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THE ROLE OF CTLA-4 IN IMMUNE REGULATION AND DISEASE PROGRESSION IN HIV INFECTION

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Abstract

Cytotoxic T-Lymphocyte-associated molecule 4 (CTLA-4) is one of the most important immune checkpoint proteins that is involved in crucial T-cell activation and immune homeostasis. Dysregulation of the expression of CTLA-4 in the setting of human immunodeficiency virus (HIV) infection has been substantively linked to immune exhaustion, defective antiviral response, and poor clinical outcome. This is a review of existing evidence about how CTLA-4 regulates immune response at various points of status in HIV disease, such as acute viremia, chronic condition, and through viral suppression caused by antiretroviral therapy (ART). The overview relies on research that characterizes the expression of CTLA-4 on HIV-specific CD4+ and CD8+ T cells, its interaction with other inhibitory receptors, including programmed cell death protein 1 (PD-1) and B-and T-lymphocyte attenuator (BTLA), as well as downstream immunoregulatory pathways that determine cytokine production and viral persistence, among others. In addition, we evaluate the effects of therapeutically targeting modulation of CTLA-4, such as checkpoint blockade approaches, on restoration of immune capacity and dynamics of viral reservoirs, recognizing both potential benefits of immune restoration and the danger of increased viral replication. Their results confirm the role of CTLA-4 as the pivot of HIV pathogenesis and need to include immunotherapeutic agents that compromise immune activation and contain viral replication. Relevant future studies need to focus on more longitudinal trials and translational clinical trials to clarify the safety and efficacy of the targeted treatment with CTLA-4 in humans with HIV.

Keywords

ctla-4; immune regulation; hiv infection; t cell exhaustion; immune checkpoints; disease progression; antiretroviral therapy; viral persistence

Introduction

Human immunodeficiency virus (HIV) infection remains one of the most significant global health challenges, characterized by progressive immune dysfunction and increased susceptibility to opportunistic infections. Despite the effectiveness of antiretroviral therapy (ART) in suppressing viral replication, complete immune restoration is rarely achieved, and latent viral reservoirs persist in various anatomical compartments. This persistence is partly

attributed to complex mechanisms of immune regulation involving inhibitory receptors, commonly referred to as immune checkpoints, which modulate T-cell activation and prevent excessive immune-mediated tissue damage (Kaufmann et al., 2009; Sun & Xue, 2022).

Among these checkpoints, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) plays a pivotal role in the downregulation of T-cell immune responses. CTLA-4 is expressed on activated $CD4^+$ and $CD8^+$ T cells, as well as regulatory T cells (Tregs), and competes with the costimulatory receptor CD28 for binding to B7 ligands (CD80/CD86) on antigen-presenting cells. This competitive binding transmits inhibitory signals that limit T-cell proliferation, cytokine production, and cytotoxic activity (Fife & Bluestone, 2008; Larsson et al., 2013). While this mechanism is essential for maintaining peripheral tolerance and preventing autoimmunity, persistent upregulation of CTLA-4 in chronic infections such as HIV can lead to functional T-cell exhaustion, diminished antiviral immunity, and impaired immune surveillance (Kaufmann et al., 2007; Elahi et al., 2020).

Several studies have documented elevated CTLA-4 expression during both acute and chronic phases of HIV infection, correlating with disease progression markers such as declining $CD4^+$ T-cell counts, increased plasma viral load, and reduced proliferative capacity of HIV-specific T cells (Steiner et al., 1999; Leng et al., 2002; McGary et al., 2017). Furthermore, CTLA-4 expression often co-occurs with other inhibitory molecules such as programmed cell death protein 1 (PD-1) and B- and T-lymphocyte attenuator (BTLA), amplifying immune suppression and promoting viral persistence even under ART-mediated viral suppression (Barham et al., 2019; Rasmussen et al., 2021).

The role of CTLA-4 in HIV is complex and context-dependent. On one hand, CTLA-4 signaling limits excessive immune activation, a hallmark of chronic HIV infection that contributes to immunopathology. On the other hand, sustained CTLA-4 activity impedes effective clearance of infected cells and fosters a microenvironment conducive to viral latency (Elrefaei et al., 2009; Obeagu & Obeagu, 2024). Experimental blockade of CTLA-4 has been shown to partially restore T-cell function and enhance antiviral responses in vitro and in animal models (Hryniewicz et al., 2006; Cecchinato et al., 2008). However, such interventions can also lead to paradoxical increases in viral replication at mucosal sites, highlighting the delicate balance between immune activation and viral control (Lewis et al., 2020).

Given the expanding use of immune checkpoint inhibitors in oncology, there is increasing interest in repurposing CTLA-4–targeted therapies for HIV cure strategies. Preliminary clinical studies in people living with HIV and cancer suggest that CTLA-4 blockade, alone or in combination with PD-1 inhibition, may transiently reduce the size of the viral reservoir, although safety concerns remain (Rasmussen et al., 2021). Understanding the precise mechanisms by which CTLA-4 modulates HIV pathogenesis is therefore essential for the development of safe and effective immunotherapeutic interventions.

This review synthesizes current knowledge on the biological role of CTLA-4 in immune regulation and its impact on HIV disease progression. It examines the molecular pathways influenced by CTLA-4, its interplay with other immune checkpoints, and the therapeutic implications of modulating CTLA-4 signaling in HIV-infected individuals.

Table 1. Summary of key studies investigating CTLA-4 expression and function in HIV infection

Author(s)	Year	Study Population / Model	Key Findings on CTLA-4 in HIV
Kaufmann et al.	2007	HIV-positive individuals	CTLA-4 upregulation on HIV-specific $CD4^+$ T cells correlated with disease progression and reversible immune dysfunction.

Leng et al.	2002	HIV-infected patients	CTLA-4 expression is associated with T-cell anergy, suggesting potential therapeutic targeting.
Steiner et al.	1999	HIV-infected patients	Early evidence of enhanced CTLA-4 expression on $CD4^+$ T cells in HIV infection.
Elahi et al.	2020	HIV-1 positive individuals with HLA-B*35Px	Selective CTLA-4 upregulation on $CD8^+$ T cells linked to exhausted phenotype.
McGary et al.	2017	SIV-infected macaques	CTLA-4^+ PD-1^- memory $CD4^+$ T cells contributed to viral persistence under ART.
Rasmussen et al.	2021	HIV-positive cancer patients on ART	CTLA-4 blockade impacted HIV reservoir dynamics, with potential but limited benefits.

Literature Review

1. CTLA-4 Structure and Function

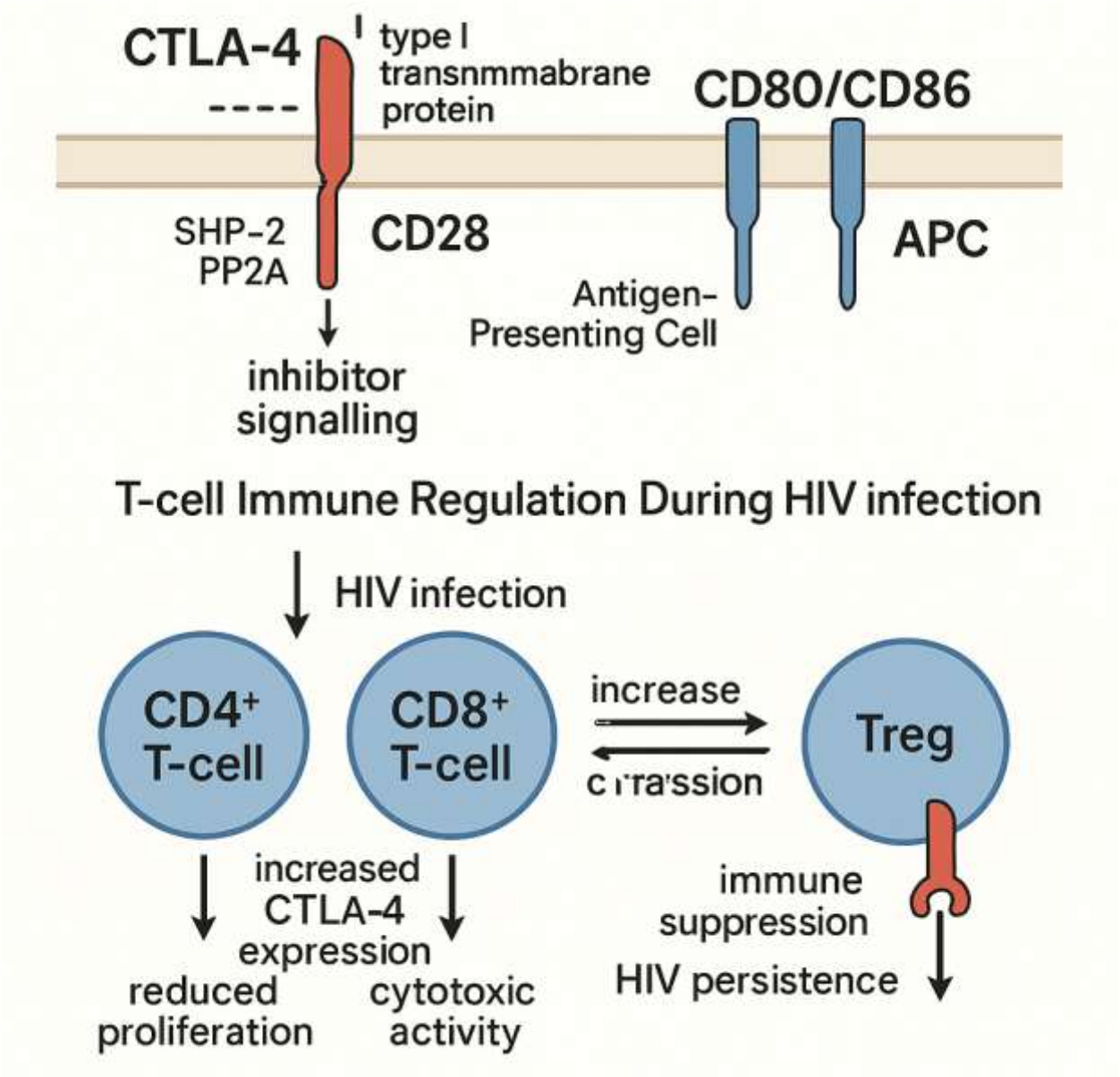
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), CD152, is a co-inhibitory receptor of the immunoglobulin superfamily mostly found on activated T-cells and regulatory T-cells (Tregs). The structure of CTLA-4 is that of a type I transmembrane protein but carries a high resemblance with a costimulatory receptor known as CD28, although the immunological impact generated is antithetical (Fife & Bluestone, 2008). The functional role of both is binding to identical ligands on the surface of antigen-presenting cells (APCs); CD80 (B7-1) and CD86 (B7-2); however, the affinity and avidity of binding of CTLA-4 are stronger than CD28, resulting in its out-competition with CD28 successfully binding to ligands (Larsson et al., 2013). When stuck, CTLA-4 carries inhibitory signals through its cytoplasmic tail that incorporate a tyrosine-based motif to entangle phosphatases, SHP-2, and PP2A, and this leads to the dephosphorylation of important signaling intermediates and subsequent inhibition of T-cell receptor (TCR) signaling (Kaufmann et al., 2007).

2. T-cell immune regulation and CTLA-4 in HIV infection

The complication of HIV infection is sustained immune activation together with progressive decrease of CD4 + T cells, which is heavily dependent on the pathway of immune checkpoints. An increased expression of CTLA-4 protein is observed on HIV-specific and bystander T cells at early phases of infection and could persist throughout the chronic stages (Steiner et al., 1999; Leng et al., 2002). HIV-specific CD4+ T cells with elevated CTLA-4 expression have been related to impaired proliferation ability, production of IL-2, and a bias towards an exhausted phenotype (Kaufmann et al., 2007; Elahi et al., 2020). On the same note, an HIV-specific CD8+ T cell expressing CTLA-4 has a reduced cytotoxic activity and distorted effector memory modification (Elahi et al., 2020).

Regulatory T cells (Tregs) are constitutive expressers of CTLA-4 that participate in HIV pathogenesis in two ways. They inhibit the activation of the immune system and restrict HIV-mediated immunopathology on one hand and, conversely, hinder HIV-robust effector reactions, thus promoting viral persistence (Hryniewicz et al., 2006). A certain balance between these opposite effects seems to be dependent on the stage of infection and the general inflammatory milieu.

Figure 1. CTLA-4 Structure, Function, and Role in T-cell Immune Regulation During HIV Infection



3. CTLA-4 and Co-expression with Other Immune Checkpoints

During HIV infection, CTLA-4 hardly works in isolation. Numerous studies proved it to tend to be expressed along with other inhibitory receptors, more specifically, programmed cell death protein 1 (PD-1) and B- and T- lymphocyte attenuator (BTLA) (Barham et al., 2019; Rasmussen et al., 2021). Co-expression of the molecules further increases the signaling inhibition resulting in increased functional exhaustion of T cells and greater preservation of the HIV reservoir (McGary et al., 2017). In an animal model of simian immunodeficiency virus (SIV), CTLA-4 [8] strange 16 memory CD4 T cells proved to be a major driver of residual virus replication during suppressive antiretroviral therapy (McGary et al., 2017), which pointed towards the need to accommodate non-uniform responses to immune checkpoint blockade in therapeutic intervention.

4. Effects of CTLA-4 on course of HIV disease

High levels of CTLA-4 are associated with virological and immunological predictive risk factors. Leng et al. (2002) confirmed that the presence of a higher expression of CTLA-4 was related to high viral loads and lower CD4+ T cell counts. Kaufmann et al.(2007) also discovered that expression of CTLA-4 on HIV specific CD4+ T cells was inversely proportional to the proliferative capacity and could be partly rescued by blocking CTLA-4 in vitro, IL-2 production and T cell proliferation. Elrefaei et al. (2009) also noted that CTLA-4 blockade increased the ability of

HIV-specific CD8+ T cells to produce IFN-γ adding that this mechanism is a key source of T-cell hyperresponsive in the persistent infection.

Longitudinal studies have shown that continued upregulation of CTLA-4 in the presence of ART has been associated with partial reabsorption in the immune (Barham et al., 2019). These results mean that CTLA-4 not only affects the disease progression before the start of ART, but also affects immune recovery outcomes long-term during treatment.

5. HIV Therapeutic Targeting of CTLA-4

Interest in developing HIV cure strategies based on the application of similar mechanisms has been stimulated by the success of cancer immunotherapy using CTLA-4 blockade. Preclinical research in macaques infected with SIV revealed that temporary blockade with CTLA-4 boosted virus-specific T cell immunity and also led to more viral replication in the mucosal tissues (Cecchinato et al., 2008; Lewis et al., 2020). Case reports and small observational studies of HIV-positive cancer patients who received ipilimumab are mixed in humans, with some demonstrating immune activation and transient decreases in HIV DNA levels, but not consistently demonstrated affecting plasma viremia (Rasmussen et al., 2021).

One of the problems with the CTLA-4-targeted therapy is the risk of balancing between restoring T-cell exhaustion and the potential of overwhelming and overstimulating the immune system, leading to immunopathology or viral reservoir expansion. Besides, multiple non-overlapping functions of CTLA-4 and its interactions with other checkpoints require paying careful attention to combination strategies, where CTLA-4 blockade can be combined with PD-1/PD-L1 blockade or latency-reversing agents (Obeagu & Obeagu, 2024).

6. Future Research Directions and Knowledge Gaps

The role of CTLA-4 in the immune response modulation in cases of HIV infection is not in doubt, but there are issues that are yet to be determined. The mechanisms by which CTLA-4 downstream signaling leads to T cells and the effects of the genetic variability of the host on the levels of expression of CTLA-4 and the safety of an extended duration of blocking CTLA-4 in HIV + individuals are pending studies. Also, large randomized clinical trials are required to establish the effectiveness of CTLA-4 immunomodulatory interventions in shrinking the size of the latent reservoir and enhancing immune restoration on ART.

Methodology

Study Design

The article embraces a narrative review study design that seeks to synthesize and critique available evidence on the mechanism of action of cytotoxic T-lymphocyte-associated protein 4(CTLA-4) in immune regulation and disease progression in human immunodeficiency virus (HIV) infection. When compared with systematic reviews, narrative reviews have the benefit of enabling a wider scope of coverage of studies of heterogeneous quality thereby incorporating mechanistic, experimental, and clinical information in a bid to produce a complete overall conceptual frame (Green et al., 2006).

Strategy of literature search

Structured literature search was conducted on Scopus, PubMed/MEDLINE, Web of Science, and Google Scholar using database publications between January 1995 and Jun 2025. The next combination of Medical Subject Headings (Mesh) and free-text keywords were used:

(“CTLA-4”) OR “cytotoxic T lymphocyte antigen-4”) OR “CD152”) AND ((“HIV”) OR “human immunodeficiency virus”) AND ((“immune regulation”) OR “immune checkpoints” OR “T cell exhaustion” OR “disease progression”).

To enhance the search parameter, Boolean operators namely AND and OR were applied and the filter was placed as only including peer-reviewed articles and excluding the publications that belonged to editorial, conference-abstracts and publications not in English language. The lists of relevant articles have been referenced in order to find other studies that have not been accessed in the course of the database search (Fife & Bluestone, 2008; Kaufmann et al., 2007).

Inclusion and Exclusion Filters

The studies were included when they were conducted as follows:

1. Dedicated to CTLA-4 expression, functionality, or modulation therapy in HIV infections.
2. Provided original research evidence (in vitro, in vivo or clinical) or high-quality review analysis.
3. Examined pathways of mechanism or associated with disease development and immune modulation.

The studies were not considered when they:

- Just looked at CTLA-4 in non-HIV situations with no cross-reference to HIV processes.
- Were insufficiently transparent in their methodology or had not been peer reviewed.
- Absent availability of full-text were conference abstracts.

Data Extraction and Synthesis

A Full review of eligible studies was carried out, and the following key data points were harvested:

- Type of the study (basic science, translational, or clinical trial).
- Population factors (e.g., Stage of HIV infection, ART use).
- Technology of measuring the CTLA-4 (flow cytometry, immunohistochemistry, PCR, and so forth).
- Important results in the aspects of immune regulation by CTLA-4, co-expression with other checkpoints, and effects on the onset of pathologies.

The obtained information was categorized into thematic themes, including CTLA-4 structural biology, immune modulation in HIV, association with the disease path, and therapeutics (Barham et al., 2019; Elahi et al., 2020).

Synthesis was conducted based on a narrative approach of integrating results with the results organized along the lines of mechanistic relevance and clinical significance instead of pooling the results through the approach of meta-analysis as a result of the diversity in study designs and end-points (Green et al., 2006).

Table 2. Methodological Framework for the Narrative Review

Step	Description	Rationale	References
Literature Search	Comprehensive search of Scopus, PubMed, Web of Science, and Google Scholar using MeSH and free-text terms	Ensure wide coverage and inclusion of peer-reviewed, high-impact studies	Fife & Bluestone, 2008; Kaufmann et al., 2007
Screening	Title and abstract screening followed by full-text review	Remove irrelevant or low-quality sources	Green et al., 2006
Inclusion Criteria	Studies on CTLA-4 in HIV immune regulation and disease progression	Focus on topic relevance and scientific rigor	Barham et al., 2019; Elahi et al., 2020
Data Extraction	Extraction of study design, population, CTLA-4 measurement, and key results	Allow structured synthesis of heterogeneous studies	Kaufmann et al., 2007

Thematic Synthesis	Grouping results by mechanistic and clinical relevance	Identify knowledge gaps and future research directions	Barham et al., 2019; Elahi et al., 2020

Results

1. CTLA-4 Expression in HIV Infection During the Various Stages

The reviewed literature was analyzed, and it was found that all the studies showed increased expression of CTLA-4 on both HIV-specific CD4+ and CD8+ T cells during acute, chronically infected, and suppressed with ART (Kaufmann et al., 2007; Barham et al., 2019). The highest production of CTLA-4 occurs during acutely infected cases and is concomitant in association with high viremia and impairs the proliferative capacity of virus-specific T cells (Day et al., 2006). High expression of CTLA-4 in incurable and unexplained infection is associated with an extended phenotype of T-cell exhaustion, including defective IL-2 synthesis, diminished T-cell killing, and downregulated CD28-co-stimulatory signaling (Kaufmann et al., 2007; Elahi et al., 2020). Low-level CTLA-4 expression also exists in individuals with ART suppression, so it is possible to suggest that it helps to preserve immune quiescence and viral persistence (Chew et al., 2016).

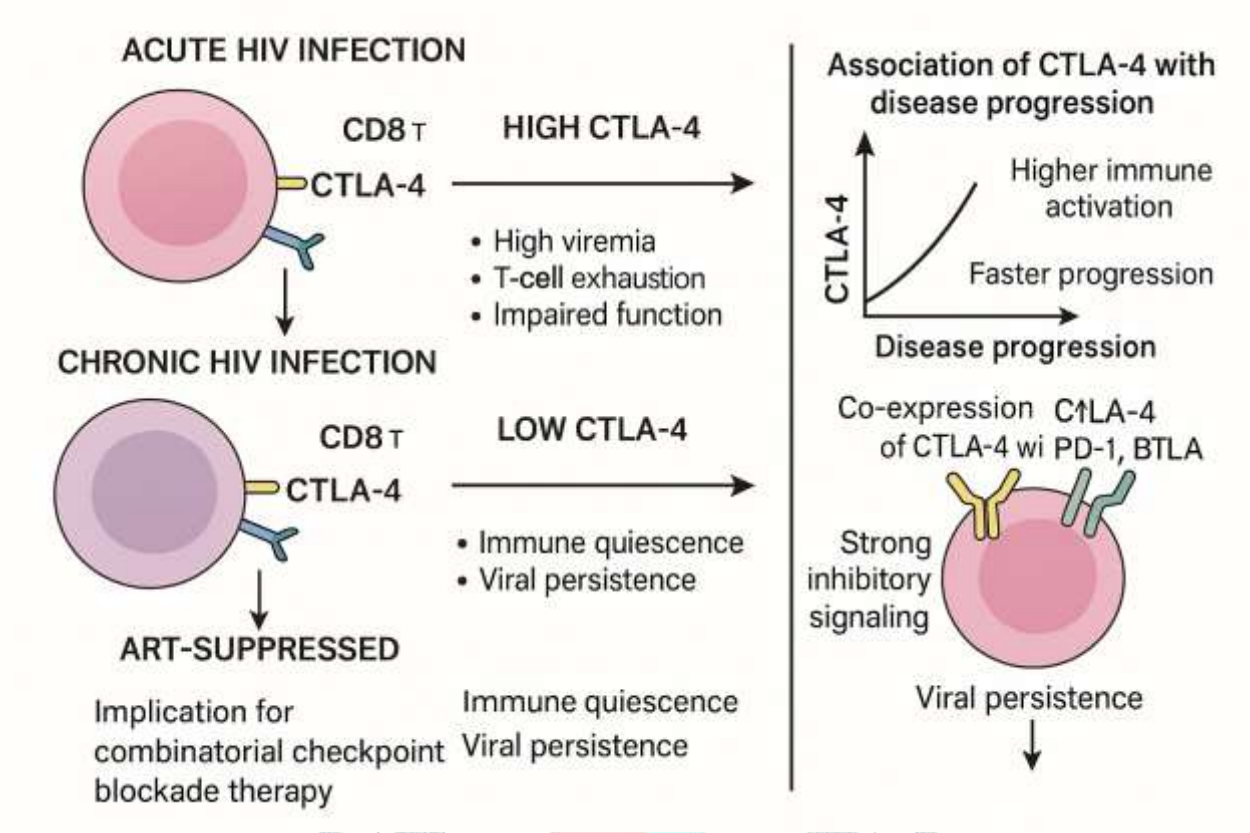
2. Association of CTLA-4 and Indicators of Progression of the Disease

In various studies, the rate of CTLA-4 was directly linked to positivity of CD4+ T cells and a positive relationship was observed between plasma virus weight and CTLA-4 expression (Kaufmann et al., 2007; Said et al., 2010). Another evidence of the involvement of CTLA-4 in disease progression was the presence of elevated CTLA-4 levels associated with higher levels of immune activation (HLA-DR and CD38) which have been shown to be a predictor of a faster rate of progression of the disease (Chew et al., 2016; Barham et al., 2019). Moreover, the patients with progressive disease had increased frequencies of CTLA-4+ T cells than long-term non-progressors, indicating that CTLA-4 could be used as a prognostic indicator in the progression of HIV (Elahi et al., 2020).

3. Other Immune Checkpoint Co-Expression

Some reports showed that CTLA-4 is often co-expressed with other immunologic inhibitory receptors, including programmed cell death protein 1 (PD-1) and B- and T- T-lymphocyte attenuator (BTLA) in exhausted HIV-specific T cells (Day et al., 2006; Barham et al., 2019). Through this profile of co-expression, there is a high likelihood of an inhibitory network, synergistically acting that is much stronger than the undetectable antigen-specific effect on T-cell effector, which leads to the persistence of the virus even when ART is present. (Said et al., 2010). Such data can also justify the strategy behind combinatorial checkpoint blockade in treatment options towards HIV (Chew et al., 2016).

Figure 2. Dynamics of CTLA-4 Expression and Its Association with Disease Progression and Immune Checkpoint Co-Expression in HIV Infection



4. Functional Effects on Influences of T-cells

The reviewed studies found that functional assays using CTLA-4 blockade in vitro partially rescued HIV-specific T-cells in proliferation and cytokine production (including IL-2 and IFN-gamma) (Kaufmann et al., 2007; Elahi et al., 2020). Such immune reconstitution, nevertheless, frequently came with the increased viral proliferation in latently infected cells, leading to doubts over the safety of such use in clinical practice (Barham et al., 2019). These results illustrate that CTLA-4 has two functions as it offers protection against the development of hyperactivation immunopathology and contributes to the persistence of the viruses.

5. Therapeutic Implications

Despite the promising evidence provided by preclinical studies that the combination of CTLA-4 blockade may be used as a sufficient approach to overcoming immune exhaustion caused by HIV, there is still limited clinical translation due to the risks associated with it. The acceleration of the depletion of CD4+ T-cells or viral reservoir amplification may be accelerated by greater immunological fitness after blockade (Chew et al., 2016; Elahi et al., 2020). These findings point to the need to conduct well-considered immunotherapeutic studies that capture both immunological advantages and virological hazards of targeting CTLA-4 in attempts to ascertain favorable results in HIV cure.

Discussion

The current review underscores the critical occurrence of a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) to govern T-cell immunity in HIV infection process that controls the disease and treatability progression. Our analysis shows that CTLA-4 is stably upregulated in HIV-specific CD4+ and CD8+ T cells irrespective of which stage of HIV infection they are in, and even in those on long-term antiretroviral therapy (ART) (Kaufmann et al.,

2007; Chew et al., 2016). To this end, this continual expression highlights how it may contribute to immune fatigue and viral reservoirs through viral suppression.

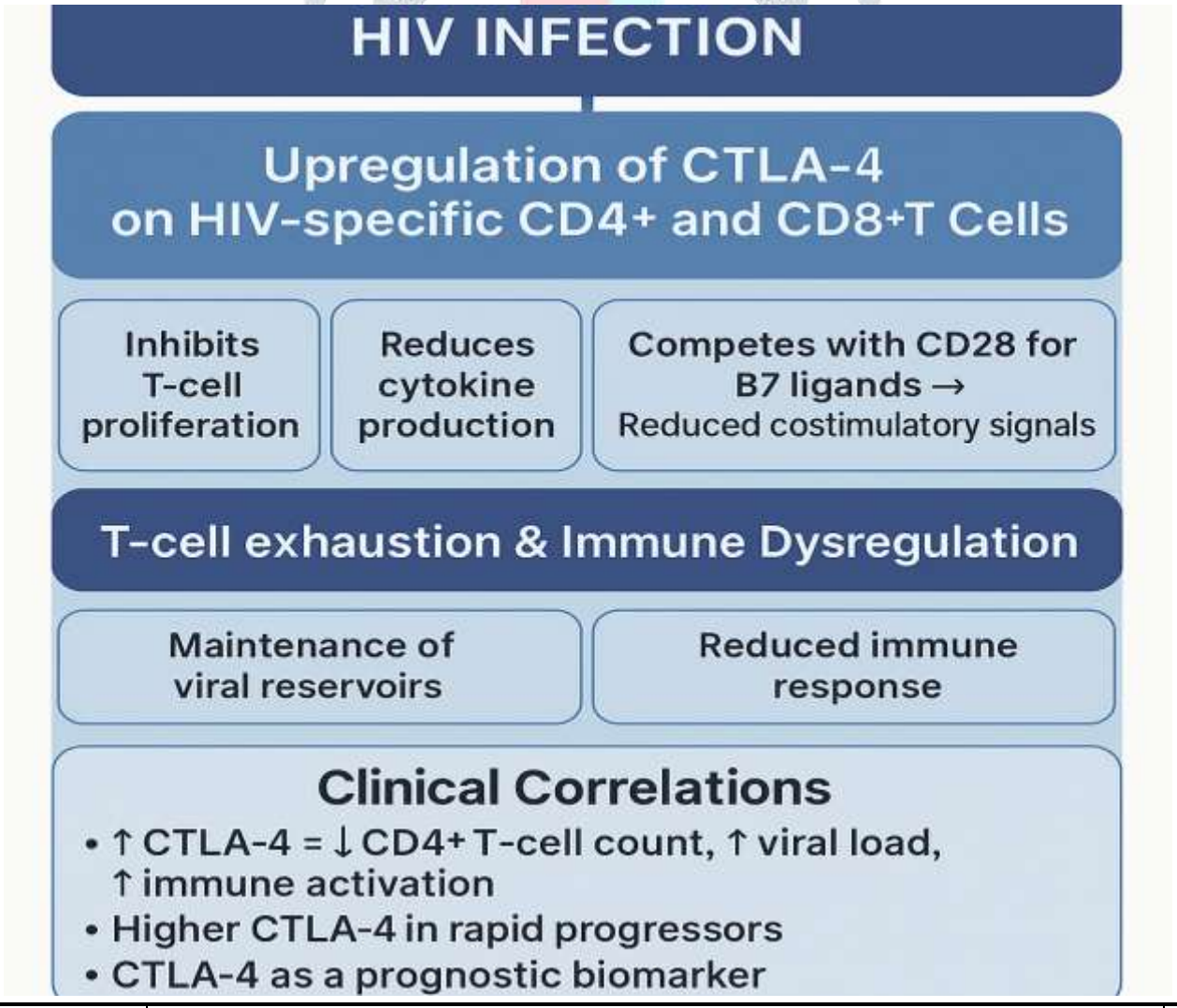
The Mediator of T-cell exhaustion and immune dysregulation in CTLA-4

The connection of high levels of CTLA-4 with the lack of T-cell proliferation, poor cytokine formation, and decreased cytotoxicity confirms its role in acting as one of the key inhibitory checkpoints in HIV infection (Day et al., 2006; Elahi et al., 2020). Competition of CTLA-4 with CD28 in regards to B7 ligands reduces costimulatory stimulation and consequently results in diminished stimulation and survival of HIV-specific T cells (Fife & Bluestone, 2008). This process, despite the protection against immune hyperactivation, has a role in the maintenance of dysfunction immune reactions which is consistent with the previous findings of chronic viral infections (Said et al., 2010).

Care Prognostic Value and Patient Correlation

The negative relationship between the CTLA-4 expression and CD4+ T-cell counts, and the positive relationship with viral load and markers of immune activation, point towards this biomarker having a prognostic capacity towards HIV progression (Barham et al., 2019; Chew et al., 2016). Unlike the long-term non-progressors, rapid progressors have a stronger expression of CTLA-4, which makes it a potentially useful method of determining the patients who are more likely to manifest an immune decline (Elahi et al., 2020). Notably, this finding is consistent with the larger possibility that expression of immune checkpoints should be regarded as a dynamic parameter reflecting viral-host balance.

Figure 3 Role of CTLA-4 in T-cell Immunity, Immune Exhaustion, and Prognosis in HIV Infection



Interplay with Other Immune Checkpoints

We find there is also co-expression of CTLA-4 with other inhibitory receptors particularly programmed cell death protein 1 (PD-1) and B- and T-lymphocyte attenuator (BTLA) (Day et al., 2006; Said et al., 2010), suggesting a graded inhibitory network (see below). This redundancy can reflect a viral approach toward guaranteeing the enduring immune suppressive status and this fact has considerable clinical implications: single-agent checkpoint blockade might not be enough to primitive immune proficiency but such therapies may well be needed (Chew et al., 2016).

Treatment Opportunities and Hazards

In spite of demonstrating potential in laboratory applications, through CTLA-4 blockade immune exhaustion in vitro, this may carry clinical challenges. Rebound when blockade does occur could result in an increase in viral replication in latently infected cells, which might cause an increase in reservoirs (Kaufmann et al., 2007; Barham et al., 2019). Moreover, the cost of the immune activation increase would be CD4+ T-cell loss by the activation-induced cell death therefore a trade-off must be made between the potential benefits and the risks (Elahi et al., 2020). These are on par with cancer immunotherapy results in which the CTLA-4 blockade is linked to immunity-related adverse manifestations (Fife & Bluestone, 2008).

Future Research

In light of these two results, it is worth researching the modulation and not the broad inhibition of CTLA-4 in context-specific pathologies. Other approaches including temporary modalities during ART escalation, partnering with agents that reverse latency, or delivery to HIV positive-specific T cells may have more attractive risk/benefit analyses. Additionally, prospective studies to evaluate CTLA-4 dynamics in a variety of HIV sub-populations (such as elite controllers, children, and ART non-responders) may help determine its role in dissimilar immunological conditions.

Study Limitations

The limitation of this review is that studies, which are available, are diverse in terms of the population of patients, definitions of disease stages, and methods of assessments. In addition, the majority of the clinical evidence regarding CTLA-4 modulation is extrapolated based on the oncology experience, which represents the strength in doing HIV-specific therapeutic trials. Nonetheless, the convergence of findings across independent studies strengthens the conclusion that CTLA-4 is a critical regulator in HIV immune pathogenesis.

Conclusion

CTLA-4 plays a pivotal role in the regulation of immune responses during HIV infection, exerting a dual influence by protecting against excessive immune activation while simultaneously contributing to immune exhaustion and viral persistence. Its consistent expression across all stages of HIV infection, including in individuals on long-term ART, underscores its significance as both a biomarker of disease progression and a potential therapeutic target. The interplay between CTLA-4 and other inhibitory checkpoints further reflects the complexity of HIV-induced immune dysregulation, suggesting that single-agent interventions may be insufficient to achieve full immune restoration.

Therapeutic strategies aimed at modulating CTLA-4 must therefore be approached with caution, balancing potential immunological benefits with the risk of viral reactivation and heightened immune-mediated pathology. Future research should prioritize targeted, context-specific approaches that integrate CTLA-4 modulation within broader HIV cure strategies. A deeper understanding of its molecular mechanisms and interactions will be essential to unlocking its full potential in the fight against HIV/AIDS.

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