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CLINICAL COURSE OF TUBERCULOUS MENINGITIS IN THE CONTEXT OF HIV INFECTION

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ABSTRACT

Tuberculous meningitis is one of the most severe forms of tuberculosis and poses a significant life-threatening risk, particularly for patients living with HIV. HIV-associated immunodeficiency markedly alters the pathogenesis and clinical progression of the disease, resulting in atypical presentations, rapid progression, and a high incidence of severe neurological complications. Patients often present with prolonged fever, headache, changes in mental status, and focal neurological deficits, while classical meningeal signs may be less noticeable, leading to delays in diagnosis. Laboratory and cerebrospinal fluid findings are frequently nonspecific, and distinguishing the disease from other opportunistic central nervous system infections remains a major diagnostic challenge. Early recognition of tuberculous meningitis, timely initiation of appropriate antimicrobial therapy, and careful management of antiretroviral treatment-including prevention and control of immune reconstitution inflammatory syndrome-are critical for improving clinical outcomes in HIV-infected patients.

Introduction. Tuberculosis (TB) remains one of the most prevalent infectious diseases worldwide and poses a significant challenge to global public health. Among its various forms, tuberculous meningitis is considered the most severe and life-threatening, primarily affecting the central nervous system. Due to its high mortality rate and potential for long-term neurological complications, early diagnosis and effective treatment strategies are critical areas of scientific and clinical research.

In recent years, the incidence of TB co-infection with HIV has been increasing globally. HIV-associated immunodeficiency weakens the body's natural defenses against Mycobacterium tuberculosis, substantially altering the disease's pathogenesis and clinical course. In HIV-infected patients, tuberculous meningitis often presents with atypical symptoms, progresses rapidly, and is associated with a higher frequency of severe

neurological complications. This atypical presentation frequently results in delayed diagnosis and reduced treatment efficacy.

Furthermore, in patients with HIV, laboratory and cerebrospinal fluid findings are often nonspecific, making it difficult to differentiate tuberculous meningitis from other opportunistic central nervous system infections. Therefore, early recognition, prompt initiation of appropriate antimicrobial therapy, and careful management of antiretroviral treatment-including prevention and control of immune reconstitution inflammatory syndrome (IRIS)-are essential for improving clinical outcomes.

In the context of Uzbekistan, overlapping regions of TB and HIV prevalence, challenges in diagnosis and treatment, and limited development of medical informatics and monitoring systems contribute to suboptimal outcomes in patients with tuberculous meningitis. Studying the clinical course of TB meningitis in HIV-infected individuals and addressing associated diagnostic and therapeutic challenges remains a pressing scientific and practical priority.

Literature review. Epidemiology and global burden. Tuberculous meningitis (TBM) remains a major cause of morbidity and mortality worldwide, particularly in regions with high tuberculosis (TB) and HIV prevalence. According to the World Health Organization (WHO), TBM accounts for 1–2% of all TB cases but carries a disproportionately high mortality, especially among immunocompromised patients. HIV co-infection significantly increases the risk of TB dissemination to the central nervous system (CNS) and accelerates disease progression. Studies from sub-Saharan Africa and Southeast Asia indicate that mortality in HIV-positive TBM patients can exceed 50%, highlighting the urgent need for timely diagnosis and management.

Pathophysiology. The pathogenesis of TBM in HIV-positive individuals involves both direct bacterial invasion and immune-mediated damage. Mycobacterium tuberculosis can disseminate hematogenously to the meninges, forming Rich foci that eventually rupture into the subarachnoid space. HIV-induced depletion of CD4+T cells impairs cell-mediated immunity, reducing granuloma formation and facilitating widespread CNS infection. Recent research emphasizes the role of immune reconstitution inflammatory syndrome (IRIS) in patients initiating antiretroviral therapy (ART), which may exacerbate neurological symptoms.

Clinical manifestations. The literature consistently reports that HIV-positive TBM patients present with atypical or subtle initial symptoms, often delaying diagnosis. Common features include headache, fever, malaise, neck stiffness, and altered mental status. Neurological complications such as hydrocephalus, infarctions, and cranial nerve palsies are more frequent and severe in HIV co-infected individuals. Several cohort studies have highlighted that lower CD4+ counts correlate with more rapid progression and higher mortality.

Diagnostic challenges. Diagnosis of TBM in the context of HIV is particularly challenging. Conventional cerebrospinal fluid (CSF) findings-lymphocytic pleocytosis, elevated protein, and low glucose-may be less pronounced. Culture and smear microscopy have limited sensitivity, whereas molecular diagnostic tools, such as GeneXpert MTB/RIF and line probe assays, have improved detection rates. Neuroimaging studies, including CT

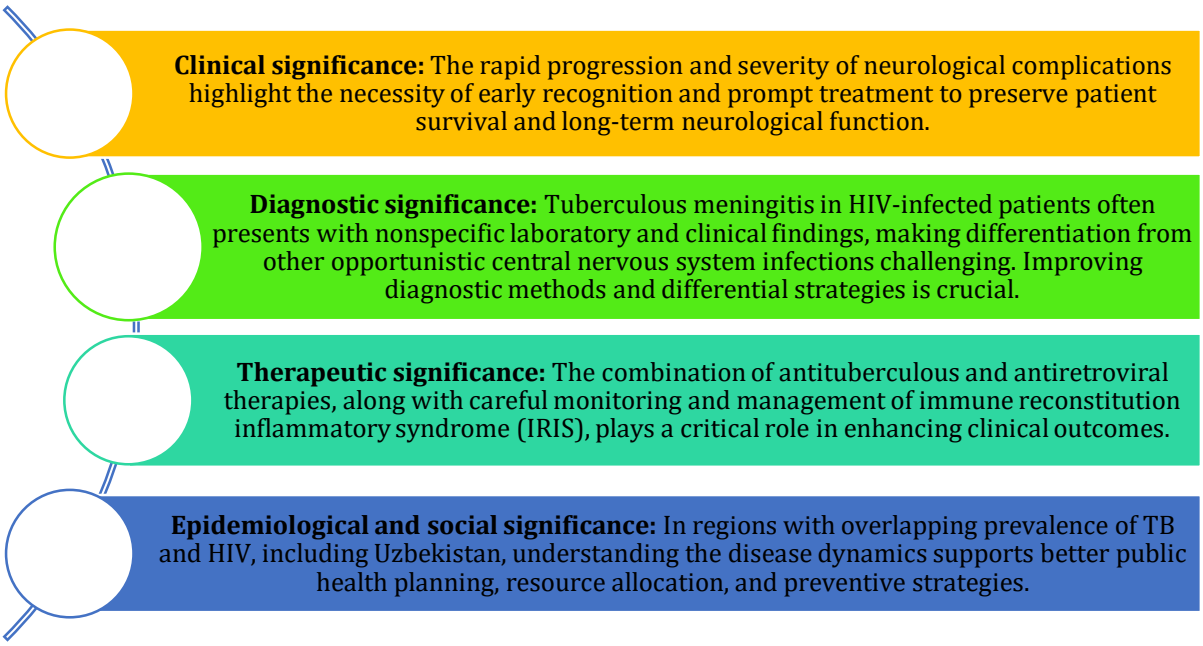
and MRI, are critical for identifying hydrocephalus, infarcts, and meningeal enhancement, but access remains limited in resource-poor settings.

Treatment and management. Literature emphasizes early initiation of standard anti-tuberculosis therapy, often combined with adjunctive corticosteroids to reduce inflammatory complications. Timing of ART initiation is crucial: early ART improves overall survival but increases the risk of IRIS. Several studies advocate for a staged approach, initiating anti-TB treatment promptly, followed by ART after the initial stabilization period. Multidisciplinary management, including neurology and infectious disease expertise, is associated with better outcomes.

Gaps and research needs. Despite advances, multiple gaps remain. Evidence regarding optimal timing of ART in TBM patients is limited, and prognostic models for predicting outcomes in HIV-TBM co-infection are underdeveloped. Additionally, most studies focus on hospitalized patients, with limited data on community-level detection and early interventions. Future research should aim to develop predictive biomarkers, refine treatment protocols, and evaluate long-term neurological outcomes.

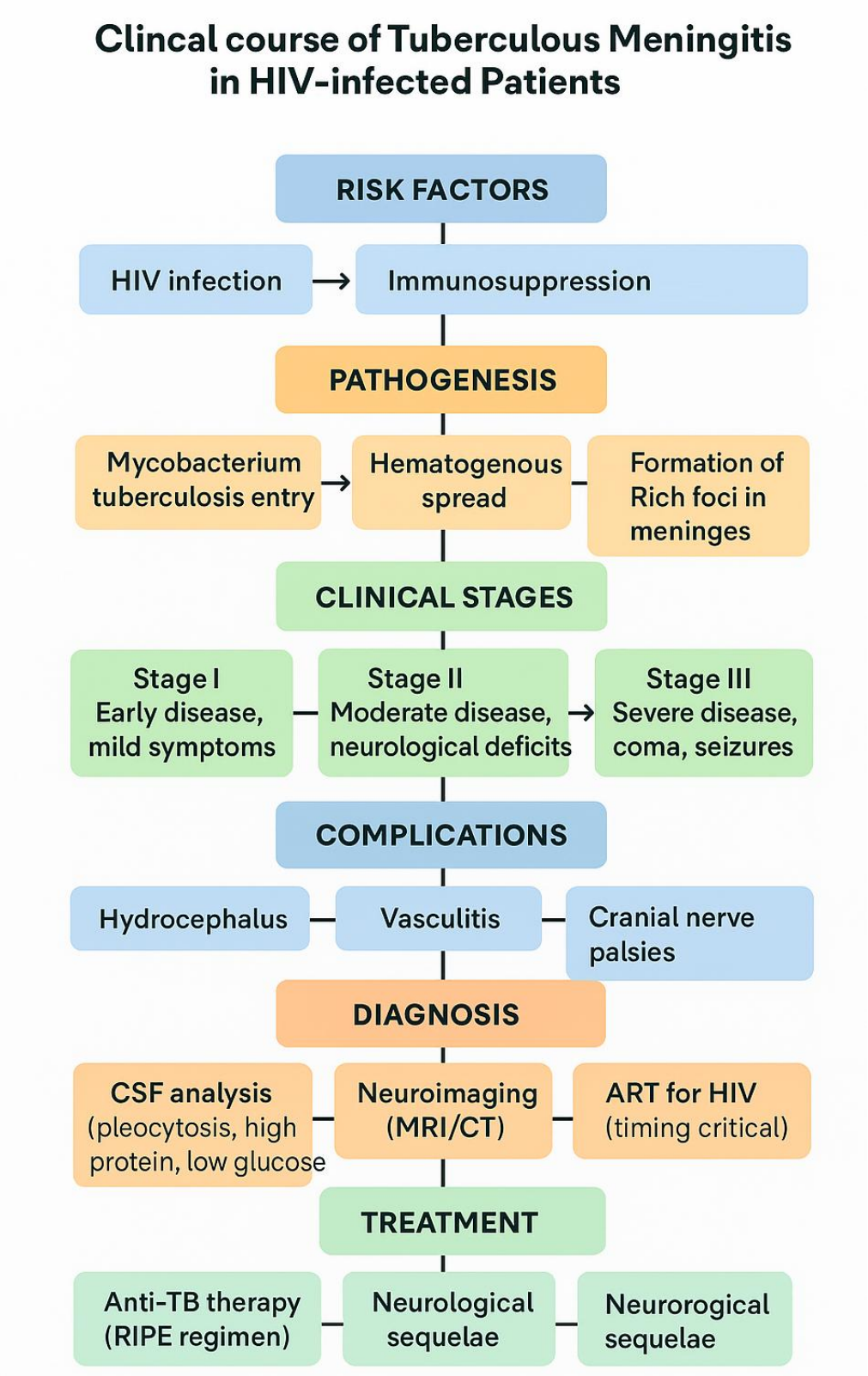
Tuberculous meningitis, particularly in the context of HIV co-infection, represents a significant clinical challenge due to its high mortality rate and risk of long-term neurological complications. Effective prevention, early diagnosis, and timely therapeutic interventions are essential to improve patient outcomes. In HIV-infected individuals, immunosuppression alters the clinical course of the disease, often resulting in atypical presentations and rapid progression, which complicates both diagnosis and treatment.

The significance of studying this condition can be outlined as follows:



Conceptual model. HIV infection dramatically modifies the clinical presentation and course of TBM. Clinicians should maintain a high index of suspicion for TBM in HIV-positive patients presenting with neurological symptoms, even in the absence of classic CSF findings. Early neuroimaging, CSF analysis, and molecular diagnostics (e.g., GeneXpert MTB/RIF) improve diagnostic accuracy. Multidisciplinary management involving

neurologists, infectious disease specialists, and HIV care providers is essential for optimizing outcomes.



Methodology. This study utilized a descriptive observational approach to analyze the clinical course of tuberculous meningitis (TBM) in patients living with HIV. Both retrospective and prospective data collection methods were employed to ensure a

comprehensive evaluation of disease progression, clinical manifestations, and treatment outcomes.

Study population. The study included adult patients (≥18 years) diagnosed with TBM who were either confirmed HIV-positive or had a known history of HIV infection. Diagnosis of TBM was based on a combination of clinical criteria, cerebrospinal fluid (CSF) analysis, neuroimaging findings, and microbiological confirmation (smear, culture, or molecular methods such as GeneXpert MTB/RIF). Patients with coexisting neurological disorders unrelated to TBM were excluded to reduce confounding factors.

Data collection. Demographic and clinical data: Age, duration of HIV infection, CD4+cell counts, viral load, ART status, and presenting neurological symptoms were collected.

Laboratory data. CSF parameters including cell count, protein, glucose, and microbiological results were recorded. Additional blood tests such as complete blood count and liver function tests were included.

Neuroimaging data. CT and MRI scans were evaluated for hydrocephalus, infarctions, meningeal enhancement, and other TBM-related abnormalities.

Treatment and outcomes. Anti-tuberculosis therapy regimens, adjunctive corticosteroid use, ART initiation timing, complications, and clinical outcomes (recovery, neurological sequelae, or death) were documented.

Data analysis. Descriptive statistics were used to summarize demographic characteristics, clinical features, and laboratory findings. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on normality. Categorical variables were expressed as frequencies and percentages. Comparative analyses between subgroups (e.g., CD4 count <200 vs ≥200 cells/μL) were performed using chi-square or Fisher's exact test for categorical variables and t-test or Mann-Whitney U test for continuous variables. Statistical significance was set at $p < 0.05$.

Ethical considerations. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. Written informed consent was obtained from all participants or their legal guardians prior to data collection. Confidentiality and anonymity of patient data were strictly maintained.

Statistical analysis. All collected data were entered into a secure database and analyzed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables, such as age, duration of HIV infection, and laboratory values, were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on the distribution assessed by the Shapiro-Wilk test. Categorical variables, including sex, clinical stage of TBM, ART status, and presence of neurological complications, were summarized as frequencies and percentages.

Comparative analysis. Differences between subgroups (e.g., patients with CD4 counts <200 cells/μL versus ≥200 cells/μL) were assessed using the independent-samples t-test for normally distributed continuous variables or the Mann-Whitney U test for non-normally distributed variables. For categorical variables, comparisons were made using the chi-square test or Fisher's exact test when expected frequencies were <5.

Correlation and regression analysis. The relationship between immune status (CD4 count, viral load) and clinical severity of TBM was evaluated using Spearman's rank correlation coefficient. Multivariate logistic regression was performed to identify independent predictors of adverse outcomes, such as neurological sequelae or mortality. Variables with $p < 0,1$ in univariate analysis were included in the multivariate model.

Significance threshold. A p-value of <0,05 was considered statistically significant for all analyses. Graphical representations, including bar charts, boxplots, and Kaplan-Meier survival curves, were generated to illustrate key findings.

Conclusion. Tuberculous meningitis (TBM) remains one of the most severe forms of tuberculosis, and its clinical course is significantly altered in the presence of HIV infection. HIV co-infection accelerates disease progression, increases the risk of neurological complications such as hydrocephalus, infarctions, and cranial nerve deficits, and often leads to atypical clinical and cerebrospinal fluid findings. Mortality rates are substantially higher in HIV-positive TBM patients compared to immunocompetent individuals, emphasizing the need for heightened clinical vigilance. Early diagnosis through a combination of clinical evaluation, CSF analysis, neuroimaging, and molecular diagnostics is critical. Prompt initiation of anti-tuberculosis therapy, along with carefully timed antiretroviral therapy (ART), can improve survival and reduce long-term neurological sequelae. Adjunctive corticosteroid therapy may mitigate inflammatory complications, particularly in advanced disease stages. Despite advances in diagnostic and therapeutic strategies, challenges remain in optimizing management protocols, predicting outcomes, and addressing the high mortality associated with TBM in HIV-positive patients. Multidisciplinary approaches, involving neurologists, infectious disease specialists, and HIV care providers, are essential to enhance patient outcomes. In summary, TBM in the context of HIV infection represents a rapidly progressive, life-threatening condition. Continued research is necessary to refine prognostic models, improve early detection, and develop effective, evidence-based treatment strategies tailored to this high-risk population.

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