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Impact of HIV immunosuppression on toxoplasmosis reactivation: immunopathological aspects, diagnostic challenges, and clinical implications

Impact of HIV-induced immunosuppression on the reactivation of toxoplasmosis: immunopathological aspects, diagnostic challenges, and clinical implications

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Summary

Coinfection with the Human Immunodeficiency Virus (HIV) and *Toxoplasma gondii* represents a major clinical challenge in public health due to the high morbidity and mortality associated with neurotoxoplasmosis. This study aimed to discuss the impacts of HIV-induced immunosuppression on toxoplasmosis reactivation, with an emphasis on the immunological mechanisms involved, the diagnostic challenges, and the clinical implications of coinfection. This is a qualitative, descriptive, narrative literature review based on articles published between 2010 and 2025 in PubMed, SciELO, LILACS, and Google Scholar. The analysis revealed that progressive depletion of CD4+ T lymphocytes, associated with CD8+ T lymphocyte and NK cell dysfunction, favors parasite reactivation. Neurotoxoplasmosis stood out as a serious complication, marked by high mortality and permanent neurological sequelae, aggravated by diagnostic limitations in regions with low infrastructure. Furthermore, insufficient adherence to antiretroviral therapy and inequalities in access to healthcare were identified as critical factors. The conclusion is that, despite advances, gaps persist in the detailed understanding of immunological mechanisms and the implementation of accessible diagnostic strategies. Therefore, the need for integrated public policies, greater adherence to ART, and multicenter research to support effective interventions is reinforced.
Keywords: HIV. *Toxoplasma gondii.* Neurotoxoplasmosis. Coinfection. Immunity.

Abstract

The coinfection of Human Immunodeficiency Virus (HIV) and *Toxoplasma gondii* represents a major clinical and public health challenge due to the high morbidity and mortality associated with neurotoxoplasmosis. This study aimed to discuss the impacts of HIV-induced immunosuppression on T. gondii reactivation, focusing on immunological mechanisms, diagnostic challenges, and clinical implications of the coinfection. A narrative literature review was conducted, qualitative and descriptive in nature, based on articles published between 2010 and 2025 in PubMed, SciELO, LILACS, and Google Scholar. Findings revealed that the progressive depletion of CD4+ T lymphocytes, associated with CD8+ dysfunction and impaired NK cell activity, favors parasite reactivation. Neurotoxoplasmosis emerged as a severe complication, characterized by high mortality and permanent neurological sequelae, further aggravated by diagnostic limitations in low-resource settings. Furthermore, poor adherence to antiretroviral therapy and inequities in healthcare access were identified as critical factors. In conclusion, despite recent advances, significant gaps remain regarding the detailed understanding of immune mechanisms and the availability of accessible diagnostic strategies. This highlights the urgent need for integrated public health policies, improved adherence to ART, and multicenter research that may support effective interventions.
Keywords: HIV. *Toxoplasma gondii.* Neurotoxoplasmosis. Coinfection. Immunity.

1. Introduction

Human Immunodeficiency Virus (HIV) infection remains one of the biggest global public health challenges, due to its high transmissibility and ability to

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promote profound immunosuppression. The virus's main target is CD4+ T lymphocytes , cells fundamental in the activation and coordination of the immune response. The progressive destruction of these cells leads to a decrease in cellular immunity, favoring the emergence of opportunistic infections and serious complications, especially in the advanced stage of the disease — Immunodeficiency Syndrome Acquired (AIDS) (UNAIDS, 2023; ABBAS et al., 2016).

Among these opportunistic infections, toxoplasmosis stands out, a zoonosis caused by obligate intracellular protozoan *Toxoplasma gondii.* The parasite has a worldwide distribution and high prevalence in tropical countries, including Brazil, where the seropositivity rate exceeds 80% in some regions (ZUFFO; JERÔNIMO; DALL'AGNOL, 2021). In individuals immunocompetent, the infection is usually asymptomatic or manifests itself mildly; however, in HIV patients, lymphocyte depletion facilitates parasite reactivation in tissues, particularly in the central nervous system, causing neurotoxoplasmosis — one of the most frequent and serious neurological complications in people living with HIV (TELLES; VIDAL, 2023; NEVES et al., 2020).

HIV/T. *gondii* co-infection represents an important clinical and immunological problem, since that parasite reactivation occurs when there is failure in the cellular immune response, characterized by decrease in CD4+ T cells, dysfunction of CD8+ T lymphocytes and reduction of pro-inflammatory cytokines such as interferon-gamma (IFN-ÿ) and interleukin-12 (IL-12), essential for parasite control (BARCELOS, 2020). This process culminates in the formation of multiple brain lesions and clinical manifestations such as seizures, motor deficits and cognitive changes, often confused with other opportunistic infections of the central nervous system (MARTINS; CRUZEIRO; PIRES, 2015).

Due to the high prevalence of coinfection, diagnostic difficulties and limitations therapies observed in immunosuppression contexts, it becomes essential to understand deepen the immunological mechanisms that govern the reactivation of *T. gondii* and its implications clinical trials in HIV-positive individuals. In view of the above, this work aims to discuss the impacts of immunosuppression caused by HIV on the reactivation of toxoplasmosis, focusing on immunological mechanisms involved and the clinical implications of coinfection.

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2 Theoretical Framework / Results

2.1 **Immunological mechanisms involved in *T. gondii*** reactivation

Infection with *T. gondii* begins, in most cases, with the ingestion of oocysts eliminated in feline feces or from tissue cysts present in raw or undercooked meat. In gastrointestinal tract, the protozoan releases sporozoites or bradyzoites, which differentiate into tachyzoites, forms of rapid multiplication and tissue dissemination. These tachyzoites invade intestinal epithelial cells and, subsequently, macrophages and dendritic cells, which act as pathways systemic dissemination of the parasite (BARCELOS, 2020; ABBAS; LICHTMAN; PILLAI, 2016).

The innate immune response is activated by the recognition of parasitic antigens by Toll-like receptors (TLRs), which induce the production of IL-12 and tumor necrosis factor alpha (TNF-ÿ), cytokines essential for the activation of TCD4+ and TCD8+ lymphocytes and NK (Natural Killer) cells. These lymphocytes, in turn, produce IFN-ÿ, the main mediator of protective immunity against parasite (SOUZA et al., 2019; TOSH et al., 2015; TIWARI et al., 2019).

The sequence of immunological events following infection with *T. gondii* is represented in Figure 2, which demonstrates the activation of dendritic cells (DC) through TLR11 receptors and TLR12, IL-12 release, activation of NK cells and CD4+/ CD8+ T lymphocytes , and the action of IFN-ÿ in the destruction of the intracellular parasite (ABBAS et al., 2016).

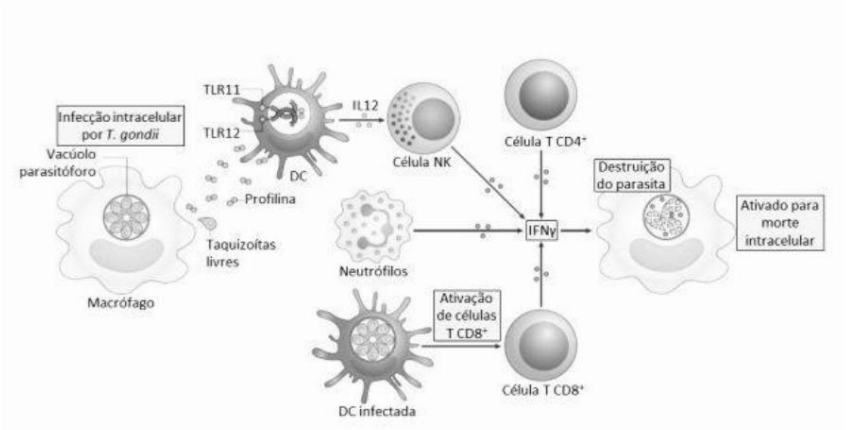

Figure 2 – Sequence of immunological events in *T. gondii* infection

Schematic representation of the cellular immune response to *T. gondii,* highlighting the activation of cells dendritic cells, CD4+ and CD8+ lymphocytes, NK cells and the role of cytokines IL-12 and IFN-ÿ of the destruction of the parasite.

Source: Adapted from Abbas et al. (2016).

In immunocompetent individuals, infection is controlled by the cellular response mediated by IFN-ÿ, produced by CD4+ and CD8+ T cells and NK cells. IFN-ÿ stimulates M1 macrophages, which

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ISSN: 2675-9128. São Paulo-SP.

Year V, v.2 2025 | submission: October 23, 2025 | accepted: October 25, 2025 | publication: October 27, 2025

produce nitric oxide (NO) and reactive oxygen species (ROS), capable of destroying the parasite intracellularly (BARCELOS, 2020). The cytotoxic action of CD8+ T lymphocytes promotes the death of infected cells through the release of perforins and granzymes, interrupting the cycle of multiplication of *T. gondii* (GAVA, 2022).

During this control process, granulomas, composed structures, are formed by activated macrophages, dendritic cells and CD4+ T lymphocytes, which organize around the cells infected, limiting the spread of tachyzoites and keeping the parasite in a latent state. The CD4+ T lymphocytes play an essential role in this mechanism, as they produce regulatory cytokines such as IFN-ÿ and interleukin-2 (IL-2), which support macrophage activation and prevent cyst rupture. When the parasite is controlled, it converts to bradyzoites, which form tissue cysts, characterizing the latency phase of the infection (GAVA, 2022).

The maintenance of latency depends on a balance between the production of IFN-ÿ and IL-12 and the control of immunoregulatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-ÿ), which prevent excessive inflammation. Deficiency of this immune axis compromises parasite control, resulting in the rupture of cysts and release of bradyzoites (SOUZA et al., 2019; ZUFFO et al., 2021).

In people living with HIV/AIDS, the progressive destruction of CD4+ T lymphocytes compromises the production of IFN-ÿ and IL-12, which reduces the activation of macrophages and CD8+ T lymphocytes, leading to failure of the cytotoxic response. Patients with CD4+ T cell counts below 100 cells/mm³ present a significantly increased risk of reactivation of the infection, with prevalence varying between 30% and 40% of cases in individuals without prophylaxis (LIU et al., 2025; MANUEL et al., 2025; OLIVEIRA et al., 2023).

In addition to the decrease in protective cytokines, there is an increase in IL-10 and TGF-ÿ, which suppress macrophage activation and favor parasite escape. Recent studies (2023–2025) demonstrate that the reactivation of *T. gondii* is associated with reduced expression of genes encoding IL-12 and IFN-ÿ, resulting in less activation of macrophages and CD8+ T lymphocytes, in addition to greater replication of tachyzoites in brain tissues (TELLES; VIDAL, 2023; GAVA et al., 2022; OLIVEIRA et al., 2023).

Immunosuppression, therefore, disrupts the immunological balance between the host and the parasite, leading to the rupture of tissue cysts and the dissemination of tachyzoites, which multiply rapidly in tissues such as brain and muscle. This reactivation characterizes the beginning of cerebral toxoplasmosis, one of the most serious complications of HIV/T. *gondii* coinfection (ZUFFO et al., 2021; FERNANDES et al., 2012; CAMPOS et al., 2014).

RCMOS – Multidisciplinary Scientific Journal of Knowledge.
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2. Material and Method

This is a narrative literature review study, with a qualitative approach and descriptive, which aimed to gather and discuss the main scientific evidence on the HIV *and T. gondii coinfection,* focusing on the impacts of immunosuppression on reactivation of parasite and clinical implications in immunocompromised individuals.

The bibliographic search was carried out between March and August 2025 in the PubMed, SciELO, LILACS and Google Scholar, using controlled and uncontrolled descriptors in Portuguese and English, combined by Boolean operators: “HIV”, “AIDS”, *“Toxoplasma gondii”,* “neurotoxoplasmosis”, “immune response” and “coinfection”. Studies published between 2010 and 2025, available in full in Portuguese, English and Spanish.

Original articles, systematic reviews and clinical studies that addressed immunological, diagnostic or clinical aspects of HIV/T. *gondii coinfection.* Excluded were duplicate articles, simple abstracts, isolated case reports and studies outside the thematic scope, presented in Table 1.

The selection of studies took place in three stages:

1. Reading of titles and abstracts for initial screening;
2. Full reading of potentially relevant articles;
3. Critical analysis and synthesis of the results according to the inclusion criteria and exclusion.

In total, 992 articles were identified in the databases, 25 in PubMed, 12 in SciELO, 6 in LILACS and 949 in Google Scholar. After removing 532 duplicates, there remained 460 articles. Of these, 47 were selected for full reading, and 31 met all criteria, composing the final review sample.

The extracted information was organized in a descriptive spreadsheet, containing the following variables: author, year, type of study, objective, main findings and limitations. The analysis of the data was carried out in a thematic and integrative way, focusing on the following axes:

- Immunological mechanisms involved in the reactivation of *T. gondii;*
- Clinical implications of HIV/T. gondii coinfection .

The process of identification, screening and inclusion of studies was represented as follows: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model, presented in Figure 1.

RCMOS – Multidisciplinary Scientific Journal of Knowledge.
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Year V, v.2 2025 | submission: October 23, 2025 | accepted: October 25, 2025 | publication: October 27, 2025

3. Results and Discussion

After detailed evaluation of the texts, 32 studies met all inclusion criteria and were selected for the composition of the research (Table 2). Based on the critical analysis of these works, a consensus was observed regarding the direct influence of immunosuppression caused by HIV in the reactivation of *T. gondii* and in the clinical manifestations resulting from this coinfection.

For a better understanding of the findings, the discussion was organized into two axes main themes: (1) the immunological mechanisms involved in the reactivation of *T. gondii,* and (2) the clinical implications of HIV/T. *gondii coinfection,* with emphasis on cellular and molecular action during the infectious process and the clinical repercussions observed in immunocompromised individuals.

Table 2 - Studies that address the immunological mechanisms and clinical implications of *HIV/ Toxoplasma gondii* coinfection .

Author	Year	Type of Study	Objective	Main Findings
Telles JPM et al.	2023	Prospective cohort	Neurological coinfections in PLWHA with cerebral toxoplasmosis	High frequency of of neurotoxoplasmosis in in immunosuppressed individuals
Coleman B et al.	2023	Retrospective	To evaluate radiological evolution after anti-T. *gondii* treatment	Persistence of lesions after therapy
Azovtseva OV et al.	2020	Retrospective	Describe the clinical course of TE in HIV	Frequent neurological symptoms and high mortality
Liu J et al.	2025	Cohort	Characterize TE imaging patterns	Multiple and annular lesions in basal ganglia
Li Y et al.	2020	Prognosis	Develop a clinical score for TE	Useful score for assessing risk
Ganiem AR et al.	2013	Cohort	Describe YOU with atypical presentation	TE can simulate meningitis
Anselmo LMP et al.	2014	Diagnosis	Evaluate CRP in the cerebrospinal fluid	PCR useful, but limited sensitivity
Bokharaei-Salim F et al.	2019	Diagnosis	Evaluate nested PCR in HIV/AIDS	High specificity

Continuation of table 2

Manuel L et al.	2025	Transversal	Determine seroprevalence in PVH	Seroprevalence of 54.5%

RCMOS – Multidisciplinary Scientific Journal of Knowledge.
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Year V, v.2 2025 | submission: October 23, 2025 | accepted: October 25, 2025 | publication: October 27, 2025

Shen G et al.	2016	Transversal	Seroprevalence in HIV/AIDS in China	Elevated IgG; risk of reactivation
Zakari MM et al.	2020	Transversal	Seroprevalence and CD4+	Association between positive IgG and lower CD4+
Zeleke AJ et al.	2017	Transversal	Seroprevalence in women HIV+	High prevalence of IgG (94%)
Rezanezhad H et al.	2017	Transversal	Compare patients with and without HAART	Lower seroprevalence in patients on ART
Martin-Iguacel R et al. 2017		Cohort	Incidence and mortality of TE in HIV in the ART era	Significant reduction in mortality
Tiwari A et al.	2019	Experimental	Evaluate cyst elimination by CD8+ T	TCD8+ eliminate T. gondii cysts
Tosh KW et al.	2015	Experimental	Evaluate IL-12 production and TNF-ÿ by monocytes	Production induced by direct contact with live parasite
Yamamoto M et al.	2012	Experimental	Analyze the role of GBPs induced by IFN-ÿ	Essential GBPs in parasite control
Fernandes MA et al.	2012	Observational	To assess reactivation in HIV+ pregnant women	Possible reactivation during pregnancy
Campos FA et al.	2014	Cohort	Incidence of congenital toxoplasmosis in HIV	Persistence even with HAART
Wang H et al.	2020	Diagnosis	Define imaging criteria for TE	Multiple lesions in basal ganglia
Tanoh AC et al.	2025	Retrospective	Describe characteristics of ET in HIV+	Diagnosis of late and sequelae
Voyiatzaki C et al.	2024	Transversal	Seroprevalence in newly diagnosed HIV patients	Differences between serological methods
Bavand A et al.	2018	Transversal	Evaluate antibodies and DNA in HIV	Association between positive DNA and IgG
Aun CS et al.	2019	Clinical	Describe presentations TE clinics	Symptoms neurological frequent

Continuation of table 2

Moro & Moreira	2020	Transversal	Assess adherence and prognosis in ART	Adherence reduces mortality
Gava M et al.	2022	Experimental	Assess cellular immunity and macrophages in HIV	Dysfunctional macrophages favor reactivation

RCMOS – Multidisciplinary Scientific Journal of Knowledge.
ISSN: 2675-9128. São Paulo-SP.

Year V, v.2 2025 | submission: October 23, 2025 | accepted: October 25, 2025 | publication: October 27, 2025

Souza JF et al.	2019	Experimental	Evaluate the role of cytokines in chronic infection	Reduction of IFN-ÿ and IL-12 favors reactivation
Rodrigues L et al.	2015	Cohort	Prevalence of neurotoxoplasmosis in AIDS	High incidence and mortality
Silva AP et al.	2018	Transversal	Serological diagnosis in PVHA	IgG positive in 85% of cases
Almeida L et al.	2021	Experimental	Analyze apoptosis in CD4+ T during coinfection	Accelerated apoptosis by HIV/T. gondii synergistic action
Oliveira F et al.	2023	Clinical	HIV/T. gondii coinfection in Brazil	Neurotoxoplasmosis as the main opportunistic infection

Source: own authorship

Acronyms used: PLWHA – People Living with HIV/AIDS; HIV – Human Immune System Virus; Human Immunodeficiency; AIDS – Acquired Immunodeficiency Syndrome; TE – Toxoplasmosis Encephalic; ART – Antiretroviral Therapy; IFN-ÿ – Interferon-gamma; IL-12 – Interleukin-12; IL-10 – Interleukin-10; TNF-ÿ – Tumor Necrosis Factor Alpha; TCD4ÿ – Helper T lymphocyte; TCD8ÿ – Cytotoxic T lymphocyte; NK – *Natural Killer;* NO – Nitric Oxide; ROS – Reactive Oxygen Species Oxygen; PCR – Polymerase Chain Reaction; DC – Dendritic Cell; WHO – Organization World Health Organization; CD4 – CD4ÿ Lymphocyte Count; *T. gondii* – *Toxoplasma gondii.*

3.2 Clinical implications of *HIV/ Toxoplasma gondii* coinfection

HIV/T. *gondii* coinfection directly impacts cellular immunity and clinical outcome of patients. HIV selectively destroys CD4+ T lymphocytes, interrupting the production of cytokines responsible for the coordinated activation of macrophages, CD8+ T cells and NK cells. With the reduction in production of IFN-ÿ and IL-12, macrophages decrease their ability to phagocytose and eliminate the parasite, becoming intracellular reservoirs of both *T. gondii* and HIV itself (GAVA, 2022; ZUFFO et al., 2021; TELLES; VIDAL, 2023).

CD8+ T lymphocytes , whose function depends on the activation of CD4+ T lymphocytes, become dysfunctional, and NK cells, responsible for the initial destruction of infected cells, undergo functional depletion (SOUZA et al., 2019; BARCELOS, 2020). In the central nervous system, microglia, which act as resident macrophage, has its phagocytic capacity reduced by the direct action of the virus, which favors the replication of tachyzoites and the formation of multiple necrotic lesions (AZOVTSEVA et al., 2020; LIU et al., 2025).

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ISSN: 2675-9128. São Paulo-SP.

Year V, v.2 2025 | submission: October 23, 2025 | accepted: October 25, 2025 | publication: October 27, 2025

Clinically, *T. gondii* reactivation manifests primarily as neurotoxoplasmosis, responsible for 30% to 40% of focal brain lesions in AIDS patients (MARTINS; CRUZEIRO; PIRES, 2015; NEVES et al., 2020; OLIVEIRA et al., 2023). manifestations include severe headache, fever, seizures, motor deficits and mental confusion, and may progress to coma in severe cases. Mortality can reach 20% to 30% when the diagnosis and treatment are not carried out early (GANIEM et al., 2013; LIU et al., 2025; MANUEL et al., 2025).

In addition to neurotoxoplasmosis, other clinical presentations include retinochoroiditis toxoplasma, pneumonitis and myocarditis, which may occur in isolation or in association, with estimated prevalence between 5% and 10% in immunocompromised individuals (REZANEZHAD et al., 2017; ZUFFO et al., 2021; BAVAND et al., 2018). Retinochoroiditis, in particular, is often underdiagnosed, but constitutes one of the main causes of acquired blindness in HIV patients positive, due to the reactivation of the parasite in the ocular tissues (SHEN et al., 2016; VOYIATZAKI et al., 2024).

Neuroimaging studies usually reveal multiple lesions with ring enhancement, located in the basal ganglia and cerebral cortex, associated with the presence of perilesional edema (COLEMAN et al., 2023; WANG et al., 2020; TANOH et al., 2025). The absence of treatment adequate or abandonment of antiretroviral therapy (ART) and prophylaxis with cotrimoxazole are directly related to fatal cases and recurrent relapses (RODRIGUES et al., 2015; ZAKARI et al., 2020; ZELEKE et al., 2017).

The diagnosis of neurotoxoplasmosis in immunosuppressed individuals represents a challenge, as isolated serology may be negative due to low antibody response (ANSELMO et al., 2014; BOKHARAEI-SALIM et al., 2019). Polymerase chain reaction (PCR) in cerebrospinal fluid is a useful tool and can detect parasite DNA in up to 60% of confirmed cases, especially when associated with radiological findings and the clinical context (BAVAND et al., 2018; LI et al., 2020; REZANEZHAD et al., 2017).

Standard treatment includes pyrimethamine, sulfadiazine, and folinic acid, continued for at least at least six weeks, followed by secondary prophylaxis until the CD4+ T count is greater than 200 cells/mm³ for more than three consecutive months (MORO; MOREIRA, 2020; ZUFFO et al., 2021). Inadequate adherence to ART and discontinuation of prophylactic cotrimoxazole remain the main risk factors for reactivation (ZUFFO et al., 2021; OLIVEIRA et al., 2023; MARTINS; CRUZEIRO; PIRES, 2015).

Recent studies indicate that maintaining primary prophylaxis with cotrimoxazole reduces the risk of reactivation of up to 80%, constituting an effective prevention strategy (GAVA et al.,

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ISSN: 2675-9128. São Paulo-SP.

Year V, v.2 2025 | submission: October 23, 2025 | accepted: October 25, 2025 | publication: October 27, 2025

2022; TELLES; VIDAL, 2023; LIU et al., 2025). However, irregular adherence to treatment antiretroviral therapy and late diagnosis remain critical factors associated with mortality (OLIVEIRA et al., 2023; ZUFFO et al., 2021).

Restoring the cellular immune response through ART is therefore essential for restore the production of IFN-ÿ and IL-12, reactivate macrophages and cytotoxic lymphocytes and reduce replication of *T. gondii.* The combination of antiretroviral therapy, continuous prophylaxis and laboratory monitoring is essential to prevent reactivation and reduce morbidity and mortality associated with HIV/T. *gondii* coinfection (TELLES; VIDAL, 2023; OLIVEIRA et al., 2023; ZUFFO et al., 2021; SOUZA et al., 2019).

Final Considerations

The present study aimed to understand the impacts of immunosuppression caused by the Human Immunodeficiency Virus (HIV) in the reactivation of latent infection by *T. gondii* and its clinical implications in immunocompromised individuals. Analysis of the 32 selected studies made it possible to determine that HIV exerts a direct influence on the immune defense mechanisms, compromising the cellular response responsible for controlling the parasite.

It was observed that the progressive destruction of CD4+ T lymphocytes significantly reduces the production of pro-inflammatory cytokines, such as IL-12 and IFN-ÿ, essential for the activation of macrophages, CD8+ T lymphocytes and NK cells. This failure in the immune axis disrupts the balance between the host and the parasite, allowing the rupture of tissue cysts and the release of bradyzoites, which convert into tachyzoites, characterizing the reactivation of toxoplasmosis.

Evidence also shows that this reactivation is accompanied by serious clinical manifestations, mainly neurotoxoplasmosis, considered one of the main causes of morbidity and mortality in people living with HIV/AIDS. The immunological alterations described affect not only parasite control but also the integrity of the central nervous system, resulting in multiple brain injuries, seizures and motor deficits.

Thus, it is concluded that HIV/T. *gondii* coinfection represents a pathological interaction complex, in which viral immunosuppression acts as a determining factor for reactivation and evolution clinical presentation of toxoplasmosis. Effective control of the infection depends on restoring the response immunological through strict adherence to antiretroviral therapy (ART) and maintenance of prophylactic measures, such as the use of cotrimoxazole.

Finally, the need for public policies aimed at prevention, diagnosis early and continuous monitoring of immunosuppressed patients, in addition to encouraging new

Year V, v.2 2025 | submission: October 23, 2025 | accepted: October 25, 2025 | publication: October 27, 2025

research on immunological biomarkers and adjuvant therapeutic strategies, capable of reducing morbidity and mortality associated with HIV/T. gondii coinfection .

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