysis

3.1 Descriptive analyzes

Descriptive analyzes were performed of all data, including their frequences were done considering their confidence intervals (CI) of 95%.

3.2 Statistical analyzes

To compare the symptoms of both diseases (TL, VL and HIV) and co-infection with HIV (TL/HIV and VL/HIV), there was performed chi-square and or Fisher's exact test, according to the data distribution. In order to identify the difference between the diseases isolated and in co-infection and their personal features (schooling, age group, pregnant woman, race/color, sex), zone of residence, treatment (Pentavalent Antimony, Amphotericin B, Liposomal Amphotericin B, Pentamidine, and other drugs) and diagnostic confirmation criteria

(clinical forms, epidemiological classification, and case evolution), there was used the same analyzes above, but followed by the post-hoc Chi-square test or Fisher's exact test (depending on the data distribution), with Bonferroni correction. Both analyzes were done in R program (version 4.2.3), with "rstatix" and "rcompanion" packages, considering a significance of 5% of p-value (KASSAMBARA, 2023; MANGIAFICO, 2024; RSTUDIO TEAM, 2023).

There was considered the temporality of both incidence and lethality and for their comparison, there was performed linear and Spearman's correlation, once the not normal distribution after evaluation with Shapiro-Wilk test. Both analyses were performed using the jamovi statistical software (version 2.3.21), considering a significance of 5%. Trend analysis for temporally incidence (by year) was performed using a joinpoint regression model. That model evaluates whether a line with multiple segments is statistically better at describing the temporal evolution of a dataset compared to a straight line or a line with fewer segments. The annual percentage change (APC) was calculated, considering a CI of 95% and significance of 5% for p-value. The following parameters were adopted: minimum of zero joinpoints and maximum of two, Monte Carlo permutation test (4499 permutations), autocorrelation of errors based on the data, and constant variance. When there is no inflection in the analysis, the trend is represented by a single straight line. The results were interpreted as follows: positive significant APCs were considered as increasing trends, negative significant APCs as decreasing trends and with no significance as stationary. These analyzes were performed in Joinpoint Regression program (version 5.2.0.1) and R, with car package and function ncvTest, to evaluate the variance of data (NCI, 2023).

It is noteworthy that for the analysis of TL isolated and TL/HIV co-infection, it was not possible to compare the variables as a function of the medications due to the lack of specific information in the database.

3.3 Spatial analyzes

The spatial distribution was performed using thematic maps of the incidence of both diseases, performed in the QGIS software (version 2.18).

In order to identify areas of hot and cold spots, there were performed spatial autocorrelation of the incidence of VL, TL, HIV, and VL/HIV and TL/HIV, per municipality, by using Moran's analysis, including Local Moran (LISA) and global (IMG) indices. In addition there was performed Moran's bivariate correlation between these diseases and variables human development (Municipal Human Development Index - HDI), education (illiteracy rate), housing (frequency of the urban population living in households connected to the water supply network and frequency of the urban population served by regular household waste collection services), work (frequency of those employed in the agricultural and mineral extraction sectors), environment (average rainfall, temperature and humidity), income (Gross Domestic Product - GDP, Gini index, unemployment rate, frequency of poor, vulnerable to poverty and extremely poor, frequency of people registered with CadÚnico or beneficiaries of Bolsa Família). For these analyzes, the neighborhood matrix was defined considering the inverse of the distance between the centroids of the municipalities, which defines that closer neighbors have greater influence than more distant neighbors. A minimum distance of 91.20 km was defined, so that all municipalities had at least one neighbor. In order to test de randomness of results and the significance of the test statistics, the analyzes were tested through 999 randomizations (empirical pseudosignificance) in order to obtain the. The analyses were performed using the GeoDa 1.22.0.2 software, and the significance of 5% for p-value was considered.

4. Ethical Aspects

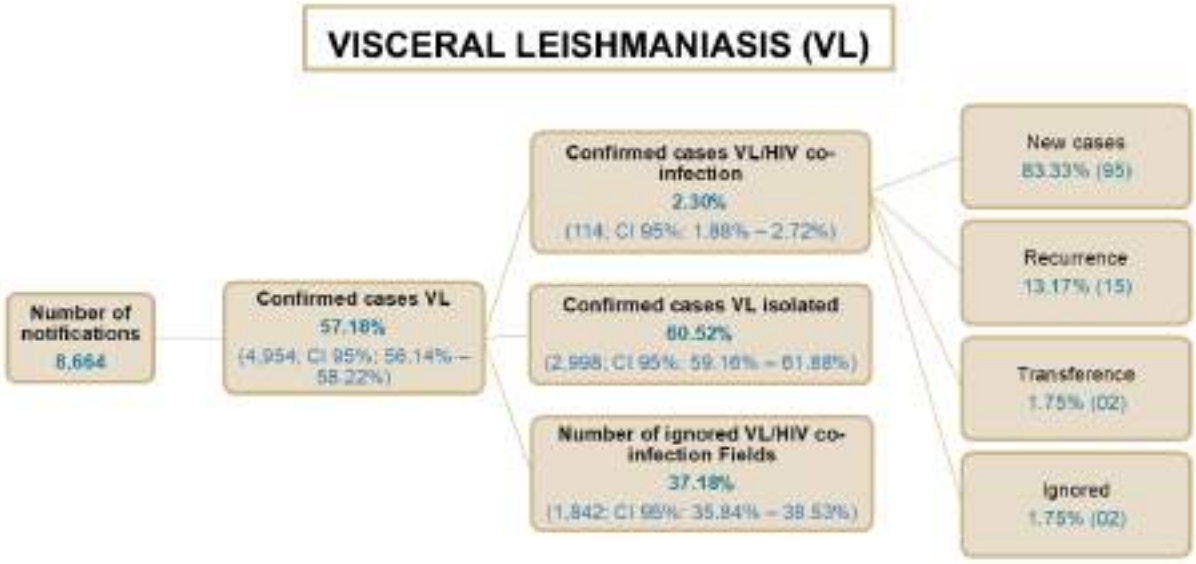
The study was authorized by SESAB and received ethical approval from the Research Ethics Committee of the State University of Santa Cruz, registered with opinion no. 4.784.218 (CAAE 47443721.4.0000.5526).

Results

VL and VL/HIV coinfection

From 2008 to 2022, 8,664 cases of VL were reported, of which 57.18% (4,954) were confirmed, 2.30% (114; 95% CI: 1.88%–2.72%) of them as VL/HIV coinfection. Of the VL/HIV cases, the majority, 83.33% (95; 95% CI: 76.49%–90.17%) had the entry type as new cases, rather than recurrence, transfer, or ignored, and this information was not present for isolated VL cases. The other 42.8% (3,710) registered VL cases were not confirmed because a change in diagnosis to other diseases, a negative result in the confirmatory test, or the period for confirmation had not ended until the present study were noted on the notification form. (**Figure 2**).

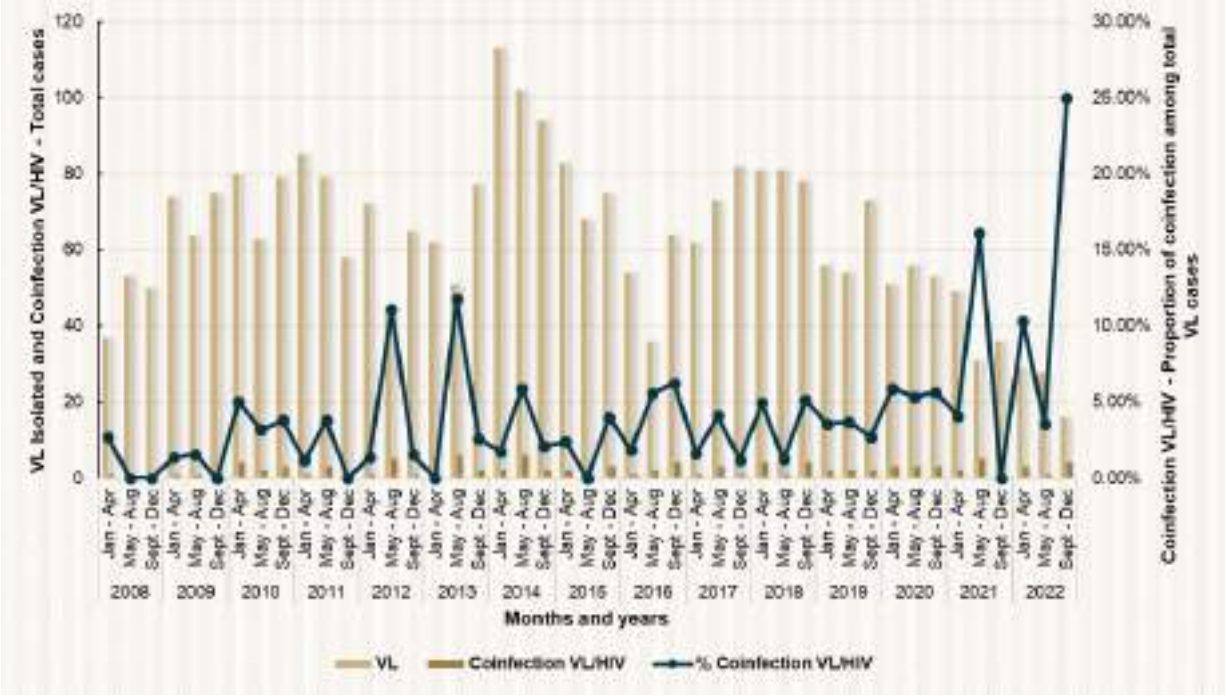
Figure 2. Number and frequency of reported cases of VL isolated and in co-infection with HIV, according to the type of entry and confirmatory status.



Regarding temporality, VL cases remained constant from 2008 to 2013 (mean: 1.72 per 100,000 inhabitants; standard deviation: 1.81), with a notable increase in 2014 (Jan-Apr: 113; May-Aug: 102; Sept-Dec: 94 cases), reduction in 2016 and subsequent decline in the following years, until 16 cases in Sep-Dec 2022 (**Figure 3**). On the other hand, the proportion of VL/HIV

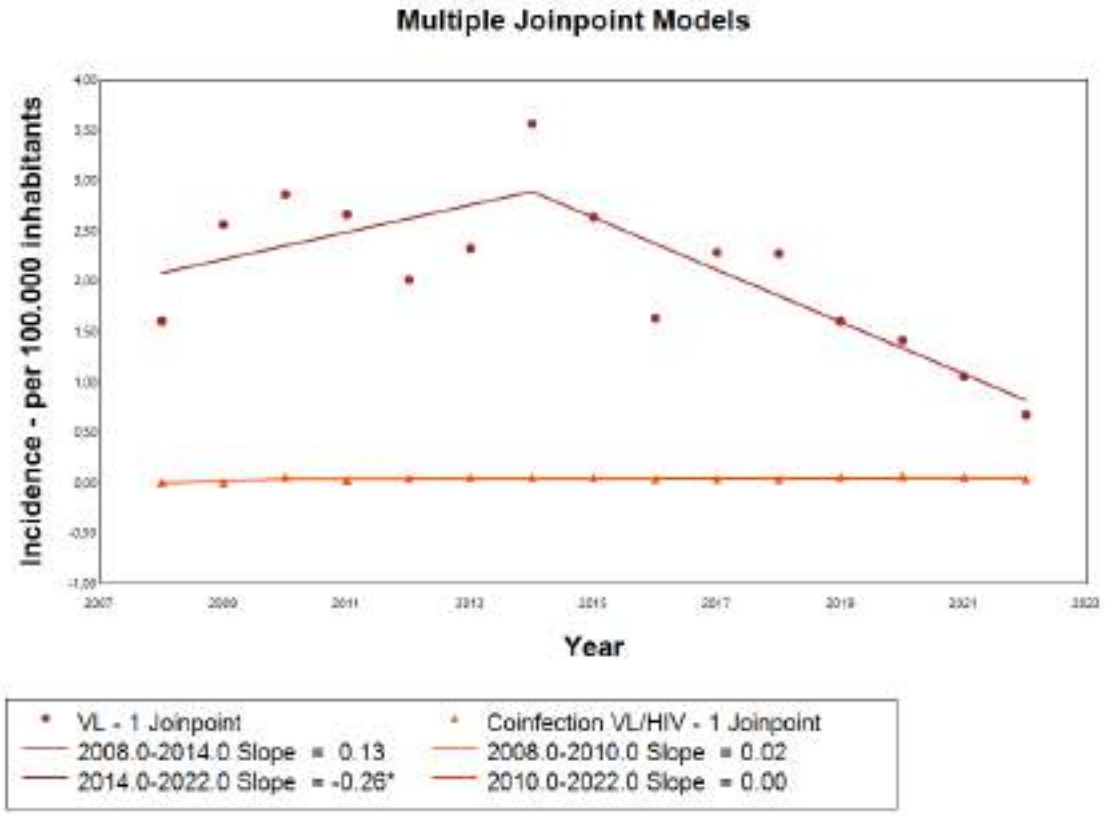
co-infection within VL cases isolated had their three highest number in the four-month period from September to December 2022, with 25% (4/16; CI 95%: 3.78% - 46.22%), in May to August 2021, with 16.13% (5/31; CI 95%: 3.18% – 29.08%) and in May to August 2013, with 11.76% (6/51; CI 95%: 2.92% - 20.61%). No significant correlation was found between the number of total VL cases and the proportion of VL/HIV co-infection cases in correlation analysis (rho = -0.272, p=0.071, R^2=0.236).

Figure 3. Number of total VL cases and proportion of VL/HIV co-infection within VL isolated, by four -month period and year of first symptoms.



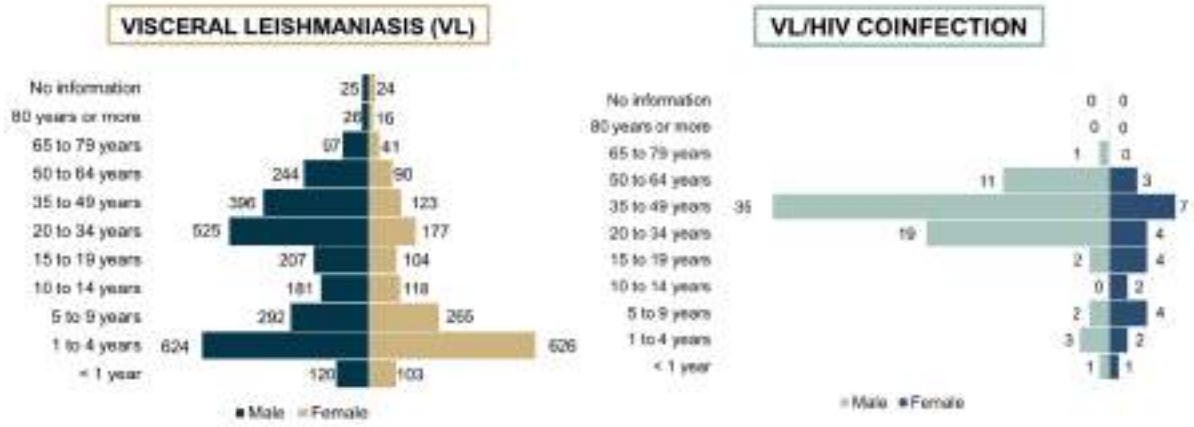
The Joinpoint regression analysis showed an increase of the incidence of VL (slope = 0,13), from 2007 until 2014, with a broke to downward trend in the period from 2014 to 2022, reducing annually an average of 26% (*average annual percent change* (AAPC) = -26%; slope: -0.26; CI 95%: -0.32 to -0.20; p-Value: 0.002), corroborating with decreasing of cases. No significant data were found on the trend of VL/HIV co-infection, and it was considered stationary and stable (APC: 0.02; CI 95%: -0.01 to 0.05; p-Value: 0.454) (**Figure 4**).

Figure 4. Trend of the Joinpoint regression coefficient of the incidence of VL and in VL/HIV co-infection in Bahia, 2008-2022.



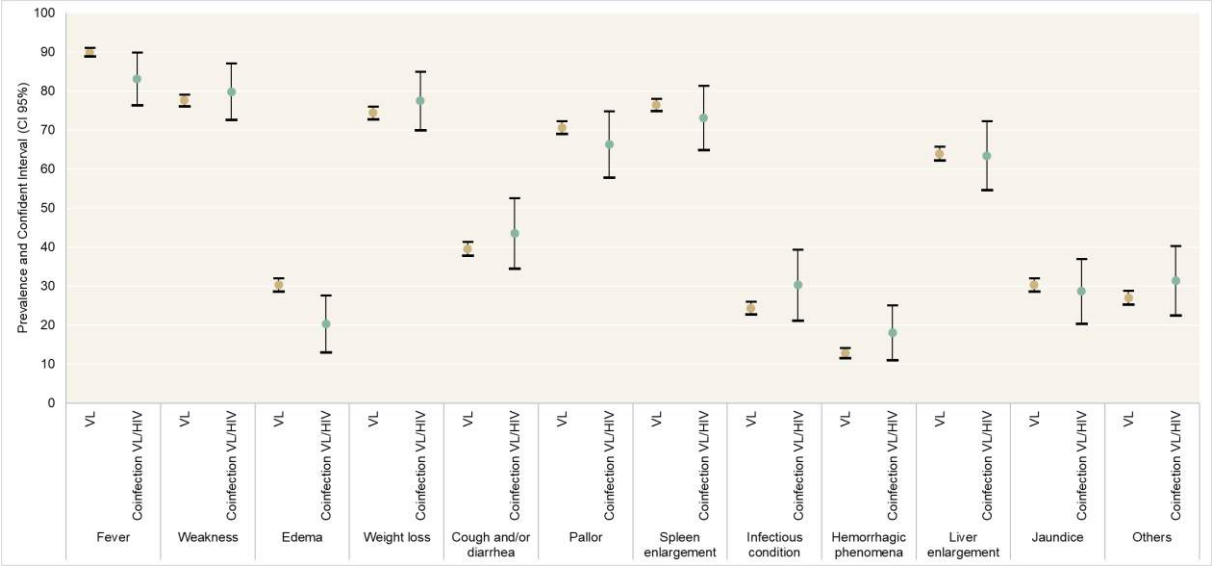
When analyzing the age pyramid of new cases, it is observed that VL isolated and VL/HIV co-infection have most cases in males (61.87%; 2737 and 73.27%; 74; respectively), but different distribution according to age group. For isolated VL, in males they are more frequent in groups from 1 to 4 (624), from 20 to 34 (525) and from 35 to 49 years (396), and in females (1687), the cases are most frequent in groups from 1 to 4 (n=626) and from 5 to 9 years (Figure 7). Regarding VL/HIV co-infection, most cases are concentrated in males in groups from 35 to 49 years (35), from 20 to 34 (19) and from 50 to 64 years (11), and in females (n=27), the high distribution of new cases is in groups of 35 to 49 (7), from 20 to 34 years (4) from 15 to 19 and from 5 to 9 years (both with 4) (**Figure 5**).

Figure 5. Age pyramid of new cases of VL and VL/HIV co-infection, according to sex, between 2007 and 2022, in Bahia, Brazil.



Related to clinical signs and symptoms of all cases (new, recurrence and hospital transference), the prevalence of fever was significantly (X^2: 5.760; p-Value: 0.016) higher (90.0%) with VL isolated than with VL/HIV co-infection (83.2%) (**Figure 6**). The presence of edema was significantly (X^2: 5.437; p-Value: 0.020) higher in VL cases (30.4%) than in VL/HIV co-infection (20.3%). For the other clinical signs and symptoms as weakness, weight loss, cough and/or diarrhea, pallor, spleen enlargement, infectious condition, hemorrhagic phenomena, liver enlargement, jaundice there were no difference at their frequences between cases of VL and VL/HIV co-infection.

Figure 6. Prevalence and respective 95% confidence intervals of clinical signs and symptoms of cases of VL and in VL/HIV coinfection, between 2007 and 2022 in Bahia state, Brazil.

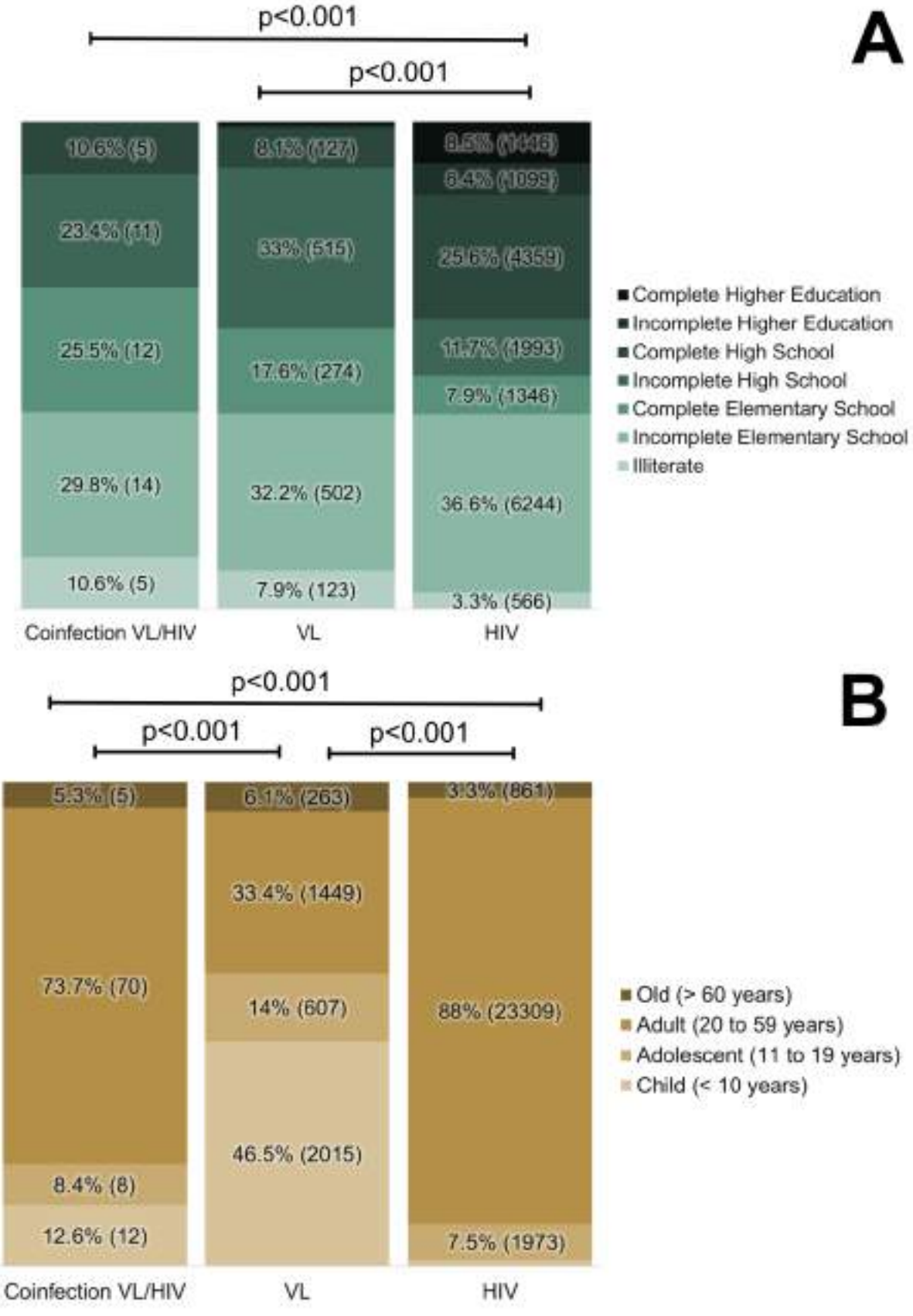


Most patients with isolated VL had completed high school (33.0%; 515/1561), with VL/HIV had completed elementary school (29.8%; 14/47) and with isolated HIV had completed elementary school (36.6%; 6244/17053) (**Figure 7A**). Significant differences in education pattern, regarding the distribution and proportion of categories, were found only between the groups with isolated HIV and VL/HIV coinfection and isolated VL (both with $p<0.001$). However, the proportions of illiterate individuals with complete elementary school and with incomplete high school were not statistically different among the three infected groups ($p=0.861$ and $p=0.191$, respectively). The field of education was ignored in 64.4% (2820), 50.5% (48) and 36.6% (9835) of the cases of VL, VL/HIV and HIV, respectively, thus they were not included at calculation of frequences.

Analyzing the data for the age group, the patients with both HIV and VL/HIV co-infection were mostly adults (88%and 73.7% respectively), however the percentage of child was higher (12,6%) in VL/HIV than HIV (1.3%), being significant differently the patterns of age group frequences between the VL and other both groups (HIV and VL/HIV; $p<0.001$ for both). On the other hand for VL isolated the major cases were child (46.5%; 2,015) and with higher frequence of adolescents (14.0%) than the other cases with a statistical different pattern

between them ($p<0.001$) (**Figure 7B**). However, the absence of a significant difference between adolescents and the old ($p=0.775$) suggests a similarity between these two groups in the context analyzed.

313 **Figure 7.** Characteristics associated with schooling (A) and age group (B) to the occurrence of
314 VL/HIV, VL isolate, and HIV isolate co-infection from 2008 to 2022 in the state of Bahia.

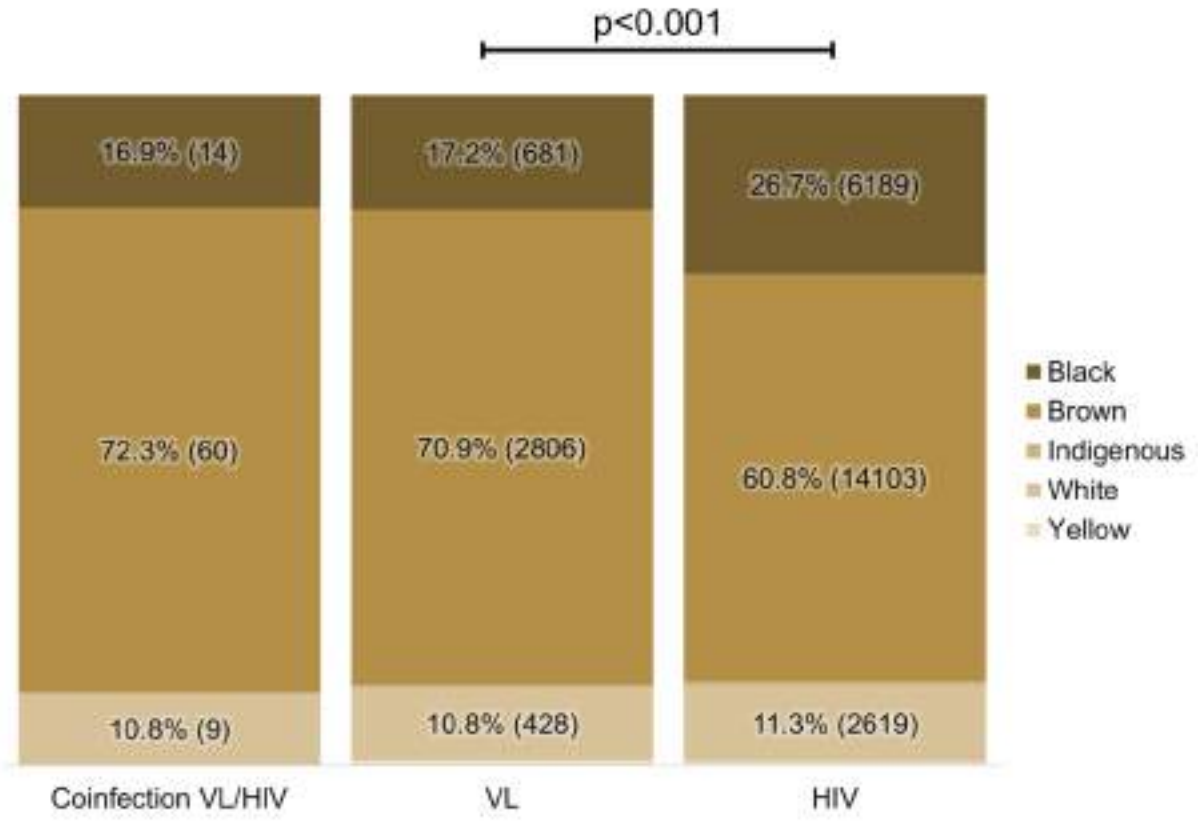


315

In the group with isolated VL, 96.3% (422) of patients were not pregnant. Among those with VL/HIV coinfection, 92.9% (13) were not pregnant. In contrast, in the HIV isolated group, 56.1% (5,968) of patients were pregnant, and 43.9% (4,678) were not. Significant differences were observed between VL/HIV and HIV isolated groups, as well as between VL isolated and HIV isolated groups ($p<0.001$), highlighting a higher prevalence of pregnant women in the HIV group. Additionally, comparisons between pregnant and non-pregnant women across groups showed a significant difference ($p<0.001$).

In the group with isolated VL, most patients were brown (70.9%; 2,806), followed by black (17.2%; 681). Among those with VL/HIV coinfection, 72.3% (60) were brown, and 16.9% (14) were black. In the HIV isolated group, brown patients also predominated (60.8%; 14,103), while 26.7% (6,189) were black (**Figure 8**). Significant differences in race/color were observed only between the isolated VL and isolated HIV groups ($p<0.001$). Additionally, significant differences were found among race/color categories, including yellow vs. indigenous ($p=0.003$), yellow vs. black, white vs. brown ($p=0.001$), and white vs. black, and brown vs. black ($p<0.001$). However, no significant differences were observed between yellow and white ($p=0.169$) or between indigenous and black ($p=0.554$).

Figure 8. Number and frequence of race/color of patients with of VL/HIV, VL isolate, and HIV isolate co-infection, from 2008 to 2022 in the state of Bahia.



Men were more frequently affected by both diseases, being 61.9% (2,709), 72.6% (1,670) and 53.1% (14,260), of them infected with VL, VL/HIV and HIV, respectively. Significant differences were observed between all couple of group cases, such as VL/HIV and VL ($p=0.032$), VL and HIV ($p<0.001$) and VL/HIV and HIV ($p<0.001$), indicating a higher prevalence of men in the VL and VL/HIV groups, while patients with HIV had a more balanced gender distribution.

Related to the residence, for VL and VL/HIV 1.1% (47 and 1, respectively) of cases lived in peri-urban area. Among the other areas (urban and rural), the most frequence of cases lived in urban, mostly for VL/HIV (79.6%; 74), and significantly higher ($p<0.001$) than for VL (52.4%; 2,228). Comparisons between rural and urban areas also showed significant differences ($p<0.001$). However, no significant differences were found between peri-urban and rural areas ($p=0.546$) or between peri-urban and urban areas ($p=1.000$).

Regarding patients treated with drugs, Pentavalent Antimony was the most frequently used for both diseases, but more frequently for VL (79.77%; 3,395/4,256) than for VL/HIV (52.0%; 51/98). Amphotericin B was the other most frequently used drug, but liposomal drugs were more frequently used than non-liposomal drugs for both diseases treated. Pentamidic drugs were administered exclusively for VL, but in less than 1% of cases. For VL, "other drugs" were also used in 7.24% of cases, and are commonly used as secondary treatment, since the elective drug is not effective or the patient cannot receive it. No drug was used in 2.84% (9) and in 97.16% (308) of the VL/HIV and VL cases, but it was not possible to identify their evolution (death or not) in the data record (**Table 1**).

The most frequent cases recorded were new cases, with 96.18% (4,381) and 86.36% of VL and VL/HIV, respectively. Recurrence was higher for VL/HIV (13.64%; 15) than for VL (3.82%; 174) and notifications marked as transfer and ignored were rare for both diseases. The most used diagnoses among positive cases of VL/HIV and VL were clinical-epidemiological (6.40% and 8.02%, respectively) and parasitological (5.23% for VL/HIV) and IFAT (5.66% for VL), reinforcing the relevance of laboratory confirmation and clinical-epidemiological evaluation in the detection of the disease. Among the negative results, clinical-epidemiological ones stand out (6.69% for VL/HIV and 8.02% for VL), indicating the importance of the clinical approach to exclude suspected cases.

Regarding the evolution of cases, cure was achieved in 10.81% (428) of VL cases and 10.84% (9) in VL/HIV co-infection. Deaths from other causes occurred in 70.88% (2,806) of VL cases and 72.29% (60) in co-infection. Deaths directly due to VL and cases of abandonment were observed exclusively in VL cases, with frequencies of 0.28% and 0.83% (11 and 33, respectively) (**Table 1**).

Table 1. Characteristics of initial drug administered, type of entry, types of diagnosis, and evolution in VL/HIV and VL coinfection from 2008 to 2022 in the State of Bahia.

Characteristic		Coinfection VL/HIV			VL		
		N	Freq (%)	CI 95%	N	Freq (%)	CI 95%
Initial Drug Administered	Amphotericin B	20	20.41	(12.43 - 28.39)	249	5.85	(5.15 - 6.56)
	Liposomal Amphotericin B	27	27.55	(18.71 - 36.40)	281	6.60	(5.86 - 7.35)
	Pentavalent Antimony	51	52.04	(42.15 - 61.93)	3395	79.77	(78.56 - 80.98)
	Pentamidine	0	0.00	-	23	0.54	(0.32 - 0.76)
	Other	0	0.00	-	308	7.24	(6.46 - 8.02)
	Not used*	9	-	-	308	-	-
	Ignored*	7	-	-	380	-	-
	Total	98			4256		
Input Type	New case	95	86.36	(79.95 - 92.78)	4381	96.18	(95.62 - 96.74)
	Relapse	15	13.64	(7.22 - 20.05)	174	3.82	(3.26 - 4.38)
	Transfer*	2	-	-	125	-	-
	Ignored*	2	-	-	122	-	-
	Total	110			4555		
Types of Diagnosis	Positive - Parasitological, IFAT and Others	2	0.58	(0.00 - 1.38)	54	0.35	(0.25 - 0.44)
	Positive - Parasitological and IFAT	12	3.49	(1.55 - 5.43)	326	2.10	(1.87 - 2.32)
	Positive - Parasitological and Others	11	3.20	(1.34 - 5.06)	223	1.43	(1.25 - 1.62)
	Positive - IFAT and Others	10	2.91	(1.13 - 4.68)	355	2.28	(2.05 - 2.52)
	Positive - Parasitological	18	5.23	(2.88 - 7.59)	445	2.86	(2.60 - 3.12)
	Positivo - IFAT	13	3.78	(1.76 - 5.79)	881	5.66	(5.30 - 6.03)
	Positive - Other	13	3.78	(1.76 - 5.79)	756	4.86	(4.52 - 5.20)

	Positive - Clinical-Epidemiological	22	6.40	(3.81 - 8.98)	1247	8.02	(7.59 - 8.44)
	Negative - Parasitological	12	3.49	(1.55 - 5.43)	370	2.38	(2.14 - 2.62)
	Negative - IFAT	11	3.20	(1.34 - 5.06)	401	2.58	(2.33 - 2.83)
	Negative - Other	14	4.07	(1.98 - 6.16)	447	2.87	(2.61 - 3.14)
	Negative - Clinical-Epidemiological	23	6.69	(4.05 - 9.33)	1248	8.02	(7.60 - 8.45)
	Not performed - Parasitological	59	17.15	(13.17 - 21.13)	3406	21.89	(21.24 - 22.54)
	Not realized - IFAT	62	18.02	(13.96 - 22.09)	2576	16.56	(15.97 - 17.14)
	Not performed - Other	62	18.02	(13.96 - 22.09)	2822	18.14	(17.53 - 18.75)
	Total	344			15557		
Evolution	Abandonment	0	0.00	-	33	0.83	(0.55 - 1.12)
	Cure	9	10.84	(4.15 - 17.53)	428	10.81	(9.84 - 11.78)
	Death from VL	0	0.00	-	11	0.28	(0.11 - 0.44)
	Death from other causes	60	72.29	(62.66 - 81.92)	2806	70.88	(69.46 - 72.29)
	Transfer	14	16.87	(8.81 - 24.92)	681	17.20	(16.03 - 18.38)
	Ignored*	12	-	-	422	-	-
	Total	83			3959		

Legend 2. *Not considered for frequency analysis; CI - Confidence Interval; IFAT - Indirect Fluorescent Antibody Test

Among new cases and recidivism, the main treatment was with antimonial pentavalent, however it was higher for new cases (80.87% and 66.44%, respectively) (**Table 2**). The patients with recidivism receive more amphotericin B liposomal and no liposomal (17.45% and 9.40%, respectively) than new cases (6.18% and 5.0%, respectively). Pentamidine was used most for new cases (21) and for transferred (2) cases. However, it is important to cite that transferred is not necessarily a severe case of the disease, it be a more accessible service for treatment.

The deaths of VL occurred mostly when using amphotericin B and amphotericin B Liposomal (15.4% for both), compared with the cure (4.7% and 5.7%, respectively) and deaths by other causes (12.7% and 12.7%, respectively) (**Table 2**). The Pentamidine was used mostly in cured cases (19) and just one death by VL. Other drugs for the treatment were used mostly in deaths by other causes (10.91%), perhaps because they are target to secondary choose or support for other complications. There was not abandoned of treatment when using Amphotericin B Liposomal.

For VL/HIV the new cases were more treated with antimonial pentavalent (59.04%) and the recidivism were treated most with amphotericin B liposomal (53.85%) followed by that amphotericin B (38.46%), such as the pattern of treatment of VL isolated. Regarding the deaths from VL the most of them was treated with antimonial pentavalent (66.67%), followed by amphotericin B (33.33%). There was no cases treated with amphotericin B liposomal that resulted in death by VL, however this drug was used in high percentage of cases that died from other causes.

Adolescent, child rand adult received more antimonial pentavalent for treat VL/HIV than older patients, which received more amphotericin B liposomal (23.65%) than that not liposomal (13.30%). No significant associations were found between confirmation criteria, evolution, or age group and type of drug ($p=0.382$, $p=1.000$, $p=0.246$, $p=0.266$, $p=0.297$, and $p=0.089$, respectively) (**Table 3**).

Table 2. Comparison of the initial drug administered with associated characteristics in VL isolated from 2008 to 2022 in the State of Bahia.

Characteristic		Amphotericin B		Amphotericin B Lipossomal		Antimonial Pentavalent		Pentamidine		Other		Total
		N	%	N	%	N	%	N	%	N	%	
Case Type	New case	216	5.50	243	6.18	3178	80.87	21	0.53	272	6.92	3930
	Recidivism	14	9.40	26	17.45	99	66.44	0	0.00	10	6.71	149
	Transfer*	12	11.01	9	8.26	74	67.89	2	1.83	12	11.01	109
	Ignored*	7	10.29	3	4.41	44	64.71	0	0.00	14	20.59	68
Evolution	Abandonment	2	8.33	0	0.00	20	83.33	0	0.00	2	8.33	24
	Care	148	4.67	180	5.69	2615	82.60	19	0.60	204	6.44	3166
	Death from VL	34	15.04	34	15.04	144	63.72	1	0.44	13	5.75	226
	Death from other causes	7	12.73	7	12.73	35	63.64	0	0.00	6	10.91	55
	Transfer*	19	7.66	19	7.66	191	77.02	0	0.00	19	7.66	248
	Ignored*	39	7.29	39	7.29	390	72.90	3	0.56	64	11.96	535
Age group	Child	109	5.46	124	6.21	1634	81.78	13	0.65	118	5.91	1998
	Adolescent	31	5.16	20	3.33	514	85.52	3	0.50	33	5.49	601
	Adult	81	5.85	86	6.21	1088	78.61	6	0.43	123	8.89	1384
	Old	27	11.74	48	20.87	128	55.65	1	0.43	26	11.30	230
	Ignored*	1	2.33	3	6.98	31	72.09	0	0.00	8	18.60	43

Legend 3. *Data not considered for chi-square analysis; Data not considered for chi-square analysis. IFAT - Immunofluorescent Antibody Test.

Table 3. Comparison of the initial drug administered with associated characteristics in VL/HIV co-infection from 2008 to 2022 in the State of Bahia.

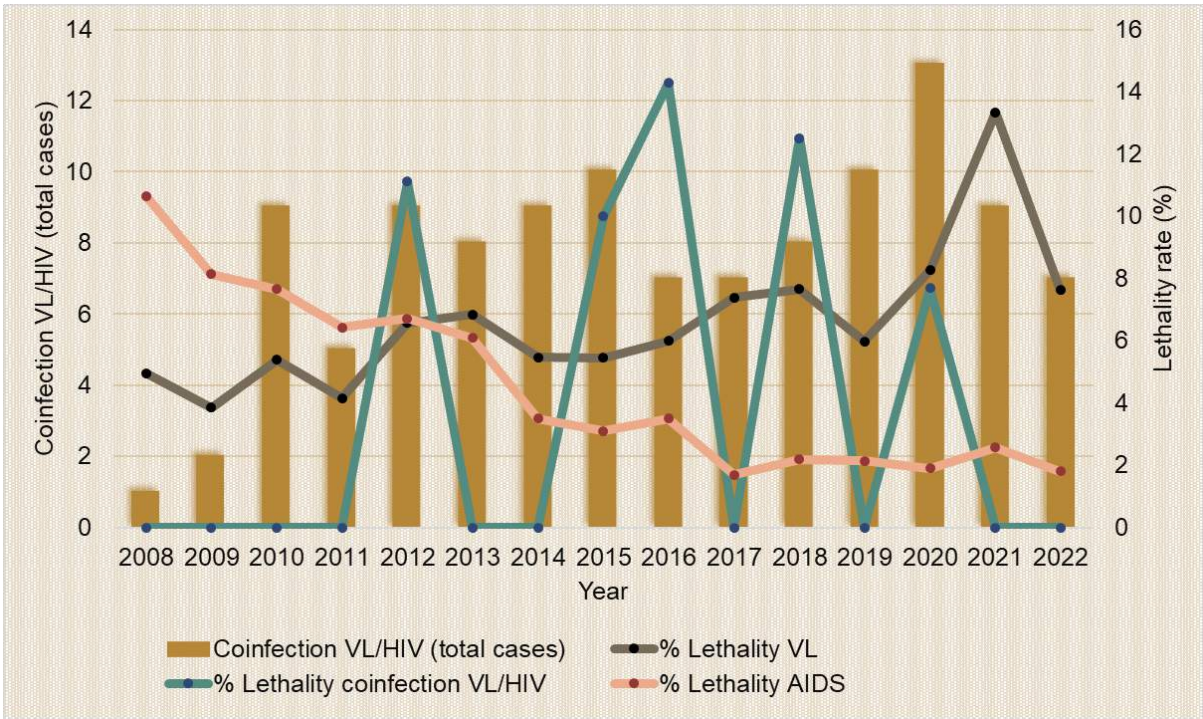
Characteristic		Amphotericin B		Amphotericin B Lipossomal		Antimonial Pentavalent		Total
		N	%	N	%	N	%	
Case Type	New case	15	18.07	19	22.89	49	59.04	83
	Recidivism	5	38.46	7	53.85	1	7.69	13
	Transfer*	0	-	1	50.00	1	50.00	2
Evolution	Care	14	22.58	14	22.58	34	54.84	62
	Death from VL	1	33.33	0	0.00	2	66.67	3
	Death from other causes	1	14.29	4	57.14	2	28.57	7
	Transfer	2	22.22	3	33.33	4	33.33	9
	Ignored*	2	-	6	35.29	9	52.94	17
Age group	Child	109	5.84	124	6.64	1634	87.52	1867
	Adolescent	31	5.49	20	3.54	514	90.97	565
	Adult	81	6.45	86	6.85	1088	86.69	1255
	Old	27	13.30	48	23.65	128	63.05	203
	Ignored*	1	2.86	3	8.57	31	88.57	35

Legend 4. *Data not considered for chi-square analysis; Data not considered for chi-square analysis. IFAT - Immunofluorescent Antibody Test.

During the period studied, the overall mortality coefficient for VL was higher than for VL/HIV (2.19, and 0.04 per 100 thousand inhabitants, respectively). The VL/HIV deaths occurred in Municipalities of América Dourada, Juazeiro, Salvador, São Francisco do Conde and Xique-Xique, both cities with one death each, located in the central-east, east, central-north and north health regions. In addition, among these deaths, 100% (n=5) of the victims had more than three VL symptoms, mainly severe symptoms, such as hemorrhagic phenomena (n=01/05) and liver enlargement (n=02/05). Regarding sociodemographic characteristics, 60% (n=03/05) of the deaths were male and of brown race/color, and 100% (n=05) of the victims only had incomplete elementary school.

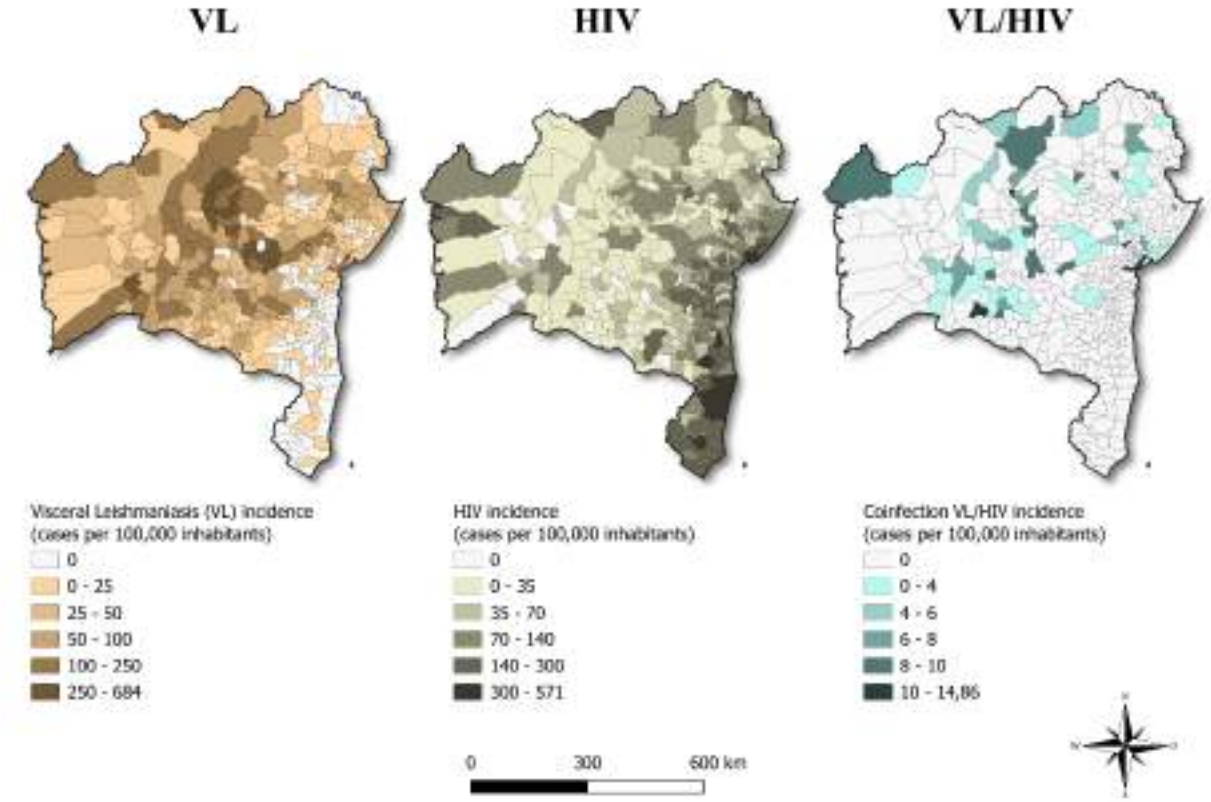
The lethality rate of VL has increased over the years, with its highest rate in 2021 (13.33%), and the lethality of AIDS has been a decreasing, thus the correlation of them was significant and inverse (rho=-0.729, p=0.003, R^2=0.287). In the case of VL/HIV, there were observed oscillation at lethality rate through the period, including zero cases in some years, however it is important to know that the number of cases of co-infection was also low in that period (maximum of 15). There was no significant correlation between lethality of VL/HIV co-infection and of AIDS (rho=-0.270, p=0.330, R^2= 0.000997) and of VL (rho=-0.190, p=0.270, R^2= 0.000865) (**Figure 9**).

Figure 9. Annual lethality rate of cases of VL, VL/HIV and AIDS in the state of Bahia, between 2008 and 2022.



The incidence of VL, HIV, and VL/HIV co-infection showed a distinct pattern of geographical distribution in the state, in which VL cases were more prevalent in the central and western areas, while HIV cases were clustered in the coastal and extreme southern regions and otherwise, the cases of VL/HIV co-infection are distributed spread throughout the state, excluding the south and extreme south sites **(Figure 10)**.

Figure 10. Spatial distribution of incidences of cases VL, HIV and VL/HIV co-infection by municipality in Bahia from 2008 to 2022.



The Moran's Global autocorrelation index (IMG) for the incidences was higher for HIV (0.581; sd = 0.0286), showing higher clusters of cases or absence of cases, followed by of VL (0.445; sd = 0.0296), and VL/HIV (0.108; sd = 0.0286).

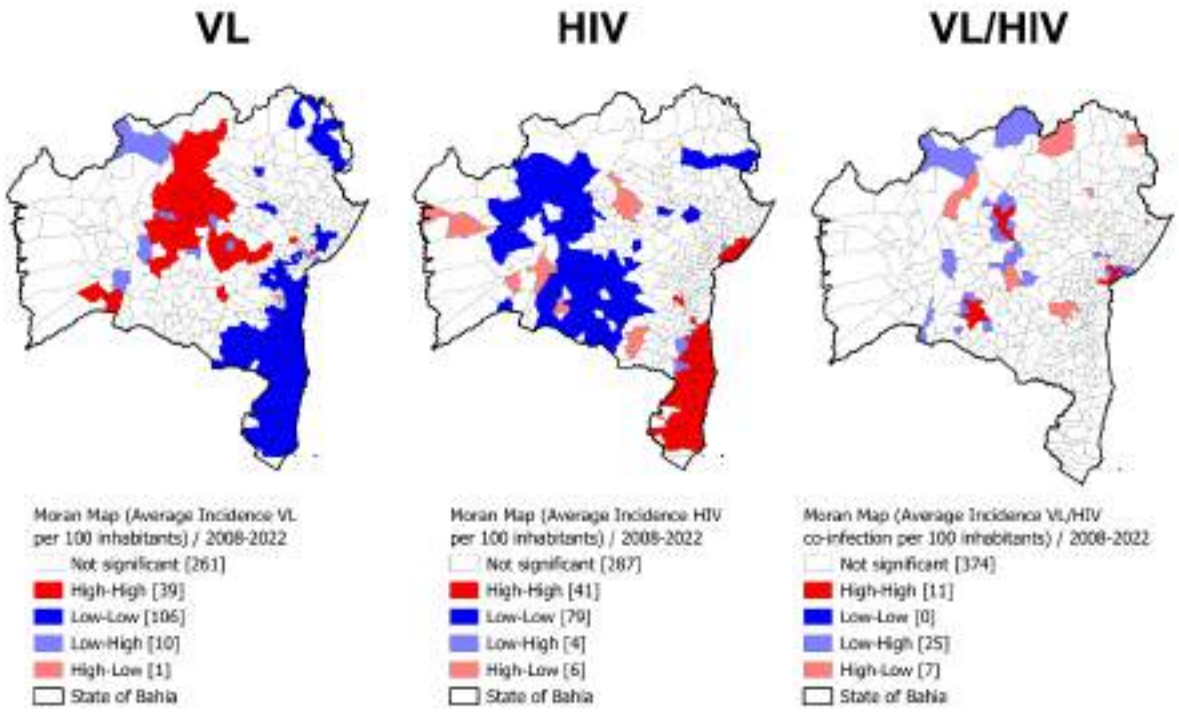
Regarding the incidence of VL, significant areas of spatial dependence were observed, as well as low or zero incidence in 25.42% (106/417) at the municipalities in the southern and extreme southern macro-regions (in dark blue "Low-Low" at **Figure 11**) and high concentration of cases in 9.35% (39) of the municipalities located in the central-eastern and central-northern macro-regions (in dark red "High-High" at **Figure 11**).

There were observed high concentration in the neighboring municipality in 6% (25) of the municipalities dispersed in all regions of the state (light blue "Low-High") and high concentration of cases in 2.64% (11) of the municipalities, located in the southwest and central-eastern macro-regions, highlighted in dark red "High-High" (**Figure 11**).

The incidence of isolated HIV cases, significant areas of spatial dependence were observed, as well as low or no incidence in 18.94% (79) of the municipalities in the southwest and west macro-regions (dark blue "Low-Low"), in addition to the high concentration of cases in 9.83% (41) of the municipalities, located in the south and far-south macro-regions, highlighted in dark red "High-High" (**Figure 11**).

In addition, regarding the incidence of isolated HIV cases, significant areas of spatial dependence were observed, as well as low or no incidence in 18.94% (79) of the municipalities in the southwest and west macro-regions (dark blue "Low-Low"), in addition to the high concentration of cases in 9.83% (41) of the municipalities, located in the south and far-south macro-regions, highlighted in dark red "High-High" (**Figure 11**).

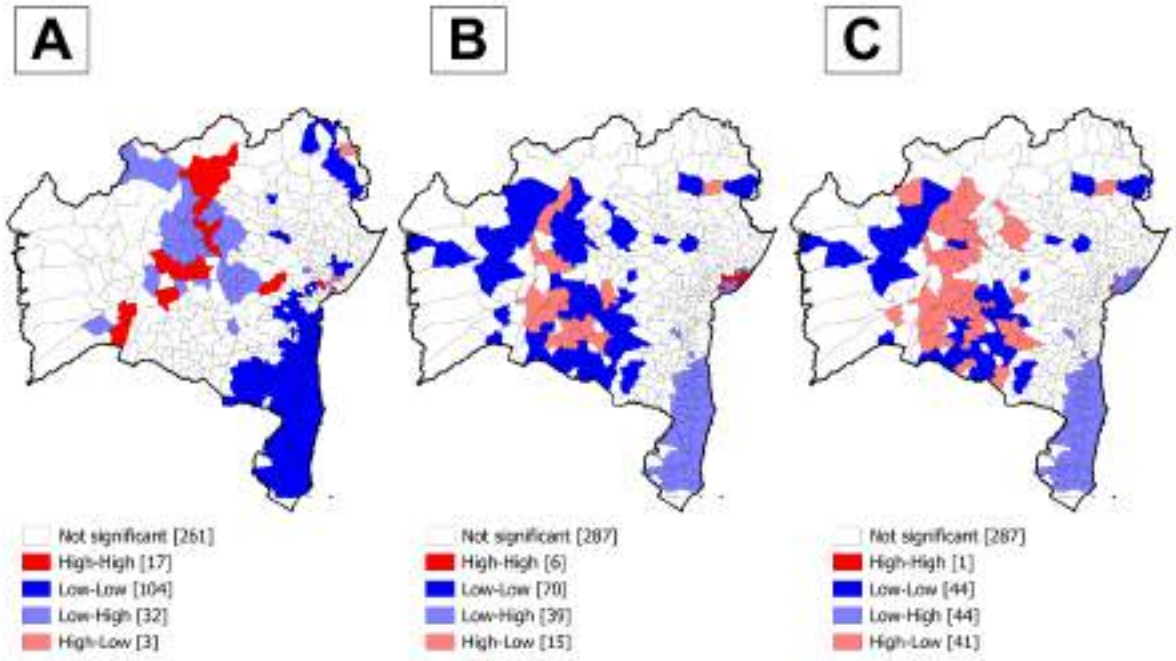
Figure 11. Moran's local indices of incidence of VL, HIV and VL/HIV cases (mean between 2008 and 2022), by municipality in Bahia state, Brazil.



Legend 5. The numbers in brackets represent the numbers of municipalities in each category.

The incidence of VL/HIV had a positive (direct) spatial correlation with the incidence of VL isolated (IMG: 0.213; sd = 0.0243). Moran's local bivariate analysis also indicated that the major municipality with significant correlation (39.85%; 104) are in the northern, southern and extreme southern areas of the state, presenting low incidence of VL/HIV coinfection and of VL isolated ("low-low" pattern; dark blue at Figure 12A). On the other hand, for the incidences of VL/HIV and HIV presented negative (inverse) correlation (IMG: -0.073; sd = 0.0212), in which there is of low coinfection and high incidence of HIV ("low-high" pattern) in 13.59% (39) of the municipalities in the southwest and west areas of the state. For the incidences of VL and HIV, there is also a negative (inverse) spatial correlation (IMG: -0.201; sd = 0.0216), with 15.33% (44) of the municipalities in the southwest and west areas of the state presenting low of VL and high of HIV ("low-hight" pattern) (**Figure 12**).

Figure 12. Local bivariate spatial correlation of the incidences of: A – VL/HIV coinfection and VL isolated; B - VL/HIV and HIV coinfection isolated; C - VL isolated and HIV isolated in the state of Bahia, Brazil, 2008-2022.



The analysis of the Bivariate IGM between VL/HIV co-infection and socio-environmental factors revealed a positive correlation for the Municipal Human Development

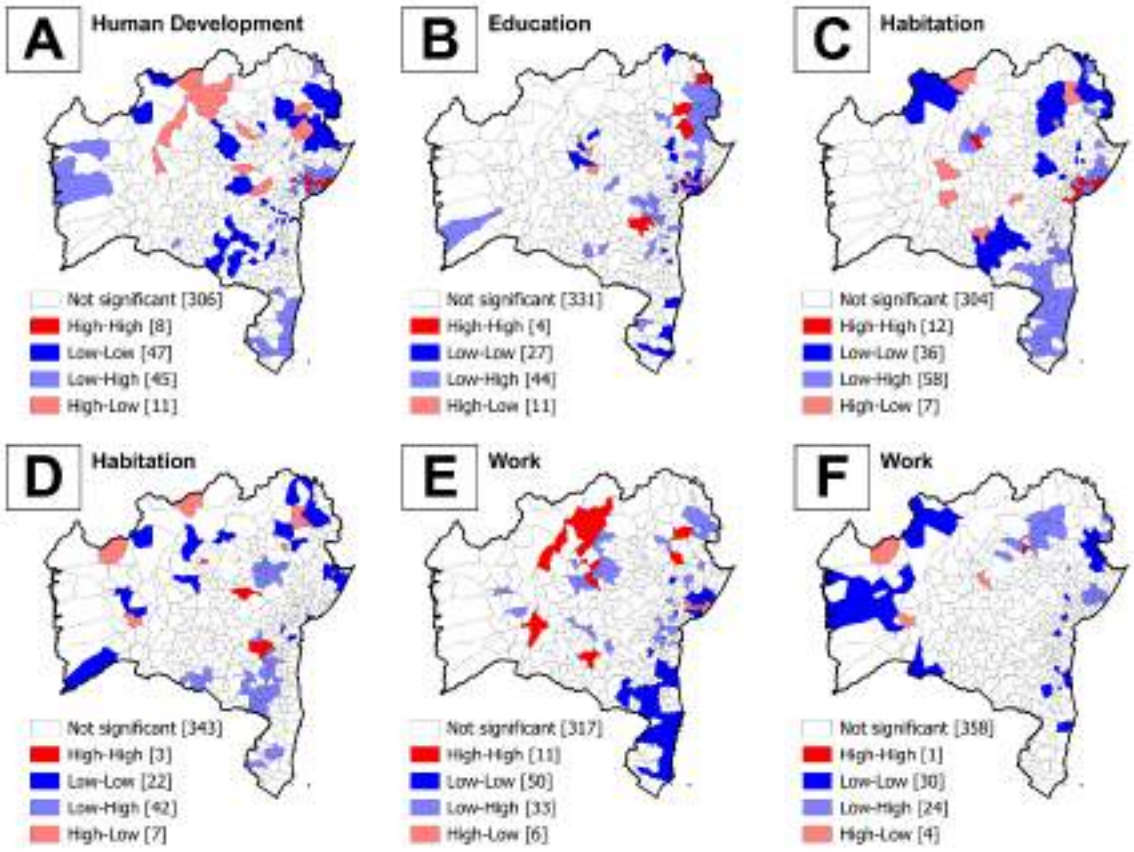
Index (IMG: 0.043; sd = 0.0212), access to piped water (IMG: 0.017; sd = 0.0206), and employment in the agricultural sector (IMG: 0.063; sd = 0.0211). In contrast, a negative correlation was found for the illiteracy rate (IMG: -0.098; sd = 0.0216), urban household waste collection (IMG: -0.066; sd = 0.021), and employment in the mining sector (IMG: -0.007; sd = 0.0215) (**Figure 13**).

A lower incidence of VL/HIV co-infection was associated with low MHDI (15.36%; 47/417), high illiteracy rates (13.29%; 55/417), and extensive waste collection coverage (12.24%; 42/417), with spatial patterns distributed mainly in the eastern, western, southwestern, and extreme southern regions. Conversely, a higher incidence of VL/HIV co-infection was observed in municipalities with greater agricultural employment (3.47%; 11/417), predominantly in the north and southwest, and in areas with better access to piped water (3.95%; 12/417), primarily in the eastern and northern regions (**Figure 13**).

Additionally, regions with significant mining employment (6.70%; 24/417) exhibited a negative correlation, indicating a lower incidence of the disease. (**Figure 13**).

Figure 13. Local bivariate spatial correlation of the incidence of VL/HIV co-infection with: A – Municipal Human Development Index (MHDI); B – Illiteracy rate; C – Percentage of the urban population residing in households connected to the water supply network; D – Percentage of the urban population served by regular household waste collection services; E – Percentage

496 of those employed in the agricultural sector; F – Percentage of those employed in the mineral
497 extractive sector, in the state of Bahia, period 2008-2022.

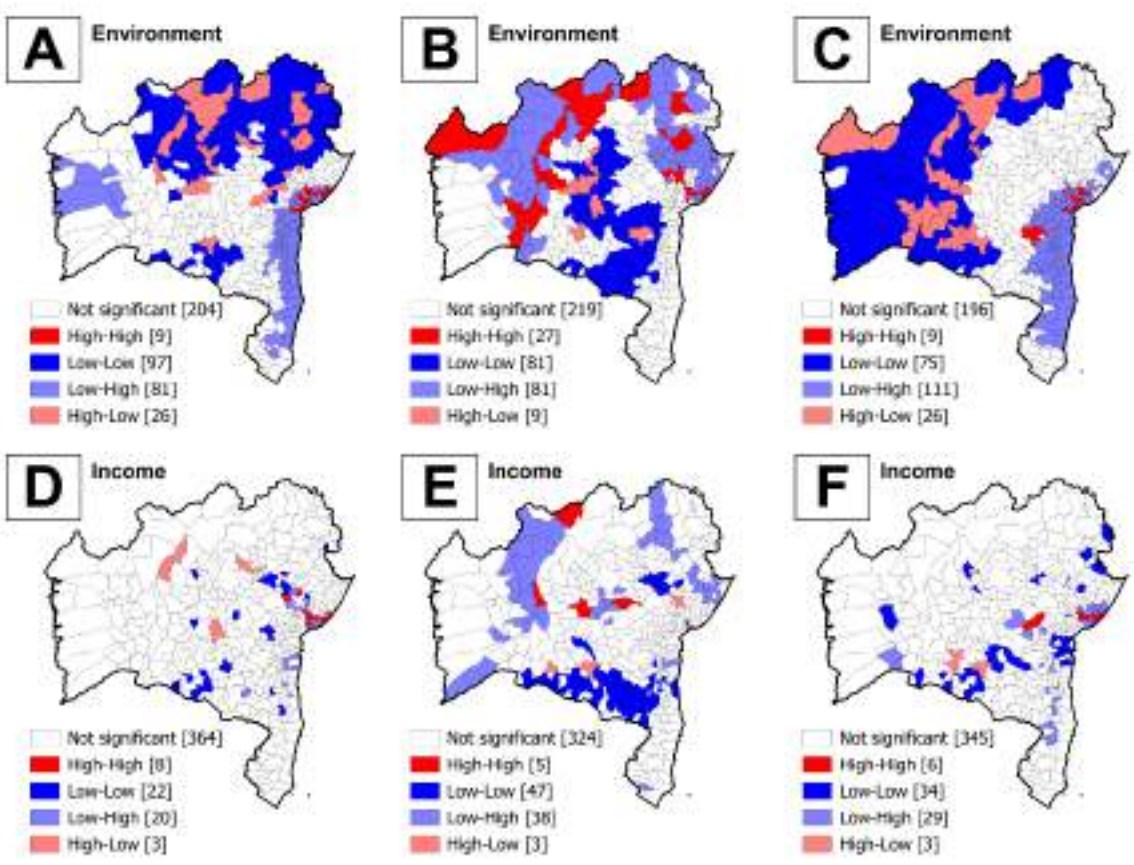


498

499 Continuing, the average rainfall (A) showed a negative correlation (IMG: -0.062; sd =
500 0.0207), with a predominance of low-low patterns in 47.55% (97) of the municipalities,
501 concentrated in the north and southwest regions. Regarding the mean temperature (B), a
502 positive association was identified (IMG: 0.060; sd = 0.0209). The high-high clusters
503 corresponded to 12.33% (27) of the municipalities, located in the central-north, north and west
504 areas, highlighted in red. These results suggest the existence of a direct influence, in which the
505 higher the incidence of VL/HIV co-infection, the higher the temperature. The mean moisture
506 content (C) exhibited a strong negative correlation (IMG: -0.155; sd = 0.0216). In this context,
507 low-high patterns prevailed in 56.63% (111) of the municipalities, distributed in the eastern,
508 southern and extreme southern regions of the state. These results highlight areas that indicate
509 low incidence of the disease and high humidity (**Figure 14**).

In the case of Gross Domestic Product (GDP) (D), a direct (positive) correlation was identified (IMG: 0.055; sd = 0.0218). High-high clusters represented 2.20% (8) of the municipalities, indicating an association between higher incidence of the disease and locations with greater economic prosperity. Nevertheless, for the Gini Index (E), a direct correlation was detected (IMG: 0.056; sd = 0.0215). High-high patterns were identified in 1.54% (n=5) of the areas, distributed in the central and northern regions of the state. Even so, the unemployment rate (F) showed an inverse association (IMG: -0.015; sd = 0.0211). In this sense, low-high clusters predominated in 8.41% (29) of the municipalities, distributed among the eastern, southwestern, and southern regions of the state of Bahia (**Figure 14**).

Figure 14. Local bivariate spatial correlation of the incidence of VL/HIV co-infection with: A – Mean Rainfall; B – Average Temperature; C – Average Humidity; D – Gross Domestic Product (GDP); E – Gini Index; F – Unemployment Rate, in the state of Bahia, period 2008-2022.



Consequently, socioeconomic variables related to poverty and access to social programs were investigated. Regarding the percentage of poor (A), it showed a positive association (IMG:

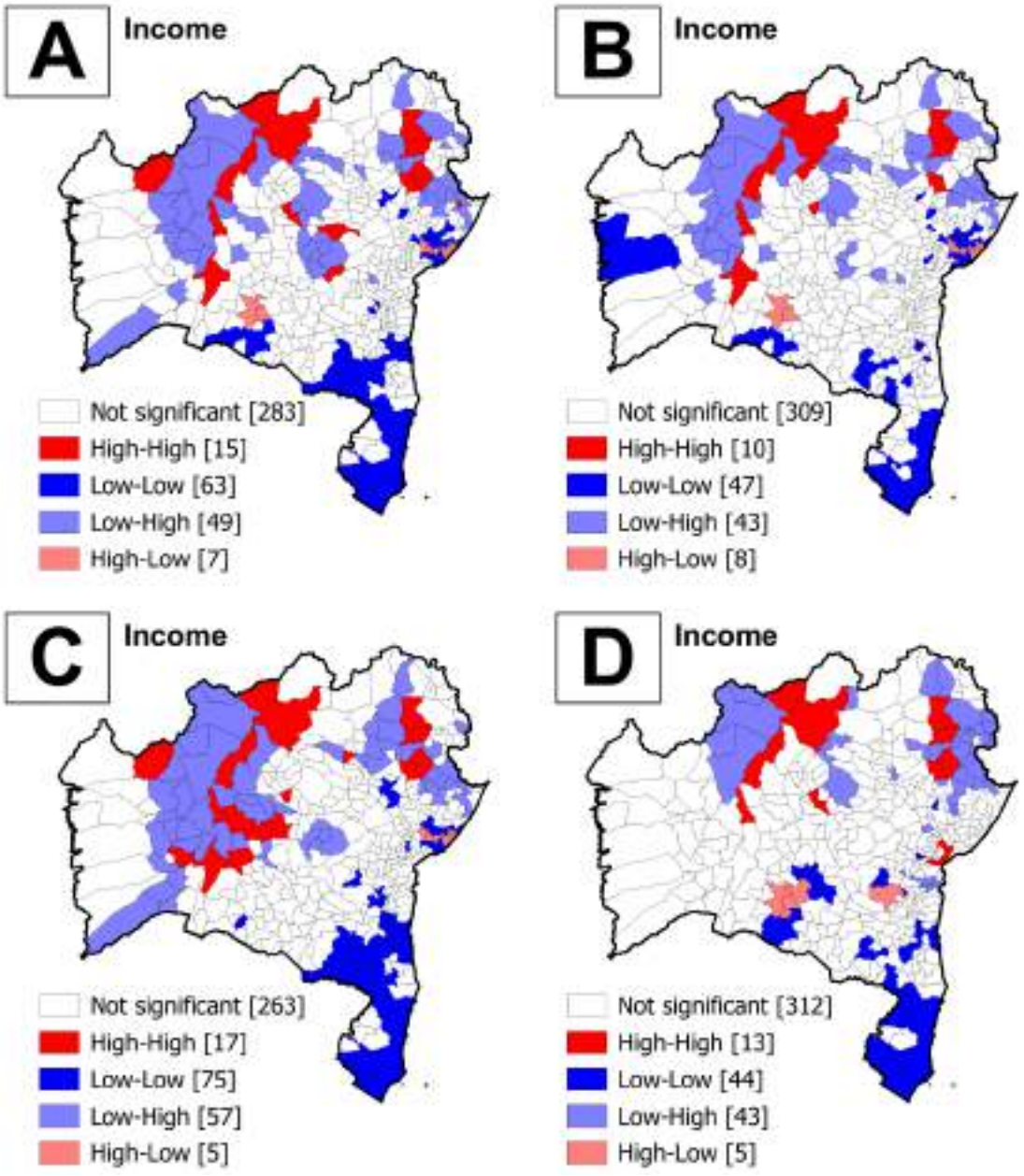
0.059; sd = 0.0214), with 5.30% (15) of the municipalities having high-high clusters, widely distributed in areas of the central-north and west regions, indicating a high incidence of the disease and a high poverty rate. The proportion of people vulnerable to poverty (B) also revealed a direct correlation (IMG: 0.042; sd = 0.0213). In this context, high-high patterns prevailed in 3.24% (10) of the municipalities, also highlighting the same regions, central-north and west (**Figure 15**).

When the percentage of extremely poor people (C) was analyzed, a positive (direct) association was found (IMG: 0.079; sd = 0.0213). Low-low patterns were predominant in 28.52% (75) of the localities, while high-high clusters were concentrated in 6.46% (17) of the municipalities, revealing areas in which both variables have a direct relationship. Finally, the proportion of people enrolled in CadÚnico or beneficiaries of Bolsa Família (D) showed a direct correlation (IMG: 0.055; sd = 0.0214). High-high clusters appeared in 4.17% (13) of the localities, while low-low patterns were recorded in 14.10% (44) of the municipalities (**Figure 15**).

These results reinforce the existence of a significant relationship between the variables analyzed. It is observed that the increase in the incidence of VL/HIV co-infection is associated with a higher proportion of people benefiting from social programs or in conditions of poverty. Conversely, the reduction in cases of co-infection corresponds to a lower proportion of those enrolled in these programs or with higher income.

Figure 15. Local bivariate spatial correlation of the incidence of VL/HIV co-infection with: A – Percentage of Poor; B – Percentage of Vulnerable to Poverty; C – Percentage of Extremely

Poor; D – Percentage of people enrolled in CadÚnico or beneficiaries of Bolsa Família, in the state of Bahia, period 2008-2022.

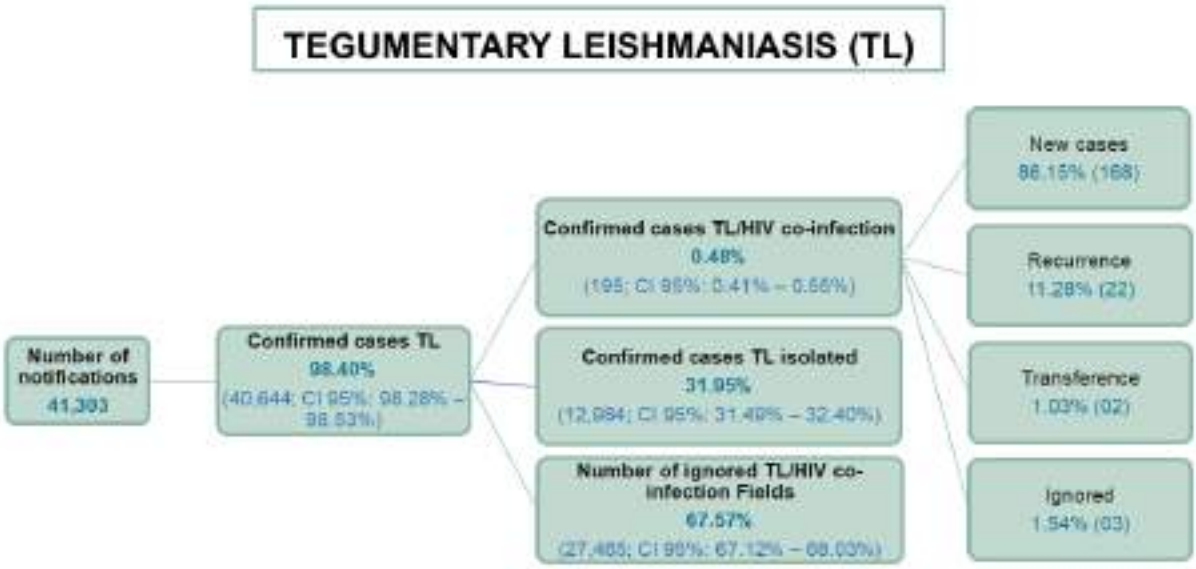


TL and TL/HIV coinfection

Also in the period from 2008 to 2022, 41,303 cases of LT were reported, of which 98.40% (40,644/41,303) were confirmed for the disease, 0.48% (195/40,644; 95% CI: 0.41% - 0.55%) of them as LT/HIV coinfection, and 86.15% (168/195; 95% CI: 81.31% - 91.00%) of the coinfected cases classified as new cases. The other 659 (1.6%) of LT were not confirmed

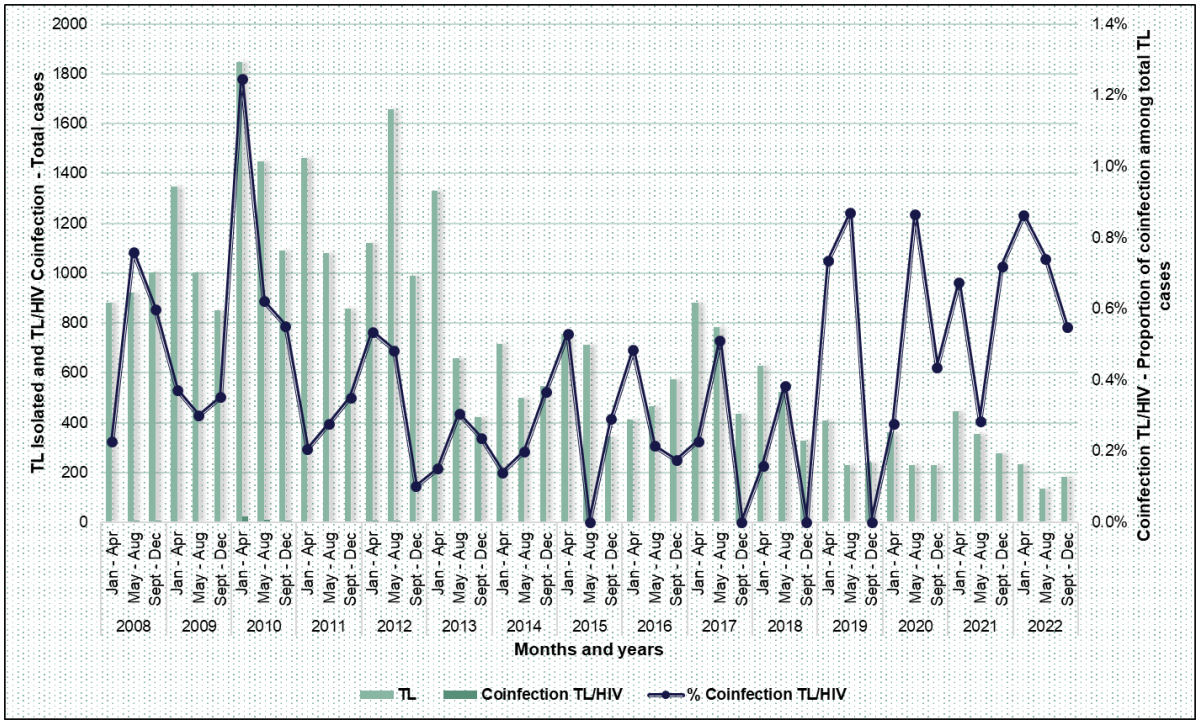
because there was a change in diagnosis, a negative result in the confirmatory test or the deadline for confirmation had not ended (**Figure 16**).

Figure 16. Description of the number of reports and frequency of cases of TL isolated and in co-infection with HIV, according to the type of entry and confirmatory status.



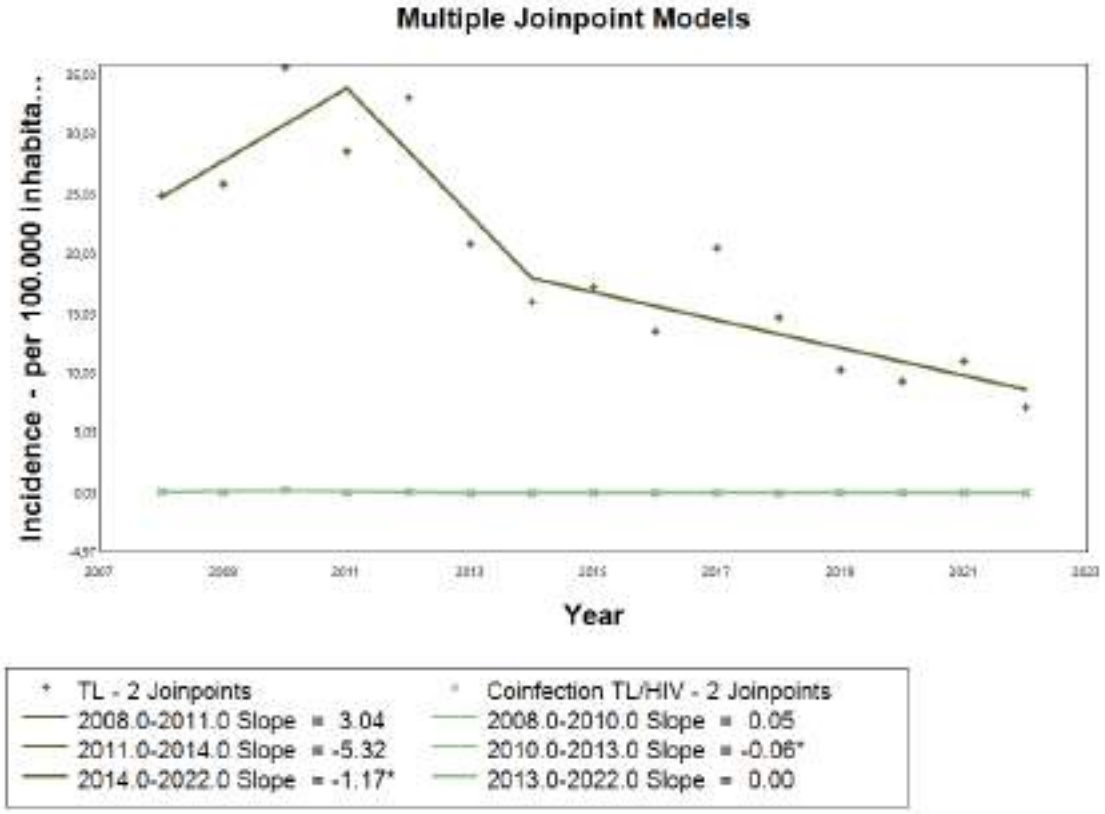
In relation to TL, the temporality of the cases shows an increase in the number of cases, with a considerable increase in 2010 (Jan-Apr: 1848), 2011 (Jan-Apr: 1463) and 2012 (May-Aug: 1658) and a decrease after that (mean: 2.98; standard deviation: 3.72). When analyzing the proportion of cases of TL/HIV co-infection, the four-month period from January to April 2010 stands out, with 1.24% (23/1848; CI 95%: 0.74% - 1.75%), with the highest proportions of TL/HIV co-infection (**Figure 17**). Although few numbers of cases were recorded in May to August 2019and 2020, they represented 0.87% TL/HIV co-infection (2/230; CI 95%: -0.33% – 2.07% and /231; CI 95%: -0.33% – 2.06%, respectively). No significant correlation was found between the number of total TL cases and the proportion of TL/HIV co-infection cases, in Spearman's correlation analysis, (rho= -0.088, p=0.563, R^2=0.005).

Figure 17. Number of total TL cases and proportion of TL/HIV co-infection within TL isolated, by four -month period and year of first symptoms.



In the case of TL, the Joinpoint regression analysis showed an increase of cases (slope: 3.04) until 2010, with significant broke to downward trend in the period until 2014 (slope: -5.23; CI 95%: -1.51 – 0.18; p-Value: 0.012), and with other broke turning to slope: -1.17 in the subsequent period. Regarding TL/HIV co-infection, there is also a similar pattern, increasing until 2010 (slope: 0.05), with significant broke to downward trend in the period from 2010 to 2013 (slope: -0.06; CI 95%: -0.08 – -0.04; p-Value: 0.025), and followed by another broke with a slope of 0.00, representing establishment of cases during the period (**Figure 18**).

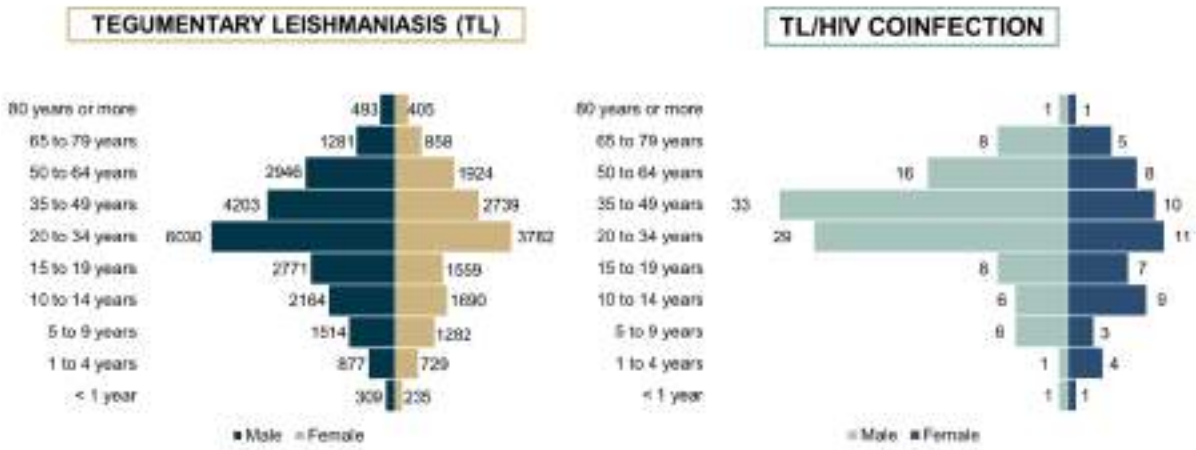
581 **Figure 18.** Trend of the Joinpoint regression coefficient of the incidence of TL and in TL/HIV
582 co-infection in Bahia, 2008-2022.



583

584 The age pyramid of new cases of isolated TL and TL/HIV co-infection also shows
585 different distribution according to age group and most frequence in males (22,588 and 109;
586 respectively). For isolated TL the cases in males are more frequent in groups from 20 to 34
587 (6030), from 35 to 49 (4,203) and from 50 to 64 years (946). In females (15,203), cases also
588 occur in greater numbers in the age groups of 20 to 34 years (3,782), 35 to 49 years (2,739) and
589 50 to 64 years (1,924), respectively (Figure 8). In cases of TL/HIV co-infection, the most
590 frequence in males is in groups from 35 to 49 (33), from 20 to 34 (29) and from 50 to 64 years
591 (6), being the age groups with the highest number of cases, respectively. For females, the
592 distribution of new cases is mostly in the groups from 20 to 34 years (11), from 35 to 49 years
593 (10) and from 10 to 14 years (9), respectively (**Figure 19**).

Figure 19. Age pyramid of new cases of TL and TL/HIV co-infection, according to sex, between 2007 and 2022, in Bahia, Brazil.

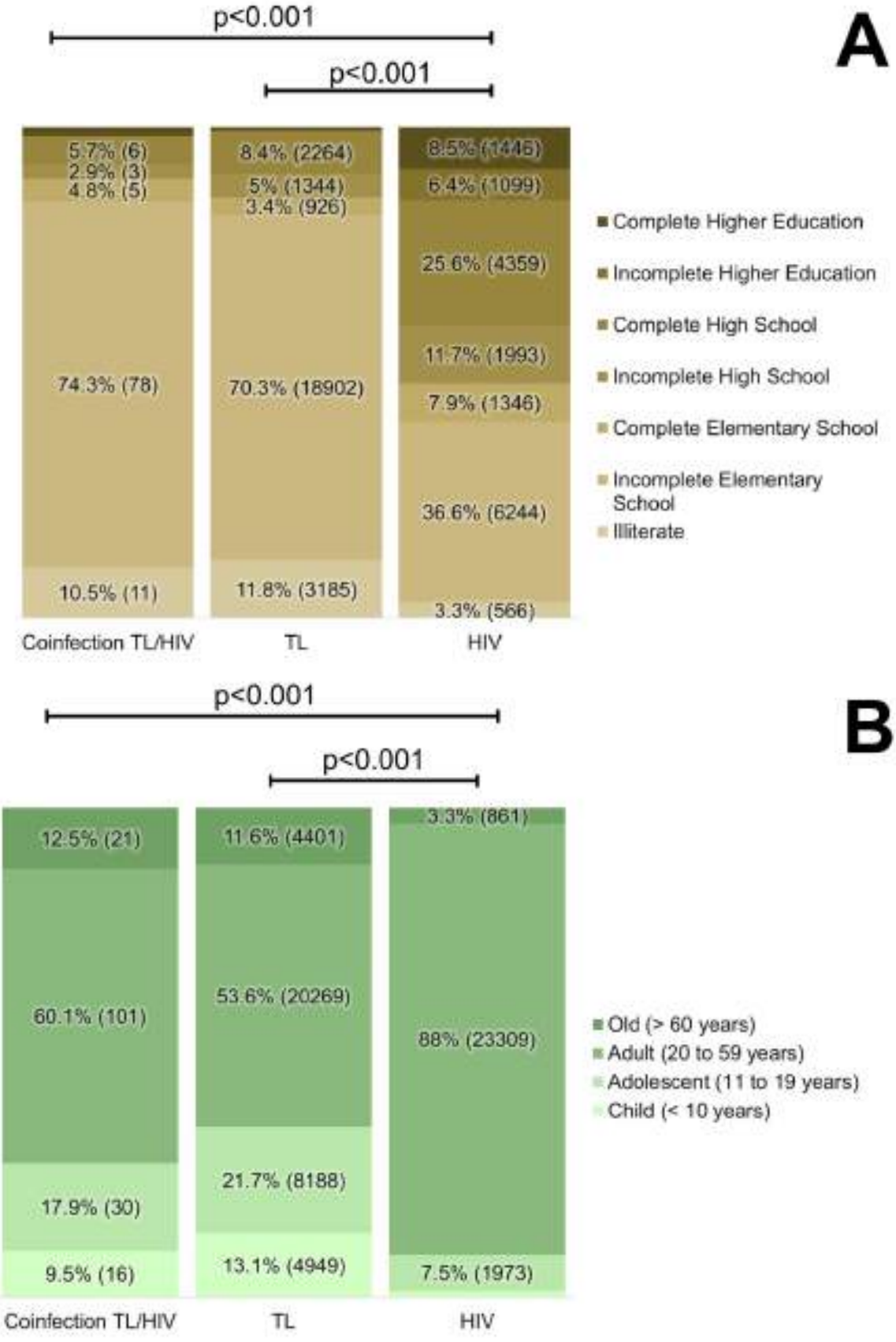


Regarding the clinical data of TL and TL/HIV co-infection, significant results were observed regarding the higher prevalence of the presence of mucosal lesions, with 8.9% (95% CI: 4.62% - 13.24%) of the cases in TL/HIV co-infection, than in cases of isolated TL, with 3.8% (95% CI: 3.50% - 4.19%; X^2: 11.352; p-Value <0.001). The skin lesions were higher frequent in both (TL and TL/HIV), with almost 100%.

In the group with isolated TL, most patients had completed primary education (70.3%; 18,902), and 11.8% (3,185) were illiterate. The education field was ignored in 28.9% (10,927) of cases. Among patients with TL/HIV coinfection, 74.3% (78) had completed primary education, 10.5% (11) were illiterate, and the education field was ignored in 37.5% (63). In the isolated HIV group, education was more diverse: 36.6% (6,244) had incomplete primary education, 25.6% (4,359) completed secondary education, 8.5% (1,446) had higher education, and the education field was ignored in 36.6% (9,835) (**Figure 20A**). Significant differences were observed between TL/HIV and isolated HIV, as well as between isolated TL and isolated HIV (p<0.001), with TL groups showing a higher proportion of incomplete primary education. However, no statistical significance was found between complete elementary and incomplete high school (p=0.419) or between complete and incomplete higher education (p=0.126).

In the group with isolated TL, adults represented the majority (53.6%; 20,269), followed by other age groups. Among TL/HIV coinfection cases, adults were also predominant (60.1%; 101). In the isolated HIV group, adults accounted for 88% (23,309), with the age group field ignored in only 1.5% (408) of cases. Significant differences were observed between TL, TL/HIV, and HIV groups ($p<0.001$), consistently reinforcing the predominance of adults across all groups (**Figure 20B**). Statistical analysis between age groups showed significant distinctions in all comparisons, including adolescents vs. adults, children vs. adults, and the elderly vs. other groups ($p<0.001$), highlighting marked differences across age categories.

Figure 20. Characteristics associated with schooling (A) and age group (B) to the occurrence of TL/HIV, TL isolate, and HIV isolate co-infection from 2008 to 2022 in the state of Bahia.

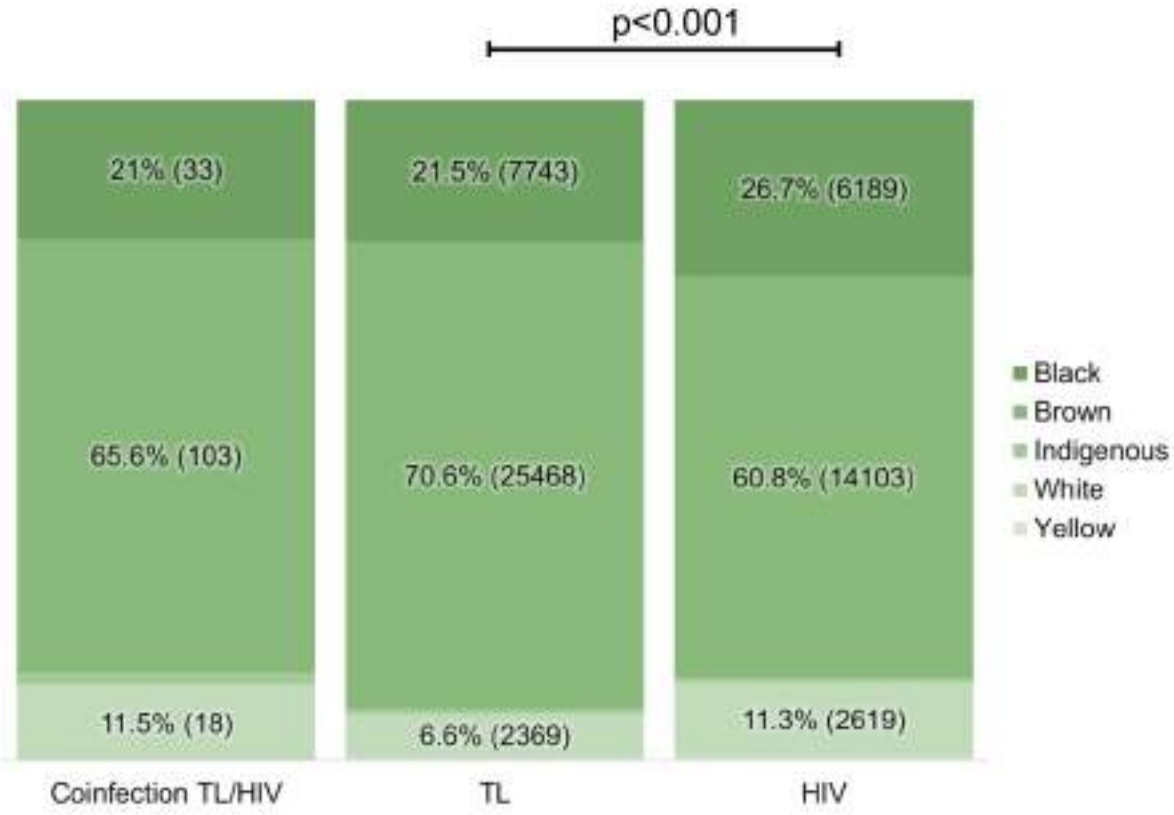


621

In the isolated TL group, 97.9% (8,853) of patients were not pregnant, and 2.1% (193) were pregnant. Among TL/HIV coinfection cases, 96.6% (28) were not pregnant, and 3.4% (1) were pregnant. In contrast, in the isolated HIV group, 56.1% (5,968) were pregnant, and 43.9% (4,678) were not. The pregnant field was ignored or not applied in 76.1% (28,761) of TL cases, 82.7% (139) of TL/HIV cases, and 60.4% (16,242) of HIV cases. These differences ($p<0.001$) highlight a higher prevalence of pregnant women in the isolated HIV group, while non-pregnant women predominated in TL and TL/HIV groups.

Considering the data regarding race/color, in the isolated TL group, most patients identified as brown (70.6%; 25,468), followed by black (21.5%; 7,743) and white (6.6%; 2,369). Among TL/HIV coinfection cases, 65.6% (103) were brown, 21% (33) were black, and 11.5% (18) were white. In the isolated HIV group, 60.8% (14,103) identified as brown, 26.7% (6,189) as black, and 11.3% (2,619) as white. The race/color field was ignored or not applicable in 4.6% (1,751) of TL cases, 6.5% (11) of TL/HIV cases, and 13.8% (3,703) of HIV cases. Significant differences were observed between TL isolated and HIV isolated groups ($p<0.001$), with a predominance of brown patients across all groups (**Figure 21**). Most comparisons between race/color categories were statistically significant ($p<0.001$), except for yellow vs. brown ($p=0.169$), yellow vs. black ($p=0.318$), and indigenous vs. brown ($p=0.115$), which showed no significant differences.

Figure 21. Characteristics associated with race/color to the occurrence of TL/HIV, TL isolate, and HIV isolate co-infection from 2008 to 2022 in the state of Bahia.



In the isolated TL group, males predominated (59.8%; 22,588) compared to females (40.2%; 15,203). Among TL/HIV coinfection cases, 64.9% (109) were male, and 35.1% (59) were female. In the isolated HIV group, males represented 53.1% (14,260), and females accounted for 46.9% (12,582). Unknown gender cases comprised 4.6% (16) in TL cases and 0.2% (46) in HIV cases. Significant differences were observed between TL isolated and HIV isolated ($p<0.001$) and between TL/HIV coinfection and HIV isolated ($p=0.003$), highlighting a higher prevalence of males across all groups. Statistical analysis also revealed significant differences between sexes overall ($p<0.001$), reinforcing the trend of male predominance.

When analyzing the TL data, for the type of entry of the notified cases, it is observed that, for isolated TL, most cases are classified as new cases, with 93.69% (10,171), while in TL/HIV co-infection this frequency is lower, with 89.33% (134). Recurrence in co-infected patients represents 10.67% of cases (16), compared to 6.31% (685) in isolated TL. Notifications

655 marked as transfer and ignored were only observed in isolated TL cases, with absolute
656 frequencies of 68 and 61, respectively (**Table 4**).

657 Similarly, when analyzing the clinical form of reported cases, most isolated TL cases
658 were cutaneous (95.86%; 10,530), while this frequency was lower in TL/HIV coinfection
659 (88.24%; 135). The mucosal form was more frequent in coinfected patients (11.76%; 18)
660 compared to isolated TL (4.14%; 455). For confirmation criteria, laboratory confirmation was
661 predominant in isolated TL (65.59%; 7,205) and lower in TL/HIV coinfection (64.05%; 98).
662 The clinical-epidemiological criterion was used in 34.41% (3,780) of isolated TL cases and
663 35.95% (55) in coinfected cases (**Table 4**).

664 Regarding the epidemiological classification, most isolated TL cases were
665 autochthonous (91.56%; n=10,058), with a lower frequency in TL/HIV coinfection (84.97%;
666 n=130). Imported cases accounted for 3.57% (n=392) in isolated TL and 8.50% (n=13) in
667 coinfected patients. Indeterminate cases were more frequent in isolated TL (4.87%; n=535) than
668 in coinfection (6.54%; n=10) (**Table 4**).

669 Finally, with regard to the evolution of reported cases, most isolated TL cases were
670 discharged due to cure (95.51%; n=10,492), while this frequency was lower in TL/HIV
671 coinfection (88.89%; n=136). Cases of abandonment occurred in 97.60% (n=244) of isolated
672 TL cases and 3.92% (n=6) of coinfections. Deaths due to TL were recorded only in isolated TL
673 cases (100%; n=22). Deaths from other causes were more frequent in isolated TL (95.40%;
674 n=83) than in coinfection (4.60%; n=4). Transferred cases were also higher in isolated TL
675 (95.36%; n=144) compared to coinfection (4.64%; n=7) (**Table 4**).

676 Data on TL isolated and TL/HIV coinfection could not be compared by medications or
677 diagnostic methods due to the absence of these details in the analyzed database.

678 **Table 4.** Characteristics of initial drug administered, type of entry, types of diagnosis, and evolution in TL/HIV and TL coinfection from 2008 to
679 2022 in the State of Bahia.

Characteristic		Coinfection TL/HIV			TL		
		n	Freq (%)	CI 95%	n	Freq (%)	CI 95%
Input Type	New case	134	89.33	(84.39 - 94.27)	10171	93.69	(93.23 - 94.15)
	Relapse	16	10.67	(5.73 - 15.61)	685	6.31	(5.85 - 6.77)
	Transfer*	2	-	-	68	-	-
	Ignored*	1	-	-	61	-	-
	Total	150			10856		
Clinical Form	Skin	135	88.24	(83.13 - 93.34)	10530	95.86	(95.49 - 96.23)
	Mucosa	18	11.76	(6.66 - 16.87)	455	4.14	(3.77 - 4.51)
	Total	153			10985		
Confirmation Criteria	Clinical-Epidemiological	55	35.95	(28.34 - 43.55)	3780	34.41	(33.52 - 35.30)
	Laboratory	98	64.05	(56.45 - 71.66)	7205	65.59	(64.7 - 66.48)
	Total	153			10985		
Epidemiological Classification	Autochthonous	130	84.97	(79.3 - 90.63)	10058	91.56	(91.04 - 92.08)
	Imported	13	8.50	(4.08 - 12.92)	392	3.57	(3.22 - 3.92)
	Indeterminate	10	6.54	(2.62 - 10.45)	535	4.87	(4.47 - 5.27)
	Total	153			10985		
Evolution	Abandonment	6	3.92	(0.85 - 7.00)	244	2.22	(1.95 - 2.50)
	Discharged by cure	136	88.89	(83.91 - 93.87)	10492	95.51	(95.12 - 95.90)
	Death from TL	0	0.00	-	22	0.20	(0.12 - 0.28)
	Death from other causes	4	2.61	(0.09 - 5.14)	83	0.76	(0.59 - 0.92)

	Transfer	7	4.58	(1.26 - 7.89)	144	1.31	(1.10 - 1.52)
	Total	153			10985		

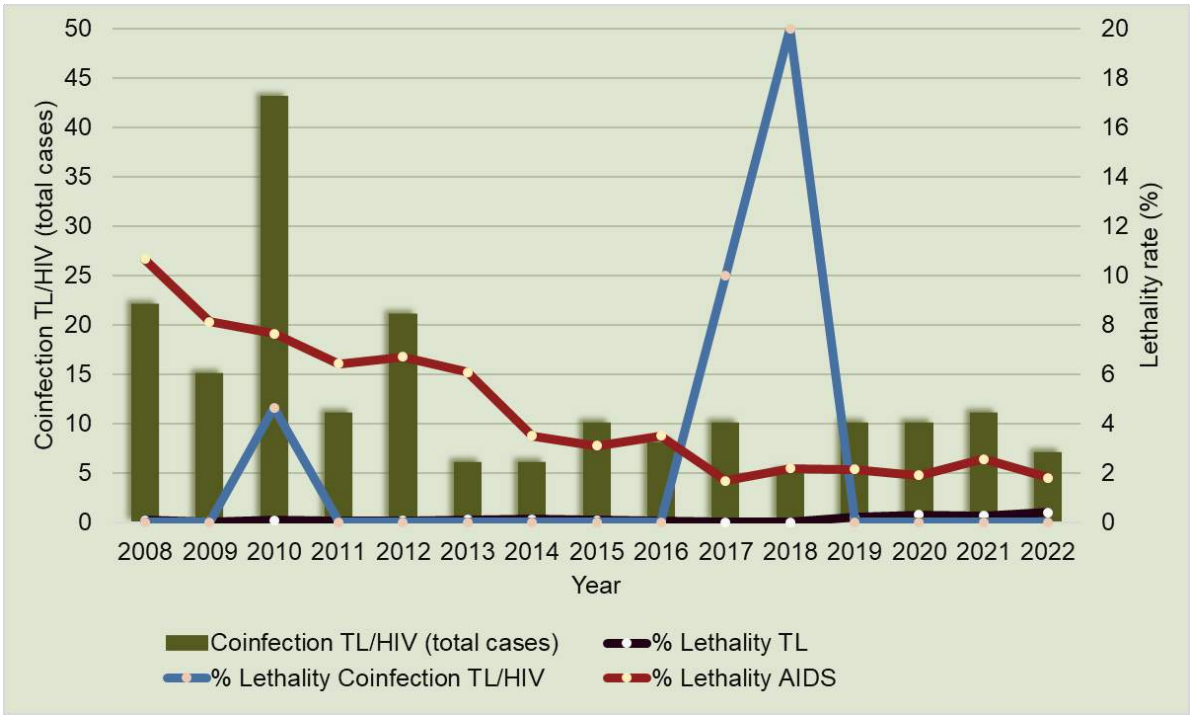
Legend 6. *Not considered for frequency analysis; CI - Confidence Interval.

The overall mortality rate for isolated LT was 0.26 per 100,000 population, while the mortality rate for LV/HIV coinfection was 0.03 per 100,000 population. As for deaths from LT/HIV, they occurred entirely in the municipalities of Ibirataia, Itabuna, Jaborandi and Pau Brasil, both with one death each, located in the south and west health regions, affecting 50% of adults (2), 25% of children (1) and 25% of the elderly (1). Regarding sociodemographic characteristics, 50% (02/04) of deaths were male and black, with 75% (3) of the victims having only incomplete elementary education and one death having incomplete high school education.

Regarding TL, the case lethality rate remains constant over the years (around 0% and 0.40%), increasing during the years 2019 to 2022, with 0.21%, 0.30%, 0.26%, and 0.40%, respectively. On the contrary, the lethality of AIDS had been a decrease over the years (from 10.66% to 1.80%). When compare lethality of both TL and TL/HIV co-infection over the years, a significant and inverse correlation was observed (rho=-0.549, p=0.034, R^2=0.176). In the case of coinfection, there were records only in 2010, 2017 and 2018, with a lethality rate of 4.65%, 10% and 20%, respectively, which is higher than the other years (around 0%). There was no significant correlation between lethality of TL/HIV co-infection and AIDS (rho=-0.232, p=0.405, R^2= 0.075) (**Figure 22**).

Figure 22. Annual lethality rate of TL, TL/HIV co-infection and AIDS in the state of Bahia.

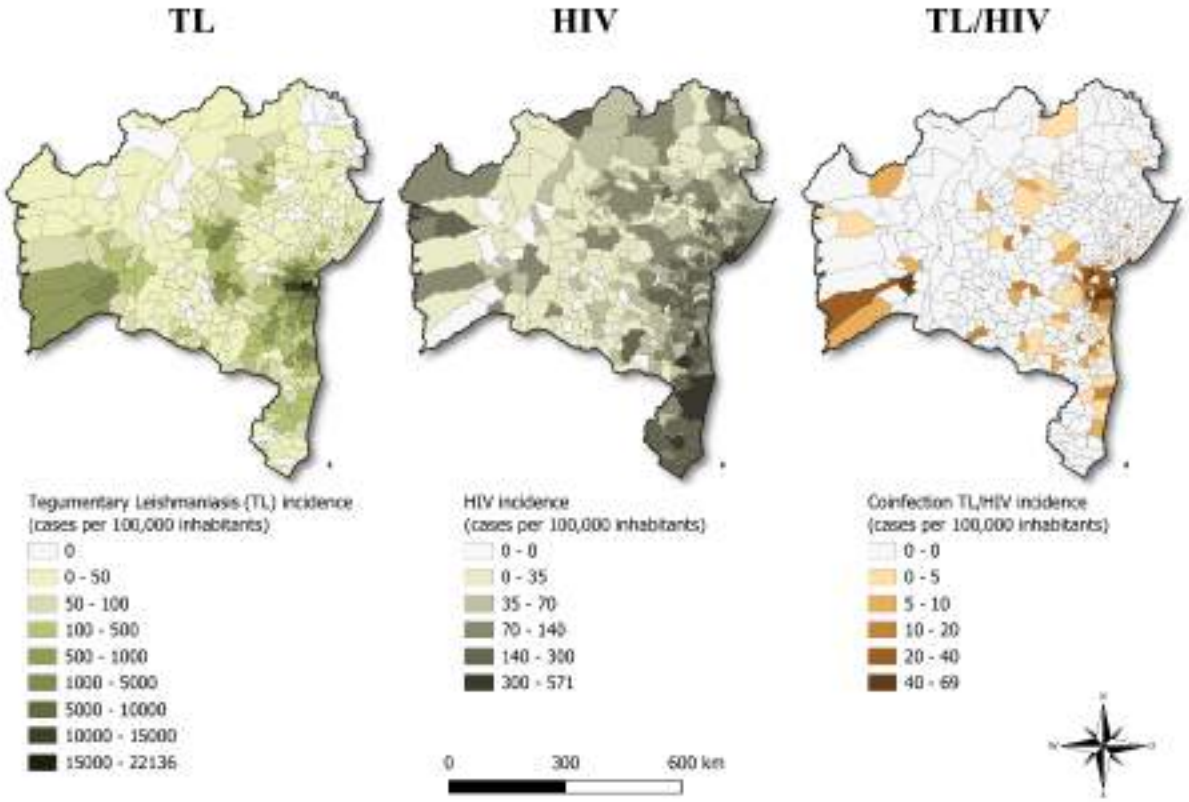
699 **Figure 23.** Annual lethality rate of TL, TL/HIV co-infection and AIDS in the state of Bahia,
700 Brazil.



701

702 Regarding the spatial distribution of TL, HIV and TL/HIV co-infection in the state, there
703 is a distinction between the patterns of both diseases. It is observed that TL cases occurred with
704 a higher incidence in the southern and western regions, while HIV cases were grouped in the
705 coastal and extreme southern areas. In addition, cases of TL/HIV co-infection are present in
706 focal sites, where their intensity is also related to the incidence of isolated VL, intercepting with
707 these municipalities (**Figure 23**).

Figure 24. Spatial distribution of incidences of TL, HIV and TL/HIV coinfection by municipality in Bahia from 2008 to 2022.



The Moran Global autocorrelation indices for the incidence of TL isolated, HIV isolated, and TL/HIV co-infection were positive, with IMG: 0.619 (sd = 0.0280), IMG: 0.581 (sd = 0.0286) and IMG: 0.426 (sd = 0.0276), respectively.

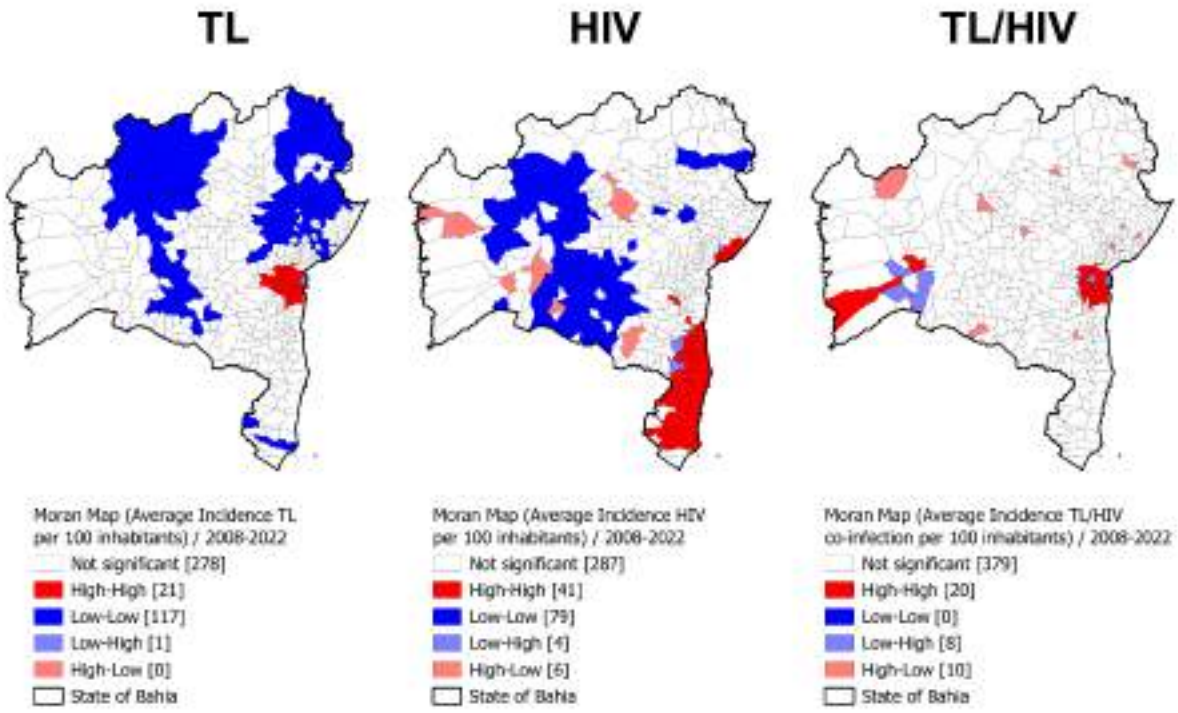
When analyzing the incidence of isolated TL cases, significant areas of spatial dependence were also observed, with a high concentration of cases in 5.04% (21) of the municipalities located in the southern region, highlighted in dark red "High-High". Low or no prevalence was also observed in 28.06% (117) of the municipalities dispersed among the southwest, central-east, central-north, and north macro-regions (dark blue "Low-Low") (**Figure 24**).

In addition, regarding the incidence of isolated HIV cases, significant areas of spatial dependence were observed, as well as low or no incidence in 18.94% (79) of the municipalities in the southwest and west macro-regions (dark blue "Low-Low"), in addition to the high

723 concentration of cases in 9.83% (41) of the municipalities, located in the south and far-south
724 macro-regions, highlighted in dark red "High-High" (**Figure 24**).

725 Finally, it is worth highlighting the incidence of TL/HIV co-infection, in which
726 significant areas of spatial dependence were observed, with a high concentration of cases in
727 4.80% (20) of the municipalities located in the south and west regions, highlighted in dark red
728 "High-High". A high incidence is also observed in the local and high chance in the neighboring
729 municipality in 2.40% (10) of the municipalities dispersed among the macro-regions of the state
730 (light red "High-Low") (**Figure 24**).

731 **Figure 25.** Moran's local indices of incidence of TL, HIV and TL/HIV co-infection.

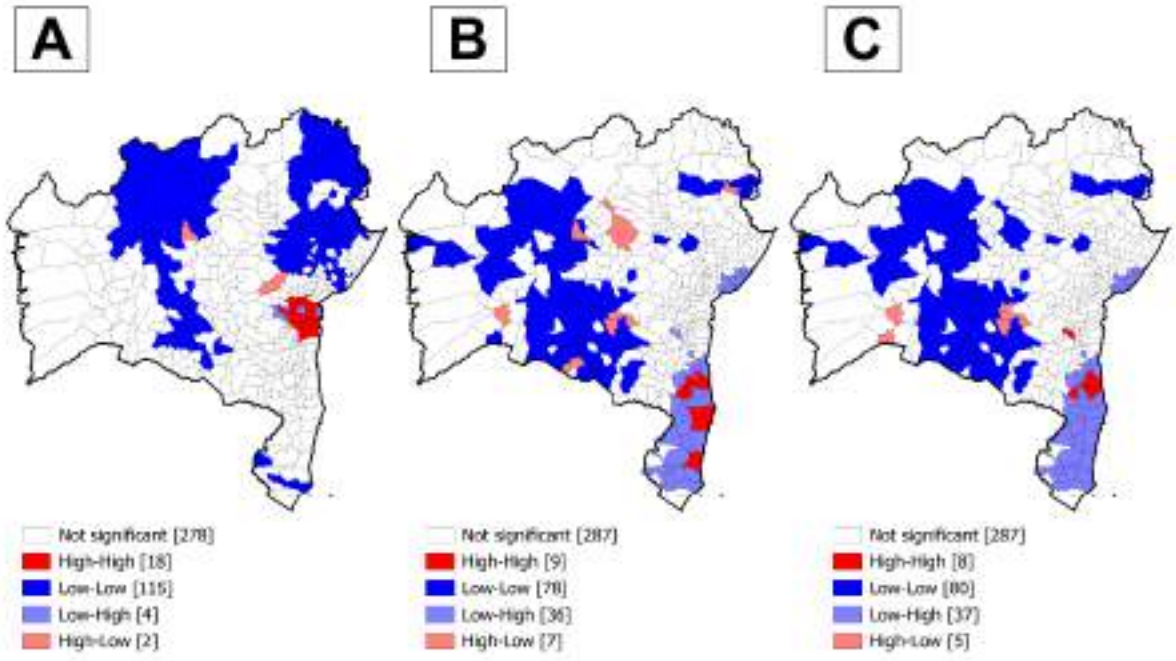


732

733 Moran's global bivariate index showed that the incidence of TL/HIV had a positive
734 (direct) spatial correlation with the incidence of TL isolated (IMG: 0.462; sd = 0.0248). In the
735 local results, it is observed that 41.37% (115) of the municipalities in the northern,
736 southwestern, and western areas of the state showed a low-low pattern between the incidence

of TL/HIV co-infection and the incidence of TL isolated. There was a predominance of direct correlation between TL/HIV co-infection and HIV isolated (IGM = 0.087; sd = 0.0223). Thus, the bivariate LISA shows that most municipalities (27.18%; 78) also had a low-low incidence of both diseases. Finally, the bivariate spatial correlation of TL isolated with HIV isolated, Moran's global statistic showed a positive correlation (IMG: 0.071; sd = 0.0214). Regarding the local Moran index, 27.87% (80) of the municipalities also had a low incidence of both diseases (**Figure 25**).

Figure 26. Local bivariate spatial correlation of the incidences of: A - TL/HIV co-infection and TL isolated; B - TL/HIV and HIV co-infection isolated; C - TL isolated and HIV isolated in the state of Bahia, 2008-2022.



Continuing with the analysis, the spatial associations related to TL/HIV co-infection and several socio-environmental variables were evaluated. In this sense, the association between TL/HIV co-infection and MHDI (A) was positive (IMG: 0.043; sd = 0.0212), with low-low clusters, mostly observed in 16.99% (52) of the municipalities, concentrated in areas of the

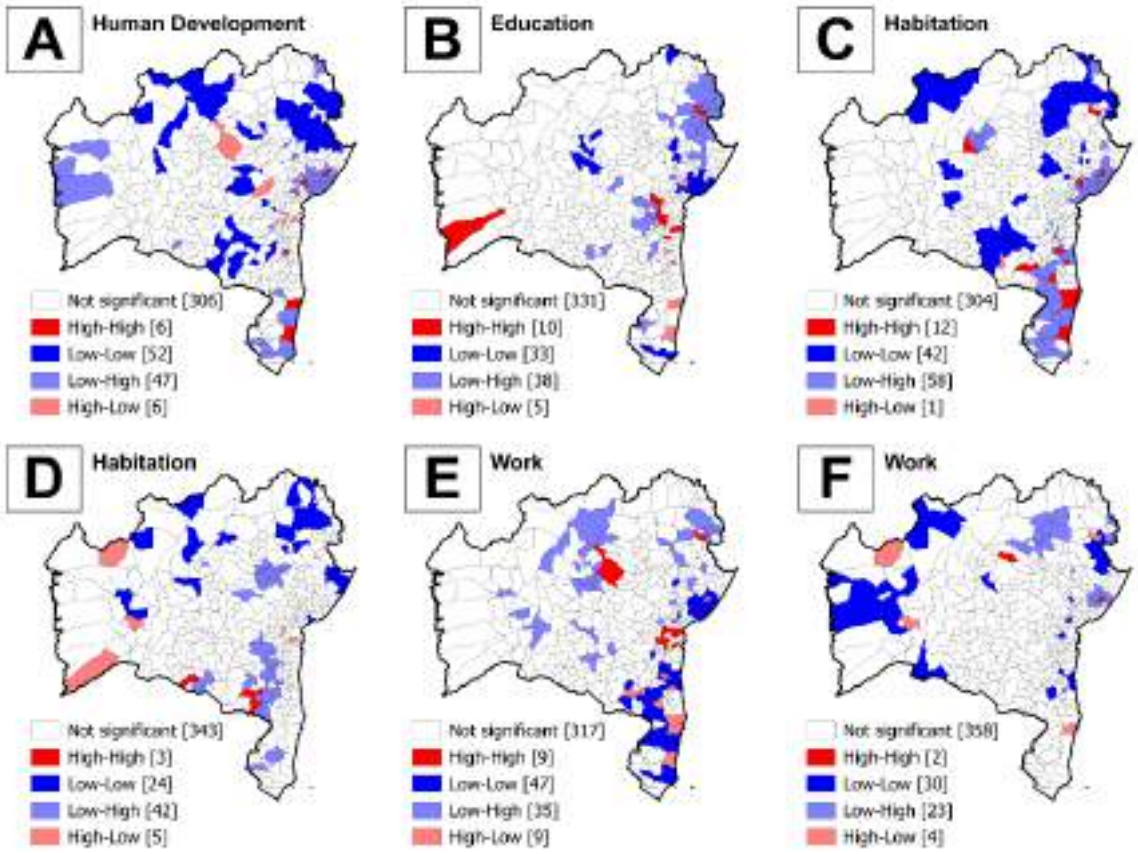
752 southwest, north, and central-north regions, indicating low incidence of the disease and low
753 MHDI. As for the illiteracy rate (B), a significant inverse correlation was identified (IMG: -
754 0.098; sd = 0.0216), reflecting a concentration of low-high patterns in 11.48% (38) of the
755 municipalities, concentrated mainly in the northern region (**Figure 26**).

756 Regarding the percentage of households with access to piped water (C), the positive
757 (direct) correlation observed (IMG: 0.017; sd = 0.0206) showed low-low clusters in 13.82%
758 (42) of the municipalities. In the case of the percentage of persons in urban households served
759 by household waste collection (D), the association was inverse (IMG: -0.066; sd = 0.0210).
760 Low-high patterns represented 12.24% (42) of the localities, suggesting that the south and
761 central-east regions have a low incidence of co-infection and a high percentage of household
762 waste collection (**Figure 26**).

763 In relation to those employed in the agricultural sector (E), there was a direct correlation
764 (IMG: 0.063; sd = 0.0211), with high-high patterns present in 2.84% (9) of the municipalities,
765 concentrated in the southwest and south regions. This result demonstrates that the higher the
766 incidence of TL/HIV co-infection, the greater the professional activity in the agricultural sector.
767 On the other hand, employment in the mining sector (F) showed a negative relationship (IMG:
768 -0.007; sd = 0.0215). Low-high clusters were observed in 6.42% (23) of the localities, indicating
769 low incidence of the disease and high occupation in the mining sector, grouped in the north and
770 east of the state (**Figure 26**).

771 **Figure 27.** Local bivariate spatial correlation of the incidence of TL/HIV co-infection with: A
772 – Municipal Human Development Index (MHDI); B – Illiteracy rate; C – Percentage of the
773 urban population residing in households connected to the water supply network; D – Percentage
774 of the urban population served by regular household waste collection services; E – Percentage

of those employed in the agricultural sector; F – Percentage of those employed in the mineral extractive sector, in the state of Bahia, period 2008-2022.



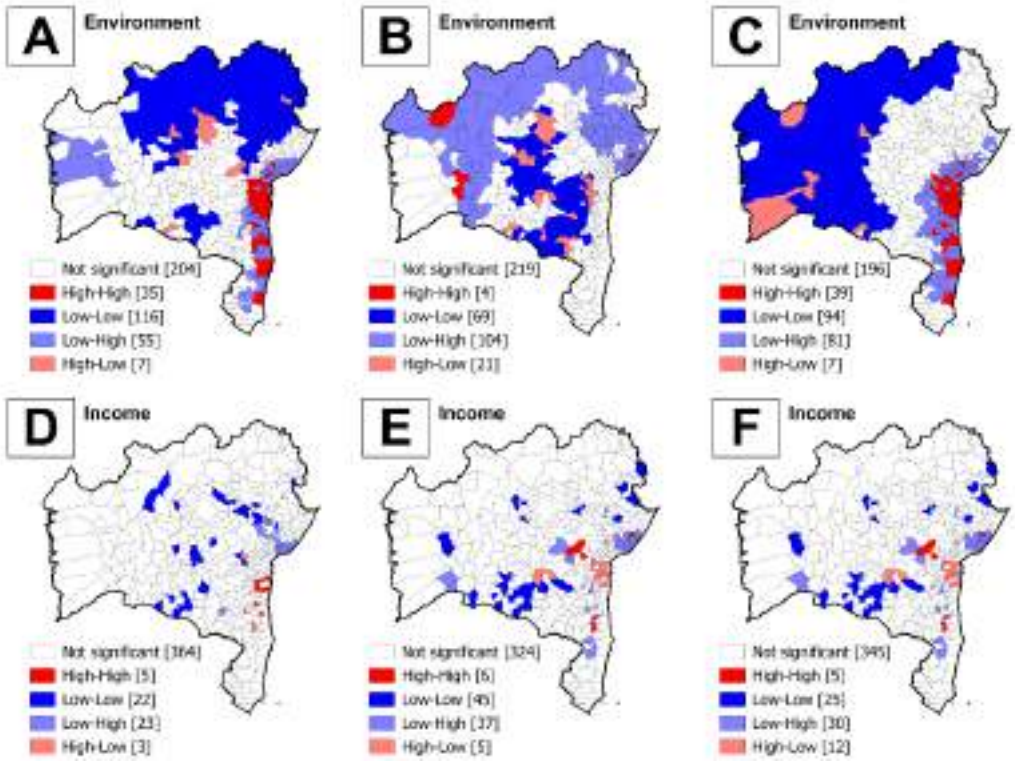
In continuity, the bivariate analysis of TL/HIV co-infection with mean rainfall (A) revealed a negative (inverse) correlation (IMG: -0.062; sd = 0.0207), with low-high patterns predominant in 26.96% (55) of the municipalities. This result demonstrates a low incidence of the disease and an increase in the average rainfall in areas of the east, south and extreme south regions of the state. For the mean temperature (B), a positive (direct) relationship was observed (IMG: 0.060; sd = 0.0209). High-high clusters were recorded in 1.83% (4) of the municipalities, indicating that vulnerability to co-infection may be associated with high temperatures (**Figure 27**).

Regarding the mean moisture content (C), the inverse correlation detected (IMG: -0.155; sd = 0.0216) showed patterns of low-high LISA in 41.33% (81) of the municipalities, indicating low incidence of the disease and an increase in the average humidity in areas of the eastern, southern and extreme southern regions of the state. On the other hand, the GDP (D) showed a

positive association (IMG: 0.055; sd = 0.0218), with high-high LISA patterns located in 1.37% (5) of the areas analyzed, predominating specifically in the southern region of the state of Bahia (**Figure 27**).

In the case of the Gini index (E), which measures economic inequality, it showed a direct correlation (IMG: 0.056; sd = 0.0215). High-high clusters corresponded to 1.85% (6) of the municipalities, while low-low patterns were found in 13.89% (45), both found in the south and southwest regions of the state, respectively. These results suggest that areas of greater vulnerability to TL/HIV co-infection are associated with high socioeconomic inequality. Finally, the unemployment rate (F) showed a negative (inverse) association (IMG: -0.015; sd = 0.0211), with low-high patterns predominant in 8.70% (30) of the municipalities in the west, east, and south regions of the state (**Figure 27**).

Figure 28. Local bivariate spatial correlation of the incidence of TL/HIV co-infection with: A – Mean Rainfall; B – Average Temperature; C – Average Humidity; D – Gross Domestic Product (GDP); E – Gini Index; F – Unemployment Rate, in the state of Bahia, period 2008-2022.

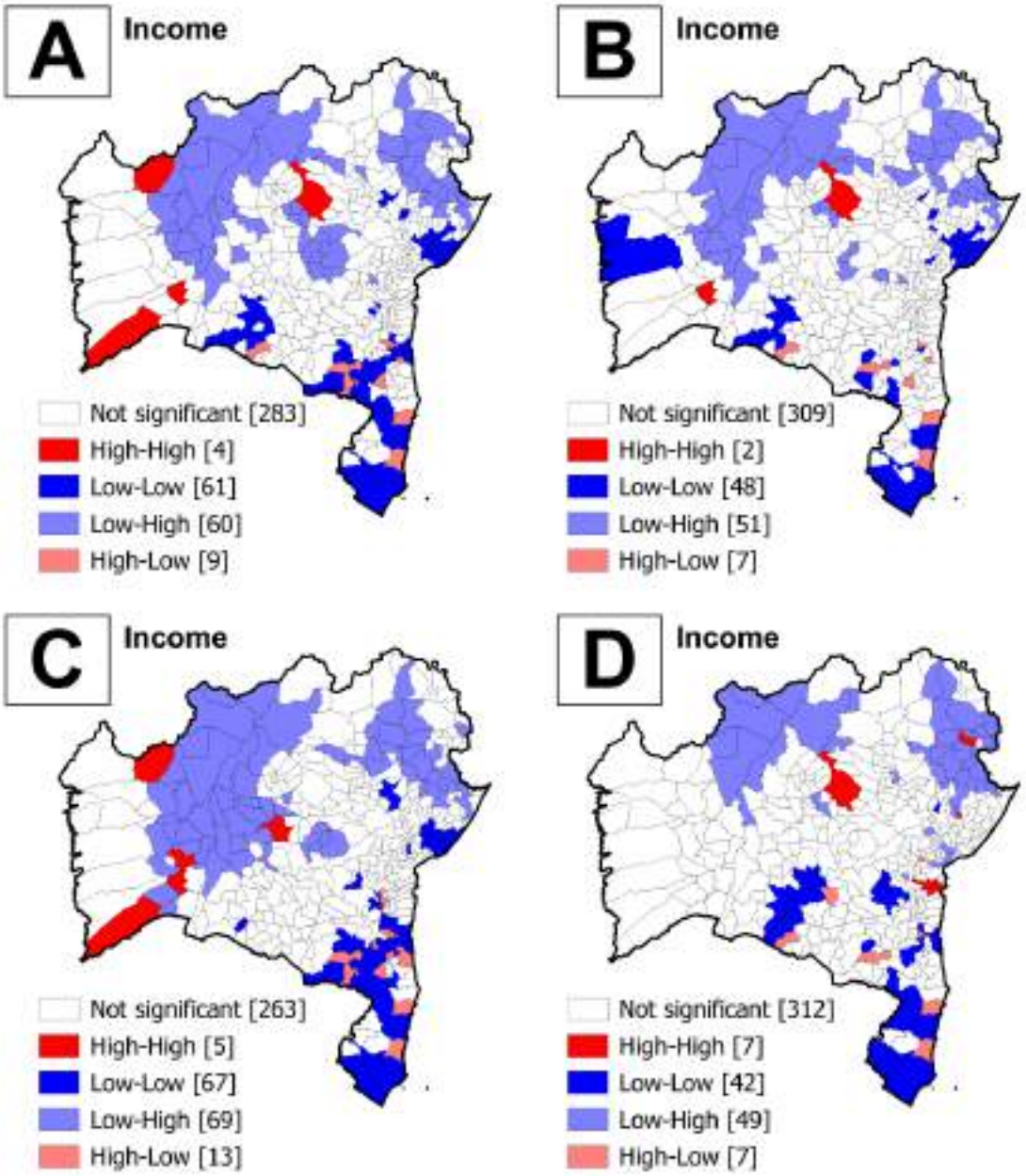


Moving forward in the analysis, the percentage of people living in poverty (A) showed a positive (direct) association (IMG: 0.059; sd = 0.0214). High-high clusters were present in 1.41% (4) of the north-central and western areas of the state. Regarding the proportion of people vulnerable to poverty (B), the correlation was also positive (IMG: 0.042; sd = 0.0213). Low-low clusters accounted for 15.53% (48) of the localities, while high-high patterns were observed in 0.65% (2) of the municipalities. These results demonstrate the correlation of TL/HIV co-infection with poverty-related socioeconomic indicators (**Figure 28**).

For the percentage of people in extreme poverty (C), a positive (direct) association was recorded (IMG: 0.079; sd = 0.0213). The high-high clusters corresponded to 1.90% (5) of the areas located in the central and western regions of the state. In the case of the proportion of people enrolled in CadÚnico or beneficiaries of Bolsa Família (D), the association was direct (IMG: 0.055; sd = 0.0214). The LISA high-high clusters were present in 2.24% (7), covering the areas of the central-north and south regions of the state of Bahia, indicating that in these locations when there is a higher incidence of co-infection, there will also be a higher proportion of people enrolled in social benefits (**Figure 28**).

Figure 29. Local bivariate spatial correlation of the incidence of TL/HIV co-infection with: A – Percentage of Poor; B – Percentage of Vulnerable to Poverty; C – Percentage of Extremely

Poor; D – Percentage of people enrolled in CadÚnico or beneficiaries of Bolsa Família, in the state of Bahia, period 2008-2022.



Discussion

The analysis of VL and LT cases from 2008 to 2022 revealed changes in incidence, confirmation rate, HIV coinfection and case fatality between the two diseases. The findings suggest a general trend of reduction in VL cases over the years, while TL showed an initial increase followed by a more recent decline. The case confirmation rate also varied, being higher for LT compared to VL, which may indicate differences in diagnostic accuracy or quality of

reporting. Furthermore, although HIV coinfection was more frequent in VL than in LT, case fatality was high in both cases, especially in specific periods.

VL had a confirmation rate of 57.18%, indicating that almost half of the reported cases were not confirmed. This discrepancy may be associated with the limitations of diagnostic methods, which present variability in sensitivity and specificity (RODRIGUES *et al.*, 2021), in addition to possible failures in the reporting system, such as underreporting or duplicate records (HEWAWASAM *et al.*, 2020; SILVA *et al.*, 2016). On the other hand, TL had a significantly higher confirmation rate (98.40%), suggesting greater diagnostic accuracy, possibly due to more evident clinical manifestations and greater sensitivity of diagnostic tests, such as direct parasitological examination widely available in the SUS (ESPIR *et al.*, 2016; MEDEIROS *et al.*, 2024).

VL/HIV coinfection accounted for 2.30% of confirmed VL cases, indicating a relatively low incidence. However, this association is clinically concerning, as both diseases increase the severity of symptoms, make treatment difficult, and reduce patients' chances of recovery (FONTES *et al.*, 2024; LINDOSO *et al.*, 2016). Most VL/HIV cases were classified as new (83.33%), suggesting that coinfection occurs predominantly in individuals with no previous history of leishmaniasis, which reinforces the hypothesis of greater immunological vulnerability in individuals immunosuppressed by HIV (AKUFFO *et al.*, 2018). TL/HIV coinfection was less frequent, representing only 0.48% of confirmed TL cases. Despite its low incidence, this condition is also associated with a worse prognosis due to immunological impairment and therapeutic difficulties (LINDOSO *et al.*, 2016).

Regarding lethality, an increase was observed over the years for VL, reaching the highest rate in 2021 (13.33%). In relation to VL/HIV, there was a fluctuation in lethality rates, with higher rates in the years 2016, 2018 and 2012. Similarly, a survey carried out between 2007 and 2018 in Brazil identified a co-infection rate of 8.81% among individuals with VL,

with a higher chance of death in older age groups and in the presence of HIV coinfection (CARVALHO *et al.*, 2022). Similarly, AIDS mortality in Brazil has decreased, a fact attributed to adherence to ART and health policies for prevention and treatment of HIV infection (BATISTA *et al.*, 2023; SOUSA *et al.*, 2021).

For TL, the lethality remained stable between 0% and 0.40%, with an increase between 2019 and 2022. The lethality of TL/HIV was recorded only in 2010, 2017 and 2018, reaching peaks of 4.65%, 10% and 20%, respectively. A study indicates that co-infected patients may present atypical clinical manifestations and greater resistance to conventional treatment, which may result in higher lethality rates (RIBEIRO *et al.*, 2002).

As observed in other studies, HIV-induced immunosuppression alters both the clinical course and the therapeutic approach of TL. The management of these patients represents a significant challenge, since, compared with immunocompetent individuals, they have a higher frequency of therapeutic failure, greater susceptibility to drug toxicity, and higher mortality rates (ALVAR *et al.*, 2008; COUPPIÉ *et al.*, 2004).

Joinpoint regression analysis revealed an initial upward trend in the incidence of VL between 2007 and 2014, followed by a shift to a downward trend in the period from 2014 to 2022. However, these findings differ from national and regional studies, as well as other analyses conducted in the state of Bahia, which indicate a seasonal pattern in the incidence of the disease. This discrepancy may be due to differences in methodological approaches, or the specific periods analyzed in each study (ANDRADE; SOUZA; CARMO, 2022; BRUHN *et al.*, 2024).

For TL and TL/HIV, dynamic incidence patterns were demonstrated over time. The significant increase in TL cases until 2010, followed by a sharp decline until 2014, suggests the impact of public health interventions or changes in disease surveillance during this period. These results are similar to the study carried out at the national level, which identified an overall

decrease in the number of cases, from 15.3 to 8.4 cases per 100,000 population (PORTELLA; KRAENKEL, 2021). The stabilization of TL and TL/HIV cases after 2014 may indicate changes in transmission dynamics, requiring further investigation.

However, it is possible that the observed trend is influenced by specific environmental and climatic factors, such as deforestation, temperature variations, and humidity levels, which can directly impact vector populations and disease transmission dynamics (BUZANOVSKY; SANCHEZ-VAZQUEZ, 2020; NADIA *et al.*, 2021). Additionally, socioeconomic conditions, including access to healthcare, housing quality, and sanitation, may affect susceptibility and exposure to TL. Therefore, continuous assessment of these variables is crucial to understanding their role in disease spread. Preventive strategies should be context-specific, focusing on reducing vector habitats, improving living conditions, and enhancing public health interventions aimed at mitigating transmission risks.

Regarding sex and age groups, for cases of isolated VL and VL/HIV, a higher incidence is observed in males, with peaks in the age groups of 20 to 34 years and 35 to 49 years, and for VL also in children aged 1 to 4 years. This pattern aligns with previous studies conducted in Brazil and in states of the Northeastern Region (MACHADO *et al.*, 2021b; SOUSA-GOMES *et al.*, 2011; VIANA *et al.*, 2017). The higher incidence in adult males may be linked to occupational exposure, outdoor activities, and greater mobility, which increase the likelihood of contact with the vector (NINA *et al.*, 2023; RIBEIRO *et al.*, 2021). Additionally, the prevalence of VL/HIV co-infection in young adults, particularly between 20 and 49 years, is consistent with the epidemiology of HIV, where sexual transmission is the primary mode of infection (CARVALHO *et al.*, 2013; CLOOTS *et al.*, 2021). This overlap suggests the need for integrated surveillance and prevention strategies, particularly in vulnerable populations.

For isolated TL, the age pyramid reveals a higher incidence in males, with peaks in the age groups of 20 to 34 years, 35 to 49 years and 50 to 64 years. In the case of TL/HIV

coinfection, there is a predominance of cases in men, concentrated mainly in the age groups of 35 to 49 years, 20 to 34 years and 50 to 64 years. These predisposition was also found in other Regions of the country, such as state of Minas Gerais (Southeast Region) and Pernambuco (Northeast Region), which show the profile of involvement in adult men of working age (BELO *et al.*, 2023; PINTO *et al.*, 2020; SILVA *et al.*, 2022).

In cases of isolated VL compared with VL/HIV coinfection there was significantly higher the frequency of fever, such as found in a study conducted in the state of Tocantins (COUTINHO *et al.*, 2017), and edema frequency. Both symptoms reflect differences in the inflammatory and immunological status of patients, suggesting that the immune response and clinical profile may be influenced by the presence of HIV (TAKELE *et al.*, 2023). For TL and TL/HIV, mucosal lesions were more frequency in TL/HIV coinfection compared with isolated TL. This finding is consistent with the literature, which associates coinfection with increased severity of clinical manifestations and greater parasitic dissemination, in addition to treatment failure due to the immunological deficiency caused by HIV (AMATO *et al.*, 2009, 2024).

Regarding treatment, pentavalent antimonial continues to be the first-choice drug for the treatment of VL, following the guidelines of the manual for the surveillance and control of VL; however, it presents several toxic effects (BRASIL, 2014). In contrast, for the treatment of VL/HIV coinfection, Liposomal Amphotericin B and Amphotericin B were used, respectively, following the recommendations of the manual of recommendations for diagnosis, treatment and monitoring of patients with leishmania-HIV coinfection (BRASIL, 2015). The absence of recorded treatment in 2.84% of cases of VL/HIV coinfection may indicate missing data in the records or clinical decisions influenced by patient conditions. This could be due to challenges in diagnosis, disease severity, or other factors affecting treatment initiation. Further investigations are needed to clarify the reasons behind these cases. It is worth noting that therapeutic failures are observed in coinfection, demonstrating a greater recurrence of the

disease, which can be minimized by advising adherence to antiretroviral therapy (ART) (TAKELE *et al.*, 2023).

The data highlight that most cases of VL are classified as new, while in VL/HIV a higher proportion of relapses is observed, and that could suggest that coinfection impacts the response to treatment and increases the chance of disease reactivation.

The lower frequency of positive diagnoses in coinfection by methods such as parasitology and IFAT suggests low accuracy of that diagnosis on immunosuppressed patients, possibly due to the lower immune response, including hummoral (FONTOURA *et al.*, 2018). n addition, the extremely low cure rate in coinfection (10.84%), associated with higher mortality from other causes (72.29%), highlights the severity of the interaction between the protozoan of VL and HIV, reinforcing the need for specific therapeutic and early diagnostic approaches for this vulnerable population (MACHADO *et al.*, 2021b).

However, in the case of VL, liposomal amphotericin B was significantly more used in relapses compared to pentavalent antimony and pentamidine, indicating a preference for this drug in scenarios of greater severity or resistance, due to its characteristic of lower toxicity, which supports adherence to treatment, as is suggested an Brazilian Ministry of Health (BRASIL, 2014). There was a greater use of amphotericin B and liposomal amphotericin B before deaths due to VL. There was greater use of amphotericin B and liposomal amphotericin B before deaths from VL. Both drugs are considered second-line treatment to pentavalent antimoniate, becoming the main options in more severe cases and being associated with the development of resistance by parasites (KUMARI *et al.*, 2022).

The distribution of medication used in each age groups highlighted a significant pattern: liposomal amphotericin B was more commonly used in the elderly, while pentavalent antimonial was predominant in children and adolescents. It is important to highlight that the selection of medication for treatment takes into account factors such as the presence of

comorbidities, the severity of the clinical condition and the profile of associated side effects (SCALZONE *et al.*, 2016). For example, liposomal amphotericin B is only recommended as the first choice of treatment for patients aged 50 years and older, pregnant women and children under 1 year (BRASIL, 2014).

In the case of VL/HIV coinfection, the use of pentavalent antimonial was significantly more frequent in new cases, which goes against the recommendations of the Ministry of Health, since the first-choice drug is amphotericin B. For the visceral form, the use of the liposomal formulation is recommended as a priority, while, in the tegumentary form, amphotericin B deoxycholate is indicated, both for cutaneous and mucosal manifestations (BRASIL, 2015).

Therefore, in the case of TL and TL/HIV, relapse was more frequent in co-infection, suggesting difficulties in the clinical management of these patients, associated with factors such as immunosuppression and greater severity of the disease. Co-infection of both diseases results in complex immunological interactions that can worsen the clinical condition of patients (RIBEIRO *et al.*, 2002). This immunological alteration favors the replication and dissemination of *Leishmania* in the organism, resulting in more severe and disseminated clinical manifestations of leishmaniasis in co-infected individuals. Although deaths from TL were observed exclusively in isolated cases, deaths from other causes were more frequent in co-infected individuals, indicating an influence of HIV-related conditions on mortality, especially when there is no adherence to ART (SHAW; MATIN, 2022).

VL cases are more prevalent in central and western areas, where climatic and ecological conditions favor the presence of the vector and the disease reservoir (CARDENAS *et al.*, 2006; MACHADO *et al.*, 2020b). In contrast, HIV cases are concentrated in the coastal and extreme southern regions, areas associated with higher population density, urbanization, and social vulnerability factors, such as sex tourism (OLIVEIRA-FILHO *et al.*, 2020; QUEVEDO-GÓMEZ *et al.*, 2020).

Similarly, TL has a higher incidence in the southern and western regions, associated with environmental conditions favorable to the vector. TL/HIV co-infection occurs in focal locations, the intensity of which is directly related to the incidence of isolated TL and overlaps with municipalities with a high incidence of HIV, creating high-risk areas. Similar results were found in a study carried out in 2018 in Bahia, which also identified specific regions for the predominant occurrence of each form of leishmaniasis. Both can coexist in overlapping areas, and even at the municipal level, risk levels can vary significantly (RODGERS *et al.*, 2019).

For access to piped water, a positive correlation was identified, highlighting the relevance of urban conditions in increasing the incidence of co-infection. On the other hand, solid waste collection presented an inverse correlation, showing that better sanitation conditions are associated with a lower incidence of co-infection. It is clear that urban development without planning for ecologically correct measures, which considers trade-offs between agriculture, urbanization and conservation, leads to an increase in the incidence of VL and, consequently, to an increase in VL/HIV co-infection (SANTOS *et al.*, 2021).

Occupation in the agricultural sector showed a correlation, indicating that regions with greater agricultural activity have a higher incidence of co-infection, possibly due to exposure to the vector in rural areas. In recent years, rapid deforestation has allowed the advancement of agriculture and livestock farming, thus presenting high risks of irreversible changes in biodiversity and ecosystems (ESPÍRITO-SANTO *et al.*, 2020; OLIVEIRA *et al.*, 2017).

It is known that under high temperature conditions, the life cycle of sandflies is accelerated, resulting in a faster maturation process (BRASIL, 2014) and higher temperatures favor the transmission of co-infection. On the other hand, the results of the correlation between co-infection and humidity differ from studies carried out, which show that the population density of sandflies is affected by abiotic variables such as temperature, precipitation and

humidity, and more humid environments can favor the proliferation of these vectors (COSTA *et al.*, 2013)

Studies indicate that economic inequality can aggravate vulnerability to co-infection, as populations in poverty often lack adequate access to health services and live in conditions that facilitate the spread of the disease (HOUWELING *et al.*, 2016; RIBEIRO *et al.*, 2021; VALERO; PRIST; URIARTE, 2021) In addition, although social programs such as Bolsa Família seek to mitigate the effects of poverty, dependence on these aids may indicate continued exposure to risk factors associated with co-infection. On the other hand, economically more prosperous areas may have a higher incidence of co-infection, possibly due to urbanization and better access to diagnosis, which increases case reporting (SILVA *et al.*, 2024)

In addition, lower unemployment rates may be related to greater occupational exposure to the vector in rural or peri-urban activities, especially in sectors such as agriculture and civil construction (BOZORG-OMID *et al.*, 2023; MSELLEMU *et al.*, 2024)

Finally, the study faced limitations associated with the use of secondary data, such as the presence of gaps and incomplete information on notification forms, as well as inadequately completed records. Despite these constraints, the wide availability of data mitigated possible information losses, ensuring the robustness of the analyses performed.

Conclusion

This study provided a comprehensive epidemiological and spatiotemporal analysis of VL, TL, and their co-infections with HIV in the state of Bahia, Brazil, from 2008 to 2022. The findings highlighted disparities in incidence, mortality, and spatial distribution across different regions and population groups. Concentrations of VL cases were observed in the central and western regions of Bahia, while TL cases predominated in the southern and western regions. In addition, VL/HIV and TL/HIV cases were widely dispersed, often overlapping with regions of high VL incidence.

Men were more frequently affected by all diseases, with the highest concentration in the 20–49 age group. Educational levels varied, with the majority of VL and VL/HIV patients having only primary education. Clinically, VL/HIV patients had a lower prevalence of fever and edema compared to isolated VL cases, while TL/HIV patients showed a higher frequency of mucosal lesions. Furthermore, a positive spatial correlation was found between VL/HIV incidence and MHDI, access to piped water, and employment in the agricultural sector. Climatic factors also played a role, with high temperatures showing a positive correlation with VL/HIV.

These findings reinforce the complex interplay between epidemiological, environmental, and sociodemographic factors in the transmission and progression of leishmaniasis and HIV coinfection. Therefore, improved surveillance and early detection strategies, especially in high incidence areas, are needed, as well as integrated public health policies that address the social determinants of health.

Finally, by assessing disease trends from 2008 to 2022, this study contributes information for future epidemiological monitoring and health policy planning in the state of Bahia. The integration of leishmaniasis and HIV control programs, with an emphasis on vulnerable populations, remains essential to reduce the burden of disease and improve health outcomes.

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ANEXO A - Comitê de Ética em Pesquisa

UNIVERSIDADE ESTADUAL DE SANTA CRUZ - UESC

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE EPIDEMIOLÓGICA E ESPACIAL DE CASOS DE LEISHMANIOSE VISCERAL E HIV EM COINFECÇÃO NO ESTADO DA BAHIA

Pesquisador: ANAIA DA PAIXAO SEVA

Área Temática:

Versão: 1

CAAE: 47443721.4.0000.5526

Instituição Proponente: Universidade Estadual de Santa Cruz

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.784.218

Apresentação do Projeto:

O protocolo de pesquisa intitulado " ANÁLISE EPIDEMIOLÓGICA E ESPACIAL DE CASOS DE LEISHMANIOSE VISCERAL E HIV EM COINFECÇÃO NO ESTADO DA BAHIA", apresentado pela pesquisadora "ANAIÁ DA PAIXÃO SEVA", sob número de CAAE 47443721.4.0000.5526, diz respeito a uma investigação científica realizada com dados secundários (casos de LV notificados no Estado da Bahia). Serão analisados os casos humanos suspeitos e confirmados com leishmaniose visceral com e sem coinfecção com HIV na Bahia, dentre os anos de 2003 e 2020.Os dados de cada paciente serão obtidos da Secretaria Estadual da Saúde do Estado da Bahia (SESAB). Serão analisadas características do perfil epidemiológico e espacial destas coinfecções, como: 1. Distribuição espaço-temporal de casos e das notificações; 2. Associação de fatores socioeconômicos; 3. Características epidemiológicas: sexo, faixa etária, raça/cor; 4. Tipos de entrada (caso novo e recidiva) e desfecho (cura, óbito) dos casos; 5. Tipo de tratamento; 6. Comparação da letalidade da LV e do HIV com ou sem coinfecção. Os resultados deste estudo, realizado na Universidade Estadual de Santa Cruz, serão disponibilizados para a SESAB em forma de boletim informativo.

Objetivo da Pesquisa:

De acordo com o protocolo submetido, o objetivo primário é realizar análises epidemiológicas e espaciais, no intuito de identificar o comportamento do HIV/AIDS e da Leishmaniose visceral e os

fatores associados aos casos de ambas de modo isolado e em coinfecção. O objetivo secundário é elucidar a dinâmica da Leishmaniose visceral e do HIV/AIDS no estado da Bahia, acerca da distribuição geográfica das doenças, bem como associando fatores de risco ambientais, climáticos e socioeconômicos para ocorrência de tais infecções; Identificar e comparar o perfil dos casos isolados e em co-infecção, bem como a letalidade, morbidade, faixa-etária, recidivas e abandono de tratamento. Também será avaliada a infecção concomitante e isolada de ambas no aspecto de município de residência e de notificação.

Avaliação dos Riscos e Benefícios:

Os riscos indicados pela pesquisadora se referem à quebra de sigilo dos dados dos pacientes. Entretanto, os riscos são mínimos para o caso de estudos, como este, que empregam técnicas e métodos retrospectivos de pesquisa e em que não se realiza nenhuma intervenção ou modificação intencional nas variáveis fisiológicas ou psicológicas e sociais dos indivíduos que participam no estudo.

Como benefícios, a pesquisadora aponta que serão definidos municípios sob risco de intensificar a ocorrência da doença e que, por tanto, irão requerer intervenções de prevenção e controle, assim como seus municípios vizinho. Nortear a aplicação mais eficaz de esforços e recursos para ações de prevenção, rastreio e controle da Leishmaniose visceral e da coinfecção Leishmania-HIV no estado da Bahia.

Comentários e Considerações sobre a Pesquisa:

Trata-se de uma pesquisa relevante para a saúde coletiva, dado o cenário epidemiológico apresentado pela LV no nordeste brasileiro e na Bahia, local do estudo. De acordo com o protocolo, as informações dos casos de LV serão provenientes de um banco de dados da SESAB e disponibilizadas à pesquisadora sem as variáveis nome e endereço, o que impede a identificação dos casos. Como não se trata de uma pesquisa realizada com diretamente com seres humanos, mas sim com dados da ocorrência de doenças, não há necessidade de autorização prévia dos participantes pelo processo de consentimento livre e esclarecido.

Considerações sobre os Termos de apresentação obrigatória:

A pesquisadora apresenta os termos necessários:

a) folha de rosto, devidamente preenchida e assinada pelo diretor do Departamento ao qual a pesquisadora se vincula;

b)Projeto de pesquisa na íntegra;

c) Termo de anuência da instituição que disponibilizará o banco de dados, devidamente assinado e

carimbado por seu representante;
d)Termo de compromisso de uso de dados assinado e carimbado pelos membros da equipe de pesquisa;
e) Declaração de comprometimento de entrega dos documentos físicos relativos ao protocolo de pesquisa ao CEP assim que as medidas de distanciamento social forem flexibilizadas.
g) Currículo Lattes dos pesquisadores
h) Documento que justifica a dispensa de TCLE e TALE, uma vez que os dados do banco serão disponibilizados sem identificação.

Recomendações:
Não há recomendações.

Conclusões ou Pendências e Lista de Inadequações:
Não há pendências no protocolo de pesquisa.

Considerações Finais a critério do CEP:
O Comitê de Ética em Pesquisa da UESC avaliou o Protocolo de Pesquisa "ANÁLISE EPIDEMIOLÓGICA E ESPACIAL DE CASOS DE LEISHMANIOSE VISCERAL E HIV EM COINFECÇÃO NO ESTADO DA BAHIA", CAAE 47443721.4.0000.5526, em reunião ordinária realizada em 16 de junho de 2021 e considerou que a proposta possui mérito científico e demonstra atender os requisitos atinentes à ética em pesquisa com seres humanos. Após relato e discussão do protocolo, este Colegiado emitiu parecer favorável à APROVAÇÃO. Havendo alterações necessárias no projeto, estas deverão ser encaminhadas à este CEP na forma de Emenda. No caso de eventos adversos, estes deverão ser notificados ao CEP. Solicitamos especial atenção no envio dos relatórios semestrais e final.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1733137.pdf	24/05/2021 07:23:05		Aceito
Declaração de Instituição e Infraestrutura	Termo_de_Anuencia_Institucional.pdf	24/05/2021 07:22:22	ANAIA DA PAIXAO SEVA	Aceito
Projeto Detalhado / Brochura Investigador	PROPP_Mod_Proj_Pesquisa_com_CEP.pdf	19/05/2021 08:25:57	ANAIA DA PAIXAO SEVA	Aceito
Declaração de Pesquisadores	ResponsabilidadePesquisador.pdf	17/05/2021 16:29:57	ANAIA DA PAIXAO SEVA	Aceito

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Continuação do Parecer: 4.784.219

Declaração de Pesquisadores	DeclarComprometimento.pdf	17/05/2021 16:17:58	ANAIA DA PAIXAO SEVA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	17/05/2021 15:39:16	ANAIA DA PAIXAO SEVA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TALE.pdf	17/05/2021 15:38:50	ANAIA DA PAIXAO SEVA	Aceito
Declaração de Pesquisadores	CompromissoUsoDados.pdf	17/05/2021 15:33:41	ANAIA DA PAIXAO SEVA	Aceito
Outros	LattesAnaia.pdf	17/05/2021 15:32:02	ANAIA DA PAIXAO SEVA	Aceito
Folha de Rosto	folhaDeRosto.pdf	17/05/2021 15:30:22	ANAIA DA PAIXAO SEVA	Aceito
Outros	lattesKayo.pdf	17/05/2021 14:56:04	KAYO RESENDE DIAS E ALMEIDA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

ILHEUS, 16 de Junho de 2021

Assinado por:
Maria Cristina Rangel
(Coordenador(a))

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