Jurnal Sosial dan Sains (SOSAINS)
p-ISSN 2774-7018 e-ISSN 2774-700x

# Association Between Antiretroviral Therapy Initiation Timing and Clinical Outcomes in HIV/AIDS Patients with Toxoplasmic Encephalitis at Haji Adam Malik Hospital, Medan

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***ABSTRACT***

Toxoplasmic encephalitis (TE) is a life-threatening opportunistic infection commonly observed in individuals with HIV/AIDS, particularly those with severely suppressed CD4 counts. Determining the optimal timing for initiating antiretroviral therapy (ART) in the presence of TE remains a clinical challenge due to the potential benefits of early immune recovery and the risks of immune reconstitution inflammatory syndrome (IRIS). This study aims to evaluate the clinical outcomes of early versus delayed ART initiation in HIV patients with TE. A retrospective analysis was conducted on HIV patients diagnosed with TE who underwent standard toxoplasmosis treatment. Clinical outcomes were assessed using the Glasgow Outcome Scale (GOS), and comparisons were made between patients who received ART early and those whose ART was delayed. The results revealed a statistically significant association between ART timing and clinical outcome (p=0.002), indicating that early ART initiation was correlated with more favorable neurological recovery as measured by GOS. These findings support the consideration of early ART in TE cases, with careful monitoring for potential IRIS. This study contributes to the growing body of evidence informing ART initiation guidelines in the management of HIV-related opportunistic infections.

**Keywords:** Toxoplasmic encephalitis, HIV/AIDS, antiretroviral therapy, Glasgow Outcome Scale, IRIS

## INTRODUCTION

The most common and frequent opportunistic central nervous system (CNS) infection in patients with human immunodeficiency virus (HIV) is toxoplasmic encephalitis, caused by the intracellular protozoan parasite Toxoplasma gondii. In immunocompromised patients, such as those with HIV/AIDS, a state of immunodeficiency occurs due to the progressive quantitative and qualitative depletion of T lymphocytes (T-helper cells). In HIV infection, patients typically experience a critical decline in CD4 levels (CD4 <200/µL), rendering them highly susceptible to opportunistic infections (Rahman et al., 2018).

More than 13 million people worldwide, representing roughly one-third of the global HIV population, have been infected with *Toxoplasma gondii*, frequently presenting as cerebral toxoplasmosis. The highest prevalence of toxoplasmic encephalitis (TE) in HIV-infected individuals is observed in Northern Sudan (75%), Congo (73.7%), Ethiopia (72.4%), Iran (60.7%), Papua New Guinea (59.7%),

Brazil (57%), Mexico (48.7%), and Indonesia (43.6%) (Guizetti & Frischknecht, 2021).

Assessment of clinical outcomes in patients with toxoplasmic encephalitis is essential as an evaluation tool in treatment (Dian et al., 2023). A measurement tool is needed to assess the neurological function of patients and evaluate the success of treatment, beyond simply determining whether the patient has survived or died. One proposed tool is the Glasgow Outcome Scale (GOS), which can be used to evaluate clinical outcomes in patients with toxoplasmic encephalitis. The GOS was originally designed to assess clinical outcomes in cases of brain injury (Wang et al., 2017).

The timing of antiretroviral therapy (ART) initiation remains a subject of debate. On one hand, early initiation of ART can increase the risk of Immune Reconstitution Inflammatory Syndrome (IRIS) and heightened drug toxicity or interactions (Tamar, 2020). On the other hand, delaying ART for too long can lead to a persistently high viral load, exacerbating the severity of comorbid conditions. Although controversial in some literature, early ART initiation in patients with low CD4 counts (<200) is considered beneficial as it suppresses viral replication, reduces viral load, and supports immune recovery, despite the associated increased risks of drug toxicity and IRIS (Widjaja, 2021).

Several previous studies have examined the timing of antiretroviral therapy (ART) in HIV patients with opportunistic infections, yet few have focused specifically on toxoplasmic encephalitis (TE). For instance, the study by Miro et al. (2017) highlighted that while early ART initiation can be life-saving in cases of severe immunodeficiency, it is also associated with a higher incidence of IRIS in patients with CNS infections, including TE. However, the study lacked granular data on clinical outcomes using structured neurological evaluation tools such as the Glasgow Outcome Scale (GOS) (Isa, 2020). Another study by Tural et al. (2015) emphasized the importance of prompt ART initiation in opportunistic infections but failed to provide comparative analysis across ART timing groups in relation to specific neurological outcomes in TE cases (Elsheikha et al., 2020; Imran et al., 2018). This research addresses the gaps by applying the GOS to assess functional neurological recovery and directly comparing clinical outcomes between early and delayed ART initiation groups in patients with TE (Funk et al., 2011; Group, 2015). By doing so, it offers a more precise evaluation of treatment efficacy and contributes to the development of evidence-based guidelines for ART timing in TE cases (Berlianty et al., 2022).

This study aims to determine the effect of ART initiation timing on the clinical outcomes of HIV patients with toxoplasmic encephalitis, using the Glasgow Outcome Scale as a standardized assessment tool (Anglemyer et al., 2014; Consortium, 2009; Uthman et al., 2017; Vogt et al., 2017). The research contributes to a better understanding of the therapeutic window for ART in patients with severe opportunistic CNS infections. The findings are expected to assist clinicians in making informed decisions, optimizing treatment outcomes, and reducing risks

such as IRIS. It also offers valuable input for future clinical guidelines concerning ART management in neuroinfectious complications of HIV (Qin et al., 2020).

## RESEARCH METHOD

This study was an analytical observational study employing a prospective cohort design. Primary data were collected consecutively from all patients with toxoplasmic encephalitis and HIV who visited the outpatient clinic or were hospitalized at Haji Adam Malik Hospital, Medan. Clinical outcomes were assessed at the time of admission using the Glasgow Outcome Scale. Patients included in the study met the inclusion and exclusion criteria and had signed informed consent to participate in the research. The study subjects were selected from the population of patients with toxoplasmic encephalitis and HIV treated at Haji Adam Malik Hospital, Medan. The determination of study subjects was conducted using the consecutive sampling method. The research data were analyzed statistically using the Windows-based software Statistical Product and Service Solutions (SPSS) version 26.0. Data analysis and presentation were performed in two stages: univariate analysis to evaluate the demographic and clinical characteristics of the sample, and bivariate analysis to assess the relationship between independent and dependent variables using the chi-square test.

## RESULTS AND DISCUSSION

This study included 39 HIV patients with toxoplasmic encephalitis (TE) from Haji Adam Malik General Hospital, Medan, who met the inclusion criteria. The majority of the participants were male (31 individuals, 79.5%), aged between 21 and 66 years. And 20 (51.3%) had poor GOS scores (≤3).

**Table 1. Demographic Characteristics of the Research Participants**

| **Patient Demographics** | **n = 39** | **%** |
|---|---|---|
| Age | | |
| Minimum | 21 | |
| Median | 35 | |
| Maximum | 66 | |
| Gender (n, %) | | |
| Male | 31 | 79,5 |
| Female | 8 | 20,5 |
| *Glasgow Outcome Scale* | | |
| Poor (≤ 3) | 20 | 51,3 |
| Good (>3) | 19 | 48,7 |
| Time of ARV Initiation (n,%) | | |
| Early ≤ 2 weeks | 19 | 48,7 |
| Delayed > 2 weeks | 20 | 51,3 |

There was a significant relationship between the timing of antiretroviral (ARV) initiation and clinical outcomes in toxoplasmic encephalitis patients (p=0.002). The findings indicate that earlier administration of ARV leads to better clinical outcomes, as measured by the Glasgow Outcome Scale (GOS).

**Table 2. The Relationship Between Antiretroviral Initiation Timing and Clinical Outcomes in Patients with Toxoplasmic Encephalitis**

| Timing of ARV Initiation | *Glasgow Outcome Scale* | | P Value |
|---|---|---|---|
| | Good (n, %) | Poor (n, %) | |
| *Early* <2 minggu | 14 (35,8) | 5 (12,8) | 0,002* |
| *Delayed* >2 minggu | 5 (12,8) | 15 (38,4) | |

Based on statistical analysis using the chi-square test on 39 subjects with toxoplasmic encephalitis and HIV-positive status at Haji Adam Malik General Hospital, Medan, a significant relationship was found between the timing of antiretroviral (ARV) initiation and clinical outcomes in patients with toxoplasmic encephalitis (p=0.002). The findings indicate a correlation between these variables, suggesting that earlier initiation of ARV is associated with better clinical outcomes, as measured by the Glasgow Outcome Scale (GOS) (Luma et al., 2013).

The appropriate timing of antiretroviral (ARV) initiation is crucial for patients with HIV and opportunistic infections, as their immune systems are already severely compromised and require immediate recovery (Li et al., 2024). However, overlapping drug toxicity, potential pharmacokinetic interactions with ARV medications, and the risk of developing immune reconstitution inflammatory syndrome (IRIS) can arise if ARV is initiated too early, potentially leading to worse outcomes. Conversely, delaying ARV initiation in the context of a severely compromised immune system can also result in poor outcomes (Puspitasari et al., 2016).

A prospective multicenter observational study conducted in China by Yao et al. in 2024 compared the clinical outcomes of early versus delayed ARV initiation. The study found no significant differences in clinical outcomes between the two groups, including mortality rates, occurrences of IRIS, and HIV virological and immunological outcomes.

This study aligns with research by Berlianty et al. in 2022, which observed changes in functional status among patients receiving early ARV initiation, as measured by the Glasgow Outcome Scale (GOS). Among patients diagnosed with toxoplasmic encephalitis upon hospital admission, the majority were at GOS 3 (76%). At discharge, 28% were at GOS 1 (indicating death or severe disability), while others showed improvement, with 33% at GOS 4 and 25% at GOS 5. The study found no significant differences in clinical outcomes at two weeks and one month post-therapy, possibly because HIV is a chronic disease that leads to persistent neurological deficits and slow recovery. Long-term therapy for both HIV and toxoplasmic encephalitis may be required, and noticeable improvements may not be evident within the first two weeks or even the first month of treatment.

## CONCLUSION

This study concludes that the timing of antiretroviral therapy (ART) initiation significantly influences clinical outcomes in patients with toxoplasmic encephalitis. The results show a statistically significant relationship (p=0.002), indicating that earlier initiation of ART is associated with better neurological recovery as assessed by the Glasgow Outcome Scale (GOS). These findings support the clinical recommendation for timely ART administration to improve treatment prognosis in immunocompromised HIV patients with TE. Future research is suggested to explore optimal timing windows and potential risks such as immune reconstitution inflammatory syndrome (IRIS), particularly through prospective multicenter studies with larger sample sizes to strengthen the generalizability of these findings.

## REFERENCES

Anglemyer, A., Rutherford, G. W., Easterbrook, P. J., Horvath, T., Vitoria, M., Jan, M., & Doherty, M. C. (2014). Early initiation of antiretroviral therapy in HIV-infected adults and adolescents: a systematic review. *Aids*, *28*, S105–S118.

Berlianty, B., Dian, S., & Ganiem, A. R. (2022). Glasgow Outcome Scale Assessment in Patients with Cerebral Toxoplasmosis. *Althea Medical Journal*, *9*(1), 30–36.

Consortium, W. T. S. (2009). Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *The Lancet*, *373*(9672), 1352–1363.

Dian, S., Ganiem, A. R., & Ekawardhani, S. (2023). Cerebral toxoplasmosis in HIV-infected patients: a review. *Pathogens and Global Health*, *117*(1), 14–23.

Elsheikha, H. M., Marra, C. M., & Zhu, X.-Q. (2020). Epidemiology, pathophysiology, diagnosis, and management of cerebral toxoplasmosis. *Clinical Microbiology Reviews*, *34*(1), 10–1128.

Funk, M. J., Fusco, J. S., Cole, S. R., Thomas, J. C., Porter, K., Kaufman, J. S., Davidian, M., White, A. D., Hartmann, K. E., & Eron Jr, J. J. (2011). Timing of HAART initiation and clinical outcomes among HIV-1 seroconverters. *Archives of Internal Medicine*, *171*(17), 1560.

Group, I. S. S. (2015). Initiation of antiretroviral therapy in early asymptomatic HIV infection. *New England Journal of Medicine*, *373*(9), 795–807.

Guizetti, J., & Frischknecht, F. (2021). Apicomplexans: A conoid ring unites them all. *PLoS Biology*, *19*(3), e3001105.

Imran, D., Estiasari, R., Maharani, K., Sucipto, Lestari, D. C., Yunus, R. E., Yunihastuti, E., Karyadi, T. H., Oei, D., & Timan, I. S. (2018). Presentation, etiology, and outcome of brain infections in an Indonesian hospital: A cohort study. *Neurology: Clinical Practice*, *8*(5), 379–388.

Isa, A. (2020). Measuring The Implementation Of Regulation Of The Minister Of Health Number 97 Of 2014 Concerning Delivery In Health Facilities. *Estudiante Law Journal*, 20–35.

Li, Y., Jiang, H., Zeng, Y., Lu, Y., Chen, S., Zhang, Y., Jiang, Z., Yang, T., Liu, S., & Chen, Y. (2024). Optimal Timing of Antiretroviral Therapy Initiation in Acquired Immunodeficiency Syndrome–Associated Toxoplasmic Encephalitis: A Prospective Observational Multicenter Study in China. *Infectious Diseases & Immunity*, *4*(1), 4–9.

Luma, H. N., Tchaleu, B. C. N., Mapoure, Y. N., Temfack, E., Doualla, M. S., Halle, M. P., Joko, H. A., & Koulla-Shiro, S. (2013). Toxoplasma encephalitis in HIV/AIDS

patients admitted to the Douala general hospital between 2004 and 2009: a cross sectional study. *BMC Research Notes*, *6*, 1–5.

Puspitasari, E., Yunihastuti, E., Rengganis, I., & Rumende, C. M. (2016). Prediktor mortalitas pasien HIV/AIDS rawat inap. *Jurnal Penyakit Dalam Indonesia| Vol*, *3*(1).

Qin, Y., Lu, Y., Zhou, Y., Harypursat, V., Sun, F., Yang, S., Tang, S., Li, Y., He, X., & Zeng, Y. (2020). Timing of antiretroviral therapy for HIV-infected patients with moderate to severe Pneumocystis pneumonia: study protocol for a multi-centre prospective randomised controlled trial. *Trials*, *21*, 1–7.

Rahman, T., Rahman, A., & Chakraborty, S. (2018). Infection of Toxoplasma gondii in humans and livestock animals: an emerging silent threat for Bangladesh. *Open Journal of Medical Microbiology*, *8*(4), 109–117.

Tamar, M. (2020). Implementation of Regulation of the Minister of Health of the Republic of Indonesia Number 15 of 2013 in Improving the Performance of Female Employees at South Sulawesi Provincial Government Offices. *Journal of Social and Political Sciences*, *3*(4).

Uthman, O. A., Nachega, J. B., Anderson, J., Kanters, S., Mills, E. J., Renaud, F., Essajee, S., Doherty, M. C., & Mofenson, L. M. (2017). Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. *The Lancet HIV*, *4*(1), e21–e30.

Vogt, F., Rehman, A. M., Kranzer, K., Nyathi, M., Van Griensven, J., Dixon, M., Ndebele, W., Gunguwo, H., Colebunders, R., & Ndlovu, M. (2017). Relationship between time to initiation of antiretroviral therapy and treatment outcomes: A cohort analysis of ART eligible adolescents in Zimbabwe. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *74*(4), 390–398.

Wang, Z.-D., Wang, S.-C., Liu, H.-H., Ma, H.-Y., Li, Z.-Y., Wei, F., Zhu, X.-Q., & Liu, Q. (2017). Prevalence and burden of Toxoplasma gondii infection in HIV-infected people: a systematic review and meta-analysis. *The Lancet HIV*, *4*(4), e177–e188.

Widjaja, G. (2021). New Paradigm in Health Law Education andRegulation; a Conceptual Approach Towards Indonesian National Health Law. *Multicultural Education*, *7*(10).