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CD4+ T Cell Reconstitution Biomarkers: Predicting Immune Recovery in Treatment-Naïve HIV Patients

Mpora Kakwanzi Evelyn

Department of Pharmacognosy Kampala International University Uganda
Email: evelyne.mpora@studwc.kiu.ac.ug

ABSTRACT

Antiretroviral therapy (ART) suppressed HIV replication and permitted partial restoration of CD4+ T cell immunity, yet the magnitude and tempo of immune recovery vary widely among treatment-naïve patients. Incomplete CD4 reconstitution sustained vulnerability to opportunistic infections, immune activation, and non-AIDS comorbidities despite viral suppression. This review evaluated candidate biomarkers that predict CD4+ T cell reconstitution after ART initiation in treatment-naïve HIV patients and appraised their translational potential for risk stratification and clinical decision-making. A narrative, evidence-informed synthesis was developed from peer-reviewed cohort studies, mechanistic biomarker investigations, and clinical literature addressing immune activation, inflammation, thymic function, gut barrier integrity, and lymphoid tissue remodeling in ART-mediated recovery. Baseline CD4 count and viral load explained only part of recovery heterogeneity. Biomarkers reflecting immune activation and inflammation (for example IL 6, CRP, D dimer, soluble CD14), gut barrier injury and microbial translocation (LPS related measures, intestinal fatty acid binding protein), thymic output and homeostatic signaling (T cell receptor excision circles, IL 7 axis), and T cell senescence or exhaustion phenotypes (CD57, PD 1 related markers) repeatedly associated with slower CD4 gain and persistent immune dysfunction. Composite models combining clinical variables with biomarker panels generally improved prediction compared with routine measures alone, though standardization and external validation remain limiting. Predictive biomarkers for CD4 reconstitution were biologically plausible and increasingly supported, but their routine use required pragmatic assays, validated thresholds, and equity-focused implementation.

Keywords: HIV, CD4+ T cell reconstitution, Immune activation, Thymic output, Microbial translocation.

INTRODUCTION

HIV infection induces progressive CD4+ T cell depletion through direct cytopathic effects, abortive infection-driven inflammation, and immune-mediated destruction, while simultaneously reprogramming the immune microenvironment [1, 2]. Viral replication sustains chronic immune activation, cytokine perturbation, and lymphoid tissue dysfunction, including architectural damage and fibrosis that constrain T cell trafficking and survival [3]. The biochemical and immunologic milieu that emerges is characterized by heightened inflammatory signaling, increased cellular turnover, and disrupted homeostatic pathways. A central feature is impaired mucosal immunity, particularly within the gut-associated lymphoid compartment, leading to barrier dysfunction and microbial translocation. This process amplifies systemic inflammation and contributes to the persistence of immune activation even after virologic suppression.

ART rapidly reduces plasma viremia and allows partial immune restoration, but immune reconstitution is heterogeneous [4–6]. Some treatment-naïve patients demonstrate brisk early CD4 recovery followed by gradual consolidation, whereas others exhibit blunted gains despite durable viral suppression. This variability has clinically important consequences. Individuals with incomplete reconstitution remain at higher risk for opportunistic

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infections, delayed discontinuation of prophylaxis, suboptimal vaccine responses, and an increased burden of non AIDS events linked to inflammation, including cardiovascular disease and frailty-related syndromes.

The prevailing clinical predictors, notably baseline CD4 count and baseline viral load, are informative yet insufficient. They do not fully capture the biological constraints imposed by immune activation, lymphoid tissue remodeling, thymic function, senescence, or gut barrier injury. Consequently, there is a strong rationale to identify biomarkers that anticipate the trajectory of CD4 recovery at the point of ART initiation [7]. This review proceeds in five sections. Section 1 outlines the mechanistic biology of CD4 depletion and restoration after ART. Section 2 defines clinical trajectories and metrics of immune recovery in treatment-naïve patients. Section 3 synthesizes candidate biomarker classes that predict reconstitution, from inflammation to thymic output and senescence. Section 4 discusses integrative prediction models and practical translation to care pathways. Section 5 addresses limitations, controversies, and future directions, including multi-omics approaches and feasibility in low-resource settings. The purpose of this review is to evaluate biomarker evidence for predicting CD4+ T cell reconstitution after ART in treatment-naïve HIV patients, and to clarify priorities for clinically useful, equitable implementation.

Biology of CD4+ T Cell Depletion and Immune Reconstitution After ART

CD4+ T cell depletion in HIV is multifactorial and compartmentalized. Beyond direct infection of activated CD4+ T cells, a substantial component of loss arises from inflammatory cell death pathways triggered by abortive infection in non-permissive cells, which amplifies local cytokine release and recruits additional target cells [8]. This creates a feed-forward loop in lymphoid tissues, particularly in gut mucosa where early depletion is profound. The gut compartment is not merely a site of loss but a driver of systemic immune activation: mucosal damage disrupts barrier integrity and allows microbial products to access the circulation, stimulating innate receptors and sustaining inflammatory cascades.

Immune activation contributes to CD4 decline by increasing T cell turnover, promoting activation induced cell death, and impairing lymphopoiesis [9]. Elevated type I interferon signaling, monocyte activation, and proinflammatory cytokines may hinder effective immune restoration even when viral load falls. In parallel, lymphoid tissue architecture becomes remodeled. Collagen deposition and fibrosis within lymph nodes can restrict access to survival cytokines and disrupt the stromal networks that support T cell homeostasis [10, 11]. This remodeling is especially relevant for the IL 7 axis, a central homeostatic pathway that supports naive and memory T cell survival and proliferation. If IL 7 signaling is perturbed, or if the microenvironment that presents IL 7 is structurally compromised, immune recovery may be constrained.

After ART initiation, immune reconstitution is often biphasic. The early phase is marked by redistribution and reduced sequestration of memory T cells from tissues into peripheral blood and a decline in immune activation. This produces an initial rise in CD4 count over weeks to months. The later phase reflects slower processes such as thymic output, naive T cell replenishment, and gradual restoration of lymphoid tissue function. Age, baseline immune damage, and persistent inflammation can markedly influence this second phase.

Thus, predicting CD4 recovery requires attention to biological domains that extend beyond viral suppression: the intensity of immune activation, integrity of the gut barrier, degree of lymphoid fibrosis, and functional capacity for T cell renewal through thymic and peripheral mechanisms. Biomarkers that capture these domains are conceptually aligned with the mechanisms that determine whether ART can translate virologic control into durable immune restoration.

Clinical Definitions and Trajectories of CD4+ T Cell Recovery in Treatment Naïve Patients

Clinically, immune reconstitution is often summarized by absolute CD4 count, yet this single metric masks important complexity [12]. CD4 percentage can provide complementary information, particularly where total lymphocyte counts fluctuate. The CD4:CD8 ratio has emerged as a marker reflecting broader immune normalization, integrating CD4 recovery with CD8 expansion and activation [13]. A persistently low CD4:CD8 ratio after viral suppression may indicate ongoing immune activation or senescence and has been associated in multiple cohorts with adverse outcomes.

Trajectory based metrics are particularly useful. The CD4 slope, defined as the rate of CD4 gain over time, can distinguish early responders from those with delayed recovery [14]. Many patients experience rapid early gains during the first 3 to 6 months, followed by slower increases over subsequent years. In contrast, a subset exhibits minimal gain, often termed immunologic non responders, despite achieving virologic suppression. Definitions vary, but commonly include failure to exceed a specified CD4 threshold (for example 350 or 500 cells per microliter) after a period of suppressive ART, or failure to achieve a meaningful increment above baseline. The variability in definitions complicates cross study comparisons and underscores a need for harmonized endpoints.

The clinical significance of these trajectories is substantial. Patients initiating ART with very low baseline CD4 counts remain at higher risk for opportunistic infections even as viral load becomes undetectable, and delayed

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immune recovery prolongs the period of vulnerability. Persistent immune activation and incomplete immune normalization also relate to non AIDS morbidity, including cardiovascular events, neurocognitive impairment, bone disease, and malignancy risk, suggesting that CD4 recovery is a partial proxy for deeper immune repair [15, 16].
In treatment naïve patients, baseline CD4 count and viral load predict recovery to a degree, but not deterministically. Two individuals with similar baseline values may have divergent outcomes, implying hidden biological variables. Clinical covariates such as age, coinfections, malnutrition, anemia, and markers of advanced disease may influence recovery. However, many of these features are downstream reflections of underlying immune activation, thymic reserve, or gut barrier dysfunction. This observation motivates biomarker strategies: by quantifying the mechanistic processes that limit recovery, one can potentially predict trajectory earlier and guide decisions regarding monitoring intensity, prophylaxis duration, and consideration of adjunctive interventions.

Candidate Biomarkers Predicting CD4+ Reconstitution

Biomarker candidates broadly fall into interconnected categories: virologic burden, immune activation and inflammation, gut barrier integrity, thymic output and homeostatic signaling, senescence and exhaustion, and tissue remodeling or fibrosis. The most informative biomarkers are those that map to mechanisms, can be measured reproducibly, and add predictive value beyond baseline CD4 and viral load.

Virologic markers and reservoir related proxies: Baseline plasma viral load correlates with immune activation and is an established predictor of early recovery, but it is not sufficient [17]. Measures that approximate reservoir size or persistence may relate to ongoing antigenic stimulation and immune activation, though such assays are often research oriented. In practice, the clinical utility of reservoir proxies depends on assay feasibility and whether they improve prediction in virally suppressed patients who still display poor CD4 gain.

Immune activation and inflammation markers: Persistent immune activation is one of the strongest mechanistic candidates for limiting CD4 recovery [18]. Biomarkers such as soluble CD14, soluble CD163, IL 6, high sensitivity CRP, and D dimer reflect monocyte activation, inflammatory tone, and coagulation pathway engagement [19, 20]. Elevated levels at baseline or early after ART initiation have repeatedly been associated with poorer immune recovery and increased clinical events in observational cohorts. These biomarkers plausibly reflect a systemic inflammatory set point that continues to drive lymphocyte turnover and impairs immune restoration. Interferon stimulated gene signatures and other cytokine patterns also align with this framework, though they may be less accessible for routine care.

Gut barrier injury and microbial translocation: Microbial translocation is a central amplifier of inflammation in HIV [21]. Markers such as lipopolysaccharide related measures, endotoxin core antibodies, and intestinal fatty acid binding protein, a marker of enterocyte injury, have been linked in several studies to immune activation and incomplete CD4 recovery. The conceptual strength is high because the gut is a major site of early CD4 depletion and immune dysfunction. The challenge is standardization, as microbial product assays can be sensitive to preanalytical handling and laboratory variability.

Thymic output and homeostatic signaling: Long term CD4 restoration depends on the ability to generate or maintain a diverse T cell pool. T cell receptor excision circles reflect recent thymic emigrants and provide a proxy for thymic output. Higher TREC levels, particularly in younger patients, are often associated with better naive T cell recovery and more robust CD4 gains. IL 7 is a key homeostatic cytokine; altered IL 7 levels and IL 7 receptor expression can signal disturbed homeostasis. Elevated IL 7 may reflect compensatory responses to lymphopenia, whereas impaired receptor signaling may indicate a bottleneck in translating cytokine availability into effective recovery. Proliferation markers such as Ki 67 can indicate increased turnover, which may be compensatory but can also signal activation driven depletion.

Senescence and exhaustion phenotypes: Chronic antigen exposure and inflammation drive senescence and exhaustion, particularly among CD8 and, in advanced disease, CD4 populations. Expression of markers such as CD57, PD 1, and TIM 3 has been linked to impaired immune restoration in some cohorts. These markers suggest that the immune system is constrained by functional exhaustion and replicative history, limiting proliferative capacity and survival. Their translational limitation is that flow cytometry based assays require infrastructure, standardization, and skilled interpretation[22].

Fibrosis and lymphoid tissue remodeling: Lymph node fibrosis and remodeling can restrict immune reconstitution by disrupting supportive niches and cytokine access [23]. Biomarkers related to extracellular matrix turnover and profibrotic signaling, including TGF beta linked pathways, are of interest because they represent structural constraints rather than transient inflammatory states. Although tissue based measures are most direct, circulating proxies may still provide useful signals if validated.

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Overall, the biomarker evidence supports a multifactorial model. No single marker fully predicts recovery, but panels that integrate inflammatory, gut, and thymic domains are biologically coherent and increasingly supported. The principal challenge is moving from association to prediction with actionable thresholds and feasible assays.

Integrative Prediction Models and Practical Clinical Translation

The clinical value of biomarkers is realized when they inform decisions. Integrative models aim to combine baseline clinical data with biomarker measures to predict the probability of robust CD4 recovery or the risk of immunologic non response [24]. Conceptually, a model might include baseline CD4, viral load, age, hemoglobin, and coinfection status, augmented by one or more biomarkers reflecting immune activation, gut barrier integrity, and thymic reserve. In several cohort based studies, such multivariable approaches outperform baseline CD4 and viral load alone, improving discrimination of patients likely to have slow recovery. However, predictive performance must be interpreted cautiously. Many models are developed in single cohorts, use differing endpoints, and lack external validation, raising concern for overfitting and limited generalizability.

For translation, calibration is as important as discrimination. A model that predicts high risk should do so accurately across risk strata, and its outputs should map to actionable care pathways. Potential clinical uses include deciding the intensity of early follow up, prioritizing adherence and counseling resources, and determining how long to maintain opportunistic infection prophylaxis in individuals who remain immunologically fragile despite viral suppression. Models could also guide targeted evaluation for persistent inflammation drivers such as coinfections, poor nutrition, or ongoing microbial translocation, and may prompt consideration of adjunctive measures in research settings.

Practical implementation requires attention to assay selection. IL 6, CRP, and D dimer are relatively accessible in many laboratories and have standardized platforms, making them attractive candidates for inclusion [25]. Soluble CD14 and intestinal fatty acid binding protein may be more specialized but could become feasible with broader assay availability. Flow cytometry based senescence markers may be feasible where immunology laboratories exist, but they may be less scalable in low resource contexts. Therefore, prediction strategies should be tiered. A basic model could use routine clinical variables plus widely available inflammatory markers, whereas an enhanced model could incorporate immunophenotyping and gut injury markers in specialized centers.

Importantly, models must be equity conscious. If prediction tools depend on expensive assays, they risk widening disparities by concentrating benefit in well resourced systems. Conversely, a pragmatic model that uses affordable markers could improve outcomes by identifying high risk patients for closer monitoring in settings where late presentation is common. Translation also requires clinician training to avoid misinterpretation and to prevent prediction from becoming deterministic labeling. Biomarkers should guide supportive interventions, not become a basis for therapeutic nihilism.

In summary, integrative models represent the most realistic route to clinical utility. The field now requires harmonized endpoints, multicenter validation, and implementation studies that test whether biomarker-informed stratification improves patient outcomes.

Limitations, Controversies, and Future Directions

Several limitations temper current biomarker enthusiasm. First, immune recovery is influenced by heterogeneous factors including age, sex, genetics, baseline disease stage, nutrition, and coinfections such as tuberculosis, hepatitis viruses, and chronic parasitic infections in endemic regions [26]. These variables may confound biomarker associations or alter biomarker distributions, demanding population-specific validation. Second, assay variability remains a major barrier. Many biomarkers are sensitive to specimen handling, timing relative to ART initiation, and analytic platform differences. Without standardization, thresholds derived in one study may not transfer reliably to another.

A further controversy concerns causality. Biomarkers such as IL-6 or soluble CD14 may reflect processes that constrain recovery, but they may also be downstream indicators of immune damage [27]. Distinguishing predictive from merely descriptive biomarkers requires longitudinal designs, early sampling, and mechanistic triangulation. Another challenge is endpoint heterogeneity, since immunologic non-response is defined inconsistently across studies. Harmonizing definitions, including time points and clinically meaningful CD4 targets, is essential for comparative science and model validation.

Low-resource settings introduce additional complexity and urgency. Many treatment-naïve patients initiate ART with advanced immunosuppression, and laboratory capacity for specialized biomarkers is limited. The most valuable biomarkers in such settings may be those that are robust, inexpensive, and actionable, even if they are less mechanistically precise. This raises a practical question: is a modestly predictive, widely implementable model preferable to a highly predictive model that cannot scale? From a public health perspective, scalable tools often deliver greater impact.

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Future directions are increasingly multidimensional. Multi-omics approaches, including transcriptomics, proteomics, metabolomics, and microbiome profiling, may uncover novel predictive signatures that integrate immune activation, metabolic stress, and mucosal dysfunction. Single cell profiling can resolve heterogeneity within T cell compartments, identifying subpopulations associated with recovery or failure. Yet these approaches must ultimately be translated into simplified assays suitable for routine use. Another promising direction is dynamic prediction, where early changes after ART initiation, for example, decline in inflammatory markers or shifts in the CD4:CD8 ratio, are incorporated into updated risk estimates. Such adaptive models align with the biology of biphasic recovery. In brief, the next phase of work should prioritize standardization, multicenter validation, and implementation research that tests whether biomarker-informed care improves outcomes without exacerbating inequity.

CONCLUSION

CD4+ T cell reconstitution after ART initiation is a central determinant of clinical recovery in treatment-naïve HIV patients, yet it remains heterogeneous even when viral suppression is achieved. Baseline CD4 count and viral load provide an essential starting point, but they do not sufficiently capture the mechanistic constraints imposed by chronic immune activation, mucosal barrier injury, lymphoid tissue remodeling, thymic reserve, and cellular senescence. Biomarkers reflecting inflammation and monocyte activation, including IL-6, CRP, D-dimer, and soluble CD14, repeatedly associate with slower CD4 recovery and persistent risk. Measures of gut barrier injury and microbial translocation and proxies of thymic output and homeostatic signaling add biological depth and may improve prediction when combined in multivariable models. Phenotypic markers of senescence and exhaustion further explain why some immune systems fail to restore functional diversity despite viral control. The most credible translational path is not a single biomarker but an integrated prediction framework that uses pragmatic assays, validated endpoints, and external calibration across diverse settings. Equity must remain central, ensuring that biomarker-guided care strengthens outcomes in both high-resource and low-resource contexts. Biomarker-informed risk stratification should be incorporated into prospective, multicenter implementation studies to define feasible panels and validated thresholds that guide monitoring intensity and supportive interventions for patients at high risk of incomplete CD4 recovery.

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