e-ISSN: 2747-2051

Archives of the Medicine and Case Reports

[AMCR]

https://hmpublisher.com/index.php/amcr

Cerebral Toxoplasmosis with Preserved CD4 Count (>300 cells/µL) in the HAART Era: Unmasking Immune Reconstitution Inflammatory Syndrome and the Diagnostic Utility of Cotrimoxazole

I Made Eryana[1*], Made Nopriantha[2]

[1]General Practitioner, Dharma Kerti Hospital, Tabanan, Indonesia

[2]Department of Internal Medicine, Dharma Kerti Hospital, Tabanan, Indonesia

ARTICLE INFO

Keywords:
CD4 count
Cerebral toxoplasmosis
Cotrimoxazole
HIV/AIDS
Immune reconstitution inflammatory syndrome (IRIS)

***Corresponding author:**
I Made Eryana

E-mail address:
eryk_tsr@yahoo.co.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/amcr.v6i4.830

A B S T R A C T

Cerebral toxoplasmosis (TE) typically presents in HIV-positive patients with severe immunosuppression (CD4 <100 cells/µL). However, in the era of Highly Active Antiretroviral Therapy (HAART), presentations have become atypical. We report a rare case of TE in a patient with a preserved CD4 count (>300 cells/µL), highlighting the phenomenon of unmasking immune reconstitution inflammatory syndrome (IRIS). A 22-year-old female, HIV-positive on a Tenofovir-Lamivudine-Efavirenz (TLE) regimen for one month, presented with subacute hemicrania, focal motor seizures, and complex visual hallucinations (zoopsia). Despite a CD4 count of 307 cells/µL and a suppressed viral load (<40 copies/mL), Contrast-Enhanced Computerized Tomography (CE-CT) revealed multiple ring-enhancing lesions with significant perilesional edema. The patient was diagnosed with TE-associated Unmasking IRIS. Due to the unavailability of Pyrimethamine, she was treated with high-dose Cotrimoxazole (960 mg q6h). Significant clinical improvement was observed by day 4, characterized by the cessation of seizures and hallucinations. Follow-up at two weeks confirmed sustained neurological recovery. In conclusion, a preserved CD4 count does not exclude opportunistic infections in the early post-HAART period. This case underscores the diagnostic pitfall of immune discordance and validates the efficacy of Cotrimoxazole as a primary therapeutic intervention in resource-limited settings.

1. Introduction

Toxoplasma gondii stands as one of the most successful parasitic organisms in the biological world. It is an obligate intracellular protozoan capable of infecting virtually all mammalian cells, demonstrating a remarkable evolutionary adaptation that has allowed it to permeate ecosystems globally.[1] The epidemiological footprint of this parasite is vast; it is estimated that approximately 30% of the global human population carries a chronic, latent infection. In the majority of immunocompetent hosts, the relationship between the parasite and the human immune system is one of detente. The host's immune system forces the tachyzoites—the rapidly dividing form responsible for tissue destruction—to retreat into bradyzoites, which form dormant cysts within neural and muscular tissues. These cysts remain quiescent, causing no clinical symptoms, held in check by a robust T-cell mediated immune surveillance.[2] However, this biological truce is fragile. In the context of significant immunosuppression, particularly that caused by the human immunodeficiency virus (HIV),

T. gondii emerges as a devastating opportunist. Cerebral toxoplasmosis (TE) remains the leading cause of focal brain lesions in patients with acquired immunodeficiency syndrome (AIDS), contributing significantly to morbidity and mortality, especially in resource-limited settings where healthcare infrastructure is strained.[3]

Historically, the pathophysiology of cerebral toxoplasmosis has been inextricably linked to severe T-cell depletion. The understanding of this disease was forged in the early years of the AIDS epidemic, where a clear inverse correlation was established between CD4+ T-lymphocyte counts and the risk of reactivation. The classical paradigm dictates that the reactivation of latent *T. gondii* cysts is almost exclusive to patients who have entered the advanced stages of AIDS.[4] Epidemiological data and clinical guidelines have long solidified the observation that TE occurs when CD4+ counts fall below a critical threshold of 100 cells/μL. The risk profile is exponential; incidence is highest in patients with profound immunosuppression, specifically those with counts below 50 cells/μL. This statistical strength transformed the CD4 count into a powerful diagnostic heuristic. In clinical practice, a CD4 count exceeding 200 cells/μL is often used as a robust negative predictive marker. When a patient presents with focal neurological deficits and a preserved CD4 count, clinicians traditionally rule out cerebral toxoplasmosis, redirecting the differential diagnosis toward malignancies such as primary CNS lymphoma (PCNSL), tuberculosis, or non-opportunistic etiologies. This algorithmic approach, while historically accurate, relied on the premise of a linear relationship between immune cell quantity and functional immunity.[5]

The landscape of HIV medicine was fundamentally altered by the widespread introduction of highly active antiretroviral therapy (HAART). This therapeutic revolution transformed HIV from a fatal diagnosis into a manageable chronic condition. However, while HAART has altered the natural history of opportunistic infections, it has introduced new pathophysiological complexities. The restoration of the immune system is not always seamless or uniform. Emerging literature now indicates a shift in the clinical presentation of opportunistic infections.[6] Reports suggest that 10% to 25% of cerebral toxoplasmosis cases may now present in patients with CD4 counts above the traditional danger zone. This statistical deviation represents more than a mere anomaly; it constitutes a dangerous diagnostic pitfall. When clinicians rigidly adhere to the classical CD4 thresholds, patients who fall into this gray zone of immunity face significant risks. The exclusion of TE from the differential diagnosis can lead to delayed treatment, during which the parasite causes irreversible neuronal damage, resulting in permanent neurological sequelae or death.

The precise mechanism by which *T. gondii* evades the apparently competent immune system in patients with preserved CD4 counts remains a subject of intense debate.[7] Current immunological scrutiny focuses on two primary hypotheses that explain this paradox: (i) Functional Immune Discordance: This hypothesis suggests a disconnect between the quantity of immune cells and their quality. In the early phases of HAART, or in patients with incomplete recovery, the quantitative increase in CD4 cells may not reflect the restoration of antigen-specific memory T-cell function. This state, often termed immunosenescence, implies that while the patient has a CD4 count above 200 or 300 cells/μL, these cells are functionally impaired. They fail to mount an adequate Th1 cytokine response—specifically the secretion of Interferon-gamma (IFN-γ)—which is essential for controlling intracellular parasites. Thus, the patient is functionally AIDS-defined despite numerical immunocompetence; (2) Immune reconstitution inflammatory syndrome (IRIS): The second hypothesis involves the unmasking of subclinical infection. In this scenario, the patient harbors latent *T. gondii* cysts or a low-level active infection that was clinically silent due to the lack of an inflammatory response during

severe immunosuppression. Upon the initiation of HAART, the rapidly recovering immune system detects these previously occult antigens and mounts an excessive, dysregulated inflammatory response. This phenomenon, known as unmasking IRIS, results in the paradoxical worsening of clinical symptoms and the sudden appearance of ring-enhancing lesions on neuroimaging, driven not just by the parasite but by the host's own volatile immune recovery.[8]

This diagnostic dilemma is particularly pertinent to resource-limited settings like Indonesia. Indonesia is a tropical archipelago where climatic conditions favor the survival of *T. gondii* oocysts, and close human-animal interfaces are common. Consequently, the seroprevalence of *Toxoplasma* is high, creating a vast reservoir of latent infection ready to reactivate. In such settings, the diagnostic challenge is compounded by the lack of advanced diagnostic tools. Molecular testing, such as polymerase chain reaction (PCR) of the cerebrospinal fluid, is often unavailable or prohibitively expensive. Clinicians must rely on clinical acumen, serology, and neuroimaging. Furthermore, the therapeutic landscape in these regions is constrained. The gold-standard treatment regimen—Pyrimethamine combined with Sulfadiazine—is frequently unavailable due to cost and supply chain issues. This necessitates the use of alternative regimens, primarily high-dose Cotrimoxazole (Trimethoprim-Sulfamethoxazole), which has shown promise but requires further clinical validation in high-risk, atypical presentations.[9]

Against this backdrop of immunological complexity and resource constraints, this manuscript presents a comprehensive case analysis of a 22-year-old female, HIV-positive patient on HAART. This case is distinct and scientifically novel for three key reasons: (i) Immunological Paradox: The patient developed fulminant Cerebral Toxoplasmosis despite a preserved CD4 count of 307 cells/µL. This starkly contradicts the classical CD4 <100 cells/µL threshold, serving as a critical alert to the phenomenon of functional immune discordance or IRIS in the early post-HAART period; (ii) Neuro-Phenomenology (Zoopsia): The case documents a rare and specific neurological presentation characterized by complex visual hallucinations of animals (zoopsia). This provides a unique opportunity to discuss the anatomical correlation between parietal/occipital lobe parasitic lesions and visual association pathway dysfunction, a clinical pearl often overlooked in general infectious disease literature; (iii) Therapeutic Validation in Limited Settings**:** We document the successful management of this high-risk patient using high-dose Cotrimoxazole monotherapy in the absence of Pyrimethamine. This outcome adds vital clinical evidence supporting the efficacy of accessible, low-cost generic medications for complex opportunistic infections. By dissecting the immunological profile, specific semiology, and therapeutic response of this patient, this study aims to challenge the rigid reliance on CD4 thresholds. We seek to propose a revised diagnostic algorithm that encourages a high index of suspicion for cerebral toxoplasmosis in HIV patients presenting with focal neurological deficits, regardless of CD4 count, thereby preventing diagnostic delays in the era of immune reconstitution.[10]

2. Case Presentation

A 22-year-old female presented to the Emergency Department of Dharma Kerti Hospital, a tertiary referral center in Bali, Indonesia, exhibiting a clinical profile suggestive of an acute intracranial process superimposed upon a chronic neurological decline. The patient's primary reason for admission was a severe, progressive cephalgia described as a throbbing hemicrania strictly localized to the right parietal region. While the patient reported a two-month history of insidious, low-grade headache, the clinical picture had shifted dramatically into a crescendo pattern over the five days preceding presentation. During this acute exacerbation, the pain intensity spiked to a debilitating level—recorded as

8/10 on the visual analog scale—and proved refractory to standard oral analgesic interventions, including maximal therapeutic doses of paracetamol and ibuprofen. Of particular concern was the association of the headache with projectile vomiting, a red flag symptom devoid of preceding nausea, which clinically signaled a significant elevation in intracranial pressure (ICP) resulting from the mass effect within the calvarium.

The history of present illness was further illuminated by collateral information provided by the patient's family, who had observed a distinct neurocognitive decline. They described a state of bradyphrenia—a slowing of cognitive processing—accompanied by subtle personality changes over the preceding week, indicative of compromised frontal-subcortical circuits or diffuse cerebral edema. The neurological crisis culminated three days prior to admission in a focal motor seizure with a highly specific somatotopic progression. The ictogenesis initiated in the left foot, marching systematically to the left hand and finally involving the face over a duration of approximately 60 seconds. This sequential spread is the hallmark of a Jacksonian March, a phenomenon that precisely localizes the epileptogenic focus to the contralateral motor strip (the right pre-central gyrus), following the anatomical organization of the motor homunculus.

Following the resolution of the motor activity, the patient entered a post-ictal state characterized by preserved awareness—classifying the event as a Focal Aware Seizure. However, this period was marked by a rare and scientifically illuminating symptom: complex visual release hallucinations. The patient vividly described being surrounded by small animals, specifically penguins, appearing on her bed. This phenomenon, clinically termed *zoopsia*, represents a specific form of peduncular hallucinosis. Unlike psychiatric hallucinations, these images are often silent, vivid, and recognized by the patient as unreal. In neuro-anatomical terms, the presence of zoopsia is highly specific for pathology disrupting the visual association pathways located at the temporo-parieto-occipital junction, providing a critical localization clue prior to neuroimaging.

The patient's medical background provided the essential context for interpreting these focal neurological deficits. She had been diagnosed with human immunodeficiency virus (HIV) infection only six weeks prior to this admission, presenting at WHO clinical stage III. In a timeline critical to the pathophysiology of her current condition, she had initiated a first-line antiretroviral therapy (ART) regimen consisting of a fixed-dose combination of Tenofovir (300 mg), Lamivudine (300 mg), and Efavirenz (600 mg) exactly 30 days prior to the onset of the acute neurological decline. Her self-reported adherence to this regimen was excellent (>95%), suggesting effective suppression of viral replication was underway. Epidemiologically, the patient's social history revealed a high pre-test probability for toxoplasmosis. She reported a history of high-risk sexual behavior and, more notably, significant exposure to definitive hosts of *Toxoplasma gondii*. She had owned and cared for three semi-domesticated cats since adolescence, creating a high likelihood of prior exposure to oocysts and the establishment of latent tissue cysts, which serve as the substrate for reactivation during periods of immune dysregulation. The temporal correlation between the initiation of high-efficacy ART and the sudden onset of symptoms raises the suspicion of an inflammatory unmasking event, rather than simple failure of immunity (Table 1).

Upon physical examination, the patient appeared lethargic, yet her sensorium remained intact, with a Glasgow Coma Scale (GCS) score of 15/15 (E4 V5 M6), indicating preserved reticular activating system function despite the cerebral pathology. Her hemodynamic status was stable, with a blood pressure of 110/70 mmHg, a heart rate of 88 beats per minute, a respiratory rate of 20 breaths per minute, and a normothermic temperature of 37.2°C, arguing against

a systemic septicemic process. Detailed cranial nerve interrogation revealed isocoric pupils (3 mm) with brisk reactivity to light. Fundoscopic examination ruled out papilledema, suggesting that while ICP was elevated enough to cause vomiting, it had not yet resulted in axoplasmic stasis at the optic disc. However, visual field testing uncovered a subtle left homonymous inferior quadrantanopia. This finding is neuro-anatomically significant, implicating damage to the superior optic radiations (Baum's loop) as they traverse the parietal lobe, further corroborating the localization of the lesion to the right parietal sector.

Examination of the motor system confirmed the presence of an upper motor neuron (UMN) syndrome. The patient exhibited a dense left-sided hemiparesis, graded at 4/5 on the Medical Research Council (MRC) scale, accompanied by distinct spasticity (Modified Ashworth Scale 2). Deep tendon reflexes were hyperactive (3+) on the left side compared to the right, and the pathologic Babinski sign was positive on left plantar stimulation. This constellation of signs—spastic hemiparesis, hyperreflexia, and extensor plantar response—confirmed damage to the corticospinal tract originating from the right cerebral hemisphere, consistent with the destructive nature of the suspect lesion.

Table 1. Summary of Clinical Findings on Admission

Comprehensive overview of physiological, neurological, and immunological parameters observed in the 22-year-old female patient.

PARAMETER	RESULT / OBSERVATION	REFERENCE / NORMAL	CLINICAL INTERPRETATION
I. GENERAL SURVEY & VITAL SIGNS			
Consciousness (GCS)	E4 - V5 - M6 (15/15)	15/15	Intact Sensorium
Blood Pressure	110 / 70 mmHg	< 120/80 mmHg	Normotensive
Symptomatology	VAS 8/10 Hemicrania + Projectile Vomiting	None	Raised ICP Signs
II. NEUROLOGICAL STATUS (FOCAL DEFICITS)			
Visual System	L. Homonymous Inf. Quadrantanopia + *Zoopsia*	Intact Fields	Visual Assoc. Deficit
Motor Power (Left)	Grade 4/5 (Hemiparesis) + Spasticity	Grade 5/5	R. Motor Cortex Lesion
Pathologic Reflexes	(+) Babinski Sign (Left)	Negative	UMN Lesion
Seizure History	Jacksonian March (Foot → Hand → Face)	None	Focal Aware Seizure
III. HEMATOLOGY & IMMUNOLOGY			
Hemoglobin	9.3 g/dL	12.0 - 15.0 g/dL	Mild Anemia
CD4+ T-Cell Count	**307 cells/µL**	500 - 1500 cells/µL	Preserved (>200)
HIV-1 Viral Load	**< 40 copies/mL**	Not Detected	Virologically Suppressed
IV. SPECIFIC SEROLOGY (TOXOPLASMA)			
Anti-Toxoplasma IgG	240 IU/mL (Reactive)	< 6.4 IU/mL	Latent Infection
Anti-Toxoplasma IgM	1.8 Index (Reactive)	< 0.9 Index	Acute Reactivation

Following the initial clinical assessment, an extensive diagnostic workup was initiated to delineate the precise etiology of the neurological deficits and to define the patient's current immunological status. Central to this investigation was the assessment of the HIV-1 viral load, a parameter that proved pivotal in understanding the pathophysiology of this specific presentation. Laboratory analysis revealed a viral load suppressed to fewer than 40 copies/mL. This result, achieved after only one calendar month of antiretroviral therapy (ART), indicated not only excellent patient adherence to the Tenofovir-Lamivudine-Efavirenz regimen but also a precipitous drop in viremia. In the context of the patient's preserved CD4 count (>300 cells/µL), this rapid virological suppression provided the necessary immunological substrate for the development of immune reconstitution inflammatory syndrome (IRIS). It confirmed that the clinical deterioration was not a failure of viral control, but rather a consequence of a volatile, rapidly recovering immune system mounting an inflammatory assault on a latent pathogen.

To investigate the structural correlates of the patient's focal seizures and hallucinations, a Contrast-enhanced computed tomography (CE-CT) scan of the head was performed. The imaging findings were definitive and severe, revealing a classic multifocal pathology. The scan demonstrated three distinct ring-enhancing lesions, a radiographic appearance indicative of central necrosis surrounded by an inflammatory capsule with breakdown of the blood-brain barrier. The dominant lesion, measuring 2.4 x 1.8 cm, was situated at the right parieto-occipital junction. This localization offered a precise anatomical explanation for the patient's specific semiology; the involvement of the parietal lobe correlated with the sensory-motor deficits, while the extension into the occipital association areas accounted for the complex visual hallucinations (zoopsia). In addition to the primary mass, two smaller satellite lesions were identified within the right basal ganglia, a predilection site for *Toxoplasma gondii* due to its vascular supply.

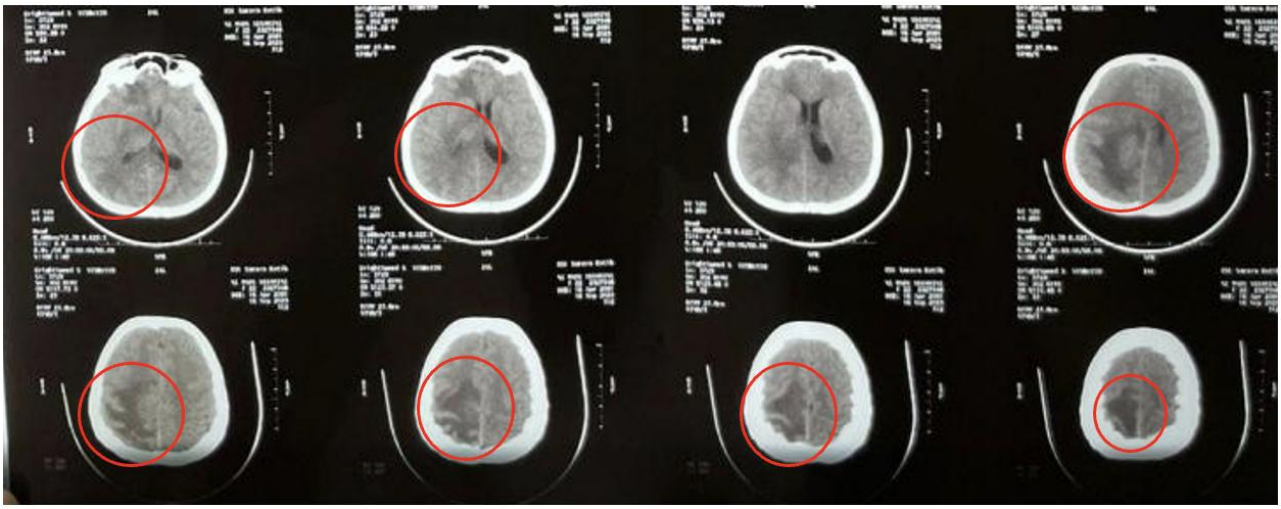

Figure 1. CT-scan of the head. The red rings reveal extensive vasogenic edema.

Of critical concern was the surrounding parenchymal reaction. The scan visualized extensive perilesional vasogenic edema, which exerted a significant mass effect upon the adjacent structures (Figure 1). This edema resulted in the partial effacement of the right lateral ventricle and a measured midline shift of 4 mm toward the contralateral hemisphere. This degree of mass effect

placed the patient at imminent risk of subfalcine herniation, underscoring the need for urgent intervention to reduce intracranial pressure independent of antimicrobial therapy. The radiological interpretation concluded that despite the atypical CD4 profile, the architecture of the lesions—multiple, ring-enhancing, and associated with profound edema—was highly suggestive of cerebral toxoplasmosis (TE).

The diagnostic challenge in this case lay in reconciling the radiographic evidence with the immunological data. The differential diagnosis for ring-enhancing lesions in an HIV-positive cohort typically includes cerebral toxoplasmosis, primary CNS lymphoma (PCNSL), and tuberculoma. In patients with preserved CD4 counts (>200 cells/µL), PCNSL is often statistically favored over TE. However, the morphological characteristics of the lesions guided the differential exclusion. PCNSL typically presents as a solitary, hyperdense lesion with a predilection for the periventricular regions and corpus callosum. In contrast, this patient presented with multiple lesions distributed across the gray-white matter junction and basal ganglia, a pattern that strongly favored a parasitic etiology. Tuberculoma remained a consideration given the endemicity of tuberculosis in Indonesia; however, the lack of systemic constitutional symptoms (fever, night sweats) and pulmonary findings lowered this probability.

Consequently, the final diagnostic formulation was Cerebral Toxoplasmosis unmasked by Immune Reconstitution Inflammatory Syndrome (IRIS). This diagnosis was supported by a convergence of evidence: the positive serological profile (Anti-Toxoplasma IgM and high-titer IgG indicating reactivation), the classical neuroimaging features, the suppressed viral load, and the pathognomonic temporal correlation with ART initiation 30 days prior. Given the resource-limited setting where stereotactic brain biopsy and Thallium-201 SPECT imaging were unavailable to definitively rule out lymphoma, the clinical team proceeded with a therapeutic trial. This approach, validated by international guidelines, posits that a rapid clinical and radiological response to anti-toxoplasma therapy serves as an *ex-juvantibus* confirmation of the diagnosis (Table 2).

The management strategy was complicated by the unavailability of Pyrimethamine, the gold-standard antifolate for TE, within the Indonesian national formulary. To circumvent this barrier, the patient was initiated on a high-dose alternative regimen of Cotrimoxazole (Trimethoprim-Sulfamethoxazole). The dosing protocol was aggressive, consisting of 960 mg (160 mg Trimethoprim / 800 mg Sulfamethoxazole) administered orally every 6 hours. This resulted in a total daily load of 640 mg Trimethoprim and 3200 mg Sulfamethoxazole, a dosage sufficient to achieve bactericidal concentrations within the cerebrospinal fluid.

To manage the significant mass effect and the inflammatory component of the IRIS response, adjuvant corticosteroid therapy was deemed essential. The patient received a loading dose of Dexamethasone 10 mg intravenously, followed by a maintenance dose of 4 mg every 6 hours. This was intended to stabilize the blood-brain barrier and reduce vasogenic edema. Gastric protection was provided via Omeprazole 40 mg intravenously every 12 hours to mitigate the ulcerogenic risk of high-dose steroids.

The validity of the working diagnosis was confirmed by the patient's rapid clinical trajectory. By Day 4 of admission, the patient exhibited a dramatic neurological recovery. The severity of the hemicrania subsided significantly, dropping to 2/10 on the Visual Analog Scale. Most notably, the penguin hallucinations (zoopsia) resolved completely, indicating the subsidence of irritation in the visual association cortex, and no further seizure activity was recorded. At the two-week follow-up (Day 14), the patient was ambulatory, with the dense hemiparesis resolving to a mild residual weakness (Motor Power 4+/5). A repeat non-contrast CT scan demonstrated a marked reduction in both the mass effect and the

extent of the cerebral edema. By Day 30, the patient was maintained on oral Cotrimoxazole (960 mg every 12 hours) and had successfully tapered off corticosteroids. Crucially, despite the high accumulation of sulfonamides, no adverse cutaneous reactions, such as Stevens-Johnson syndrome, were observed. This successful outcome not only confirmed the diagnosis of TE but also validated the efficacy of Cotrimoxazole as a life-saving, accessible therapeutic alternative in resource-constrained healthcare systems.

Table 2. Clinical Management Summary

Overview of the diagnostic formulation, therapeutic regimen, and clinical progression outcomes.

A. DIAGNOSTIC FORMULATION		
Final Diagnosis	**Cerebral Toxoplasmosis (TE) with Unmasking IRIS**	*Based on the triad of: 1) Focal neurological signs, 2) Positive Serology, and 3) Radiological evidence in the context of recent HAART initiation.*
Key Findings	• **Immunology:** CD4 307 cells/μL; Viral Load <40 copies/mL. • **Imaging (CE-CT):** Multiple ring-enhancing lesions + Basal Ganglia involvement. • **Timing:** Symptom exacerbation 30 days post-HAART.	*Suppressed viral load confirms adherence; high CD4 with new lesions supports "Unmasking" Immune Reconstitution Inflammatory Syndrome.*
Differential	EXCLUDED **Primary CNS Lymphoma**	*PCNSL typically presents as a solitary lesion. Rapid response to antibacterial therapy (Cotrimoxazole) confirmed TE diagnosis ex-juvantibus.*
B. THERAPEUTIC INTERVENTION		
Primary Therapy	HIGH DOSE **Cotrimoxazole** 960 mg (PO) every 6 hours	*Used as alternative to unavailable Pyrimethamine. Dosage provides bactericidal CNS penetration (Total: 640mg TMP / 3200mg SMX daily).*
Adjuvant Therapy	**Dexamethasone** 10mg Loading Dose → 4mg IV q6h	*Essential to manage vasogenic edema and midline shift caused by the IRIS inflammatory response.*
Supportive	**Omeprazole** (40mg q12h) + **Analgesia**	*Gastric protection required due to high-dose corticosteroid administration.*
C. CLINICAL OUTCOMES		
Acute (Day 4)	RAPID RESPONSE • Headache VAS reduced to 2/10. • **Resolution of Zoopsia** (Visual hallucinations). • Cessation of seizures.	*Clinical improvement within 96 hours is highly specific for Toxoplasmosis and validates the presumptive diagnosis.*
Follow-Up (Day 14)	**Status: Ambulatory** Residual hemiparesis improved (4+/5). CT Scan showed reduced mass effect.	*Patient successfully discharged. Steroids tapered to prevent adrenal insufficiency.*
Long Term (Day 30)	Maintenance on Oral Cotrimoxazole. NO ADVERSE EVENTS	*No cutaneous reactions (Stevens-Johnson Syndrome) observed.*

3. Discussion

This case serves as a critical clinical platform for re-evaluating the pathophysiology of central nervous system (CNS) opportunistic infections in the era of highly active antiretroviral therapy (HAART). The presentation of fulminant cerebral toxoplasmosis (TE) in a patient maintaining a CD4+ T-lymphocyte count of 307 cells/μL presents a significant challenge to the established epidemiological dogma.[11] Traditionally, clinical guidelines have relied on a rigid immunological safety threshold, operating under the premise that TE is statistically rare in patients with CD4 counts exceeding 200 cells/μL. Consequently, clinicians often use a preserved CD4 count as a robust negative predictive marker, excluding toxoplasmosis from the differential diagnosis in favor of malignancies or non-opportunistic etiologies. However, the case reported here underscores a critical diagnostic pitfall: the quantitative preservation of immune cells does not guarantee functional competence. We posit that this patient's clinical deterioration represents a textbook manifestation of unmasking immune reconstitution inflammatory syndrome (IRIS), mediated by a state of functional immune discordance, a phenomenon that has introduced new complexities to HIV management in the post-HAART landscape.[12]

The pathophysiology driving this paradoxical presentation is rooted in the volatility of immune recovery. IRIS is defined clinically as the paradoxical worsening of a pre-existing condition following the effective initiation of antiretroviral therapy.[13] In this patient, the prerequisite for IRIS—a rapid reversal of HIV-induced immunosuppression—was clearly evidenced by the precipitous drop in her viral load to fewer than 40 copies/mL after only one month of the Tenofovir-Lamivudine-Efavirenz (TLE) regimen. While this suppression indicates excellent adherence and virological success, it also sets the stage for a dysregulated immune response. The mechanism of Unmasking IRIS involves the immune system's sudden recognition of a subclinical, previously silent infection.

Prior to the initiation of HAART, the patient likely harbored latent *Toxoplasma gondii* cysts—acquired from her history of close contact with cats—within the neural parenchyma. During the period of untreated HIV infection, her immune system was too depleted to mount a significant inflammatory response against these cysts, rendering the infection asymptomatic. However, upon the initiation of therapy, the rapid expansion of CD4+ and CD8+ T-cells likely triggered a cytokine storm. These newly reconstituted immune cells trafficked to the central nervous system, recognized the specific *Toxoplasma* antigens, and unleashed an intense, focal inflammatory reaction. The timeline observed in this case is pathognomonic for this phenomenon: the patient's neurological symptoms escalated exactly 30 days after the initiation of antiretroviral therapy. In this context, the high CD4 count of 307 cells/μL should not be interpreted as a sign of protective immunity, but rather as a marker of this intense, rapid, and potentially pathological cellular expansion. This reinforces the clinical axiom that a rising CD4 count within the first three months of HAART initiation serves as a risk factor for inflammatory complications rather than a mere safety signal.[14]

The persistence of uncontrolled infection despite a CD4 count exceeding 300 cells/μL necessitates a discussion on the concept of immune discordance. This immunological enigma highlights a critical distinction between the quantity of circulating T-cells and their functional quality. While the absolute number of CD4 cells in this patient was adequate, their functional capacity to control intracellular parasites was evidently impaired. In the early phases of immune reconstitution, the rapidly repopulating T-cell pool often displays a skewed phenotype. These cells may be senescent, lack the full repertoire of antigen-specific memory functions, or fail to secrete essential cytokines such as Interferon-gamma (IFN-), which is the primary mediator of host defense against

T. gondii.[15] Furthermore, a significant proportion of these cells may be redistributing from lymph nodes rather than being newly generated naïve cells, or they may express exhaustion markers like PD-1 that limit their effector functions. Therefore, this case illustrates that the absolute CD4 count is a poor proxy for functional immunity against intracellular pathogens during the precarious early post-HAART window, and reliance on numerical thresholds can lead to dangerous diagnostic complacency.

Beyond the immunological complexity, this case offers a significant neuro-anatomical insight through the patient's report of complex visual hallucinations, specifically seeing penguins surrounding her bed. This phenomenon, clinically termed zoopsia, represents a specific variant of Peduncular Hallucinosis or Charles Bonnet-like syndrome and is of high localizing value.[16] The contrast-enhanced CT scan confirmed the presence of a lesion at the parieto-occipital junction, an area critical for the visual association pathways, specifically the ventral stream, or what pathway responsible for object recognition. Irritation of the visual association cortex by the parasitic lesion and surrounding edema can lead to Release Hallucinations. These are distinct from the auditory and menacing hallucinations typically seen in psychiatric disorders; organic visual hallucinations arising from this region are characteristically silent, vivid, lilliputian (small), and involve animals or familiar figures. The recognition of this specific semiology provided a precise clinical localization even before neuroimaging was performed, highlighting the enduring value of detailed neurological history taking in establishing an anatomical diagnosis.

The diagnostic management of this case highlights the challenges of ruling out competing etiologies in patients with preserved immunity. In Western cohorts, a patient presenting with ring-enhancing lesions and a CD4 count >300 cells/μL would statistically be more likely to have primary CNS lymphoma (PCNSL) than toxoplasmosis. Differentiating these two conditions is notoriously difficult without histopathological confirmation. Radiologically, PCNSL lesions tend to be solitary, larger (>4 cm), and often cross the corpus callosum, whereas toxoplasmosis lesions are typically multifocal and smaller, as seen in this patient. However, in resource-limited settings like Indonesia, advanced non-invasive diagnostic modalities such as Thallium-201 SPECT or magnetic resonance spectroscopy are rarely available. Consequently, the therapeutic trial becomes the primary diagnostic tool. PCNSL may show a transient response to corticosteroids due to their lymphocytotoxic effect, but it will not respond to antibiotics. The rapid clinical improvement observed in this patient within just four days of initiating high-dose Cotrimoxazole—characterized by the cessation of seizures and resolution of hallucinations—strongly supported the diagnosis of toxoplasmosis *ex-juvantibus*. Had the patient failed to improve by day 10 to 14, a stereotactic biopsy to rule out lymphoma would have been the mandated next step.[17]

This case also contributes to the body of evidence validating accessible therapeutic strategies in low-resource environments. The gold standard treatment for cerebral toxoplasmosis is the combination of Pyrimethamine and Sulfadiazine. However, Pyrimethamine is frequently unavailable or prohibitively expensive in many low-to-middle income countries (LMICs), including Indonesia.[18] This patient was successfully treated with Cotrimoxazole (Trimethoprim-Sulfamethoxazole), a widely available and inexpensive generic antibiotic. Cotrimoxazole offers excellent pharmacokinetics, with high blood-brain barrier penetration that allows it to reach 30-50% of serum concentrations in the cerebrospinal fluid. Its mechanism of action involves the sequential inhibition of folate synthesis, mimicking the synergistic effect of the standard Pyrimethamine-Sulfadiazine regimen.

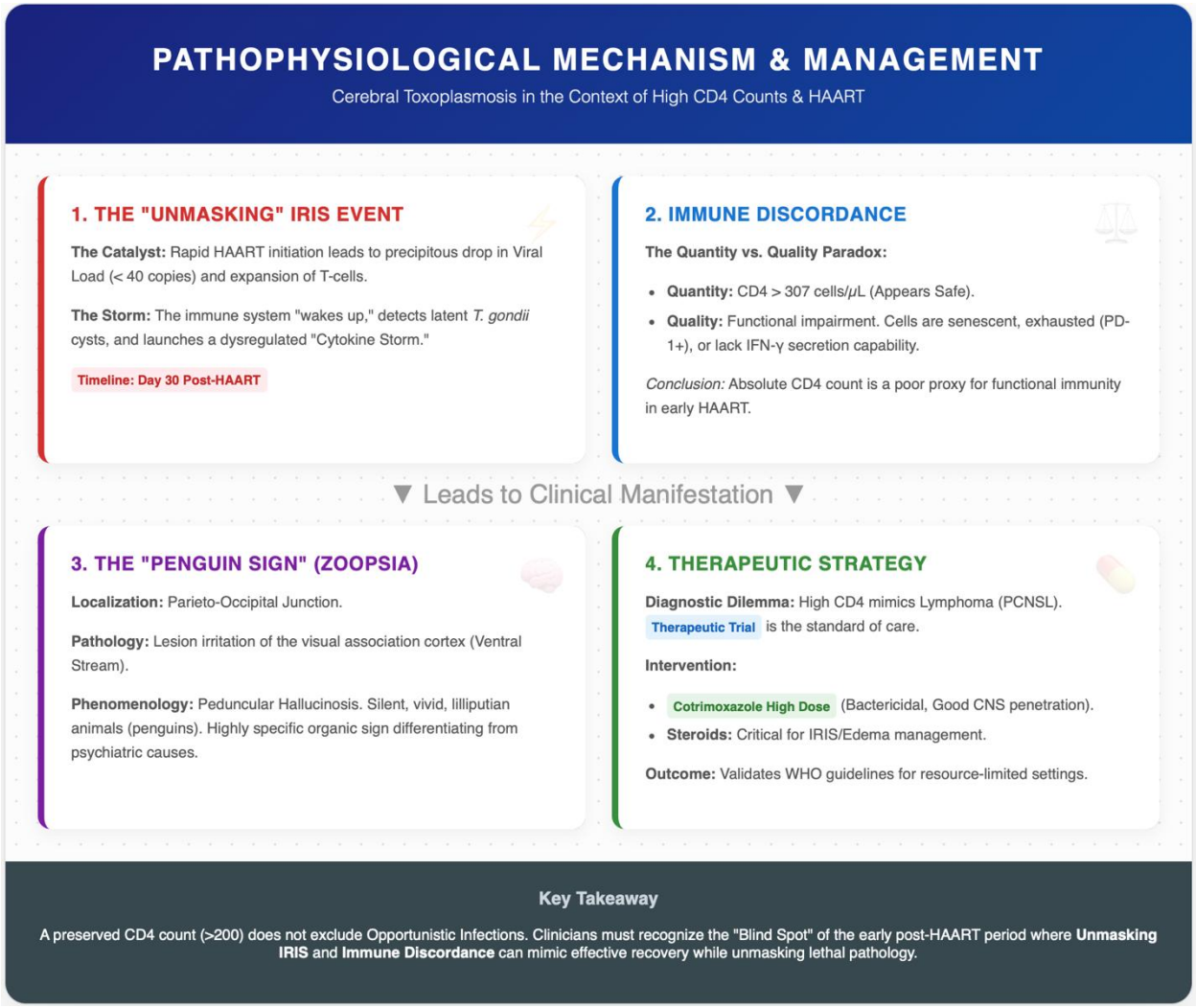

Figure 2. Pathophysiological mechanism and management.

The successful outcome in this patient, who achieved significant clinical improvement and was discharged by day four, validates the World Health Organization's recommendation to utilize Cotrimoxazole as a preferred first-line intervention in resource-limited healthcare systems.[19] It is important to acknowledge the limitations inherent in this report. The study is limited by the lack of cerebrospinal fluid (CSF) polymerase chain reaction (PCR) analysis for *T. gondii* DNA, which represents the gold standard for definitive confirmation. However, the decision to forego a lumbar puncture was clinically justified due to the significant mass effect and midline shift observed on CT, which posed a high risk of iatrogenic brain herniation. Consequently, the diagnosis remains presumptive, satisfying the Centers for Disease Control (CDC) criteria, which rely on a compatible clinical syndrome, positive serology, characteristic neuroimaging, and a rapid response to empiric anti-toxoplasma therapy.[20]

4. Conclusion

In conclusion, this case demonstrates that cerebral toxoplasmosis cannot be ruled out solely based on a CD4 count >200 to 300 cells/μL, particularly during the volatile period of immune reconstitution

immediately following HAART initiation. The phenomenon of unmasking IRIS can precipitate life-threatening opportunistic infections precisely when the immune system appears to be recovering, creating a diagnostic blind spot for clinicians relying on outdated heuristics. Clinicians must maintain a high index of suspicion for Unmasking IRIS when new neurological deficits emerge in a patient who has recently started HAART, particularly when accompanied by a rising CD4 count and a rapidly dropping viral load. The presence of complex visual hallucinations, such as the penguin sign described here, serves as a specific localizing sign for lesions involving the parieto-occipital junction and the visual association pathways. In resource-limited settings where pyrimethamine is inaccessible, high-dose cotrimoxazole serves as a life-saving, non-inferior therapeutic alternative for cerebral toxoplasmosis. The use of contrast-enhanced CT is mandatory for the evaluation of focal neurological deficits in HIV patients; non-contrast imaging is insufficient for characterizing ring-enhancing lesions and may lead to diagnostic errors. Ultimately, this case underscores that while CD4 counts are a valuable guide, they must not supersede clinical judgment. The successful management of neuro-AIDS in the modern era requires a nuanced understanding of immune discordance and a readiness to treat the patient's clinical presentation rather than their laboratory values.

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