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Mangen, 2025

ISSN: 2550-7931

International Digital Organization for Scientific Research
IDOSR JOURNAL OF APPLIED SCIENCES 10(2):29-32, 2025.
https://doi.org/10.59298/IDOSRJAS/2025/102.2932

IDOSRJAS1020000

CD4+ T Cell Exhaustion Biomarkers in Chronic HIV Infection: Prognostic Implications

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ABSTRACT

Chronic human immunodeficiency virus (HIV) infection was characterized by progressive immune dysfunction, in which CD4+ T cell depletion and exhaustion play pivotal roles. CD4+ T cell exhaustion, marked by impaired proliferative capacity and sustained expression of inhibitory receptors, contributes to poor immune reconstitution despite effective antiretroviral therapy. Biomarkers such as programmed cell death protein 1 (PD-1), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), cytotoxic T lymphocyte antigen 4 (CTLA-4), and lymphocyte activation gene 3 (LAG-3) had been proposed as key indicators of T cell dysfunction, while soluble inflammatory mediators provide complementary prognostic information. The purpose of this review was to critically evaluate the prognostic implications of CD4+ T cell exhaustion biomarkers in chronic HIV infection, focusing on their utility for predicting disease progression, therapeutic outcomes, and comorbid risks. A narrative synthesis was conducted using PubMed, Scopus, and Web of Science databases for studies published between 2012 and 2025, including clinical trials, mechanistic investigations, and translational studies of immune biomarkers in HIV. Evidence indicated that high expression of PD-1 and TIM-3 correlates with accelerated CD4+ decline, higher viral reservoirs, and increased risk of opportunistic infections. Combinatorial biomarker profiling enhanced prognostic accuracy beyond single markers. Importantly, exhaustion biomarkers also predicted responsiveness to immune-based therapies and vaccine strategies. Despite their promise, variability across cohorts and technical limitations hindered standardization. CD4+ T cell exhaustion biomarkers provided valuable insights into HIV pathogenesis and may guide prognostic assessment and therapeutic innovation.

Keywords: HIV, CD4+ T cell, Immune exhaustion, Biomarkers, Prognosis.

INTRODUCTION

Human immunodeficiency virus (HIV) remains a global health challenge, with 38 million people living with the infection in 2022 and approximately 1.5 million new cases annually despite advances in treatment [1]. Chronic HIV infection leads to progressive immune dysfunction characterized by CD4+ T cell depletion, generalized immune activation, and eventual acquired immunodeficiency syndrome (AIDS) [2]. Although combination antiretroviral therapy (ART) suppresses viral replication and prolongs survival, a significant subset of patients fail to achieve optimal immune reconstitution due to persistent immune exhaustion [3].

CD4+ T cell exhaustion represents a distinct dysfunctional state marked by reduced cytokine production, impaired proliferation, and sustained expression of inhibitory receptors such as programmed cell death protein 1 (PD-1), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), cytotoxic T lymphocyte antigen 4 (CTLA-4), and lymphocyte activation gene 3 (LAG-3). This phenotype predicts poor virological outcomes, opportunistic infections, and higher mortality risk [4]. For example, anemia is a recognized prognostic marker of HIV disease progression and may overlap mechanistically with immune exhaustion pathways [5]. Understanding and quantifying exhaustion biomarkers is thus essential for prognostic stratification and for guiding therapeutic interventions. This review first examines molecular and cellular mechanisms underlying CD4+ T cell exhaustion, then discusses key exhaustion biomarkers and their prognostic value, followed by therapeutic implications and translational challenges. The review also considers limitations in biomarker standardization and future directions for integrating exhaustion profiling into clinical management. The purpose is to provide clinicians and researchers with an evidence-based synthesis of the prognostic implications of CD4+ T cell exhaustion biomarkers in chronic HIV infection.

Mechanisms of CD4+ T Cell Exhaustion in HIV

Persistent antigenic stimulation from uncontrolled viral replication drives functional impairment of CD4+ T cells. Chronic exposure to HIV antigens results in a progressive decline in interleukin-2 (IL-2) secretion, diminished proliferative capacity, and altered transcriptional programs [6]. Sustained expression of inhibitory receptors such as PD-1, TIM-3, CTLA-4, and LAG-3 disrupts T cell receptor (TCR) signaling and promotes metabolic dysfunction [7].

Metabolic reprogramming further contributes to exhaustion, with reductions in glycolytic flux and mitochondrial dysfunction leading to impaired energy generation [8]. The exhaustion phenotype is reinforced by transcription factors such as TOX and NFAT, which regulate inhibitory receptor expression and epigenetic remodeling [9]. Importantly, these molecular changes are not fully reversed by ART, highlighting the prognostic importance of exhaustion biomarkers even in virally suppressed patients [10].

Exhaustion Biomarkers in CD4+ T Cells

i. **PD-1:** Programmed cell death protein 1 (PD-1) is a hallmark of T cell exhaustion. Elevated PD-1 expression on CD4+ T cells correlates with lower CD4+ counts, higher viral loads, and larger latent reservoirs [11]. Longitudinal studies show that patients with high PD-1 expression experience faster CD4+ decline despite ART [12].

ii. **TIM-3:** TIM-3 is associated with more severe functional impairment than PD-1 alone. High TIM-3 expression predicts reduced IL-2 production and increased susceptibility to opportunistic infections [13]. Co-expression of PD-1 and TIM-3 marks a deeply exhausted phenotype with poor proliferative recovery [14].

iii. **CTLA-4 and LAG-3:** CTLA-4 suppresses TCR signaling and is upregulated in chronic HIV infection. Elevated CTLA-4 expression is linked to diminished vaccine responsiveness and increased immune activation [15]. LAG-3, which binds MHC class II molecules, contributes to T cell dysfunction and is associated with persistent inflammation and poor ART outcomes [16].

Soluble Biomarkers

Circulating biomarkers such as soluble PD-1, IL-6, and D-dimer complement cell-surface markers by reflecting systemic immune activation. Elevated soluble PD-1 levels correlate with increased mortality and AIDS-defining events [17].

Prognostic Implications

High exhaustion marker expression predicts poor immune recovery on ART, independent of viral suppression [18]. Combinatorial assessment of PD-1, TIM-3, and LAG-3 provides stronger prognostic power than single markers, enabling stratification of patients at risk for opportunistic infections and non-AIDS comorbidities such as cardiovascular disease [19].

Patients with high PD-1 expression exhibit slower CD4+ T cell recovery after ART initiation, with average increases of 50 cells/μL compared to 120 cells/μL in those with lower PD-1 expression over 48 weeks [20]. Elevated exhaustion markers are also associated with greater HIV reservoir size, complicating cure strategies [21].

Therapeutic Implications

Exhaustion biomarkers guide the development of immune-based therapies. Checkpoint blockade targeting PD-1 or CTLA-4 restores T cell function in vitro, though clinical translation in HIV remains limited by safety concerns [22]. Therapeutic vaccines may be optimized by incorporating exhaustion biomarker profiling to identify responsive patients [23]. Nutritional and psychosocial interventions, increasingly recognized in HIV care, may also modulate immune exhaustion indirectly [3].

Limitations and Challenges

Despite their promise, exhaustion biomarkers face limitations. Expression levels vary across cohorts, influenced by host genetics, co-infections, and ART regimens [24]. Technical variability in flow cytometry and lack of standardized thresholds limit cross-study comparisons [25]. Moreover, exhaustion markers are not exclusive to HIV and may be induced by other chronic infections or cancer, reducing specificity [26].

Future Directions

Future research should prioritize multi-omic integration, combining transcriptomic, epigenetic, and proteomic data to refine exhaustion signatures [26]. Development of standardized assays for exhaustion biomarkers will facilitate clinical translation [27]. Clinical trials of immune checkpoint inhibitors in HIV must balance therapeutic efficacy with risks of immune hyperactivation [28]. Expanding biomarker studies in resource-limited settings will also ensure global applicability [29].

CONCLUSION

CD4+ T cell exhaustion biomarkers provide critical prognostic insights into chronic HIV infection. Elevated expression of PD-1, TIM-3, CTLA-4, and LAG-3 correlates with impaired immune recovery, larger viral reservoirs, and increased morbidity. Combinatorial biomarker profiling enhances prognostic accuracy and informs emerging therapeutic strategies. Nevertheless, technical challenges and inter-patient variability limit current clinical

application. Continued research integrating exhaustion biomarkers with clinical and virological data will be essential to optimize prognostic tools and therapeutic design. Clinicians and researchers should incorporate standardized CD4+ T cell exhaustion biomarker profiling into prognostic assessment and therapeutic trial design in chronic HIV infection.

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CITE AS: Mangen Joshua Fred (2025). CD4+ T Cell Exhaustion Biomarkers in Chronic HIV Infection: Prognostic Implications. IDOSR JOURNAL OF APPLIED SCIENCES 10(2):29-32, 2025.
https://doi.org/10.59298/IDOSRJAS/2025/102.2932