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Immunological Profiles in HIV Positive Patients with or without Opportunistic Infections and the Influence of Highly Active Antiretroviral Therapy: A Systematic Review and Update

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Abstract

Background: Immune abnormalities are occasioned during HIV infection consequently predisposing opportunistic infections. In part, these derangements result from impaired expression of a number of immunologically important cytokines. However, exact mechanisms behind HIV infectivity on immune system maturation and cytokine production is not well elucidated, more specifically during treatment with HAART. As such, this review compiles data from various studies with the aim of understanding alterations in cytokine network during the course of HIV infection, while assessing the impact of antiretroviral treatment towards cytokine expression.

Methods: Studies describing cytokine profiles among HIV infected cohorts with or without opportunistic infections (from January, 1990-March, 2016) were carefully inspected from various databases including; PubMed, Hinary, Medline search, Cochrane, and Google scholar for material bearing potential relevance pertaining to our review.

Results: Based on our search strategy a total of 849 research articles were initially identified. However, upon further scrutinisation 830 were excluded since they failed to fulfill all rations for inclusion after reviewing. Overall 19 studies were selected for final review which satisfied our criteria of inclusion.

Discussion: Highly active antiretroviral therapy promotes immune integrity by normalizing progenitor cell function and enhancing $CD4^+$ and $CD8^+$ T cell proliferation and activity. These actions co-operatively prolong survival and quality of life among HIV infected persons while keeping opportunistic infections at bay. Cytokine secretion is vital for T-cell function especially towards control of viral infections as they mediate effector roles as well as support immune system expansion. Elevated cytokine levels during the course of HIV infection can have positive or negative effect on viral load control or $CD4^+$ T cell lymphocyte homeostasis. For instance, TNF-α and IL-4 aid viral replication while IFN-γ is implicated in control viral replication.

Conclusion: Both HIV infection and antiretroviral treatment influence levels of circulating inflammatory cytokines. However, further investigations are warranted to define exact mechanisms of HIV disease progression coupled with cytokine expression for improving therapeutic options for HIV infected patients.

Keywords: Cytokines; Immune system; HIV; Highly active antiretroviral therapy; Opportunistic infections

Abbreviations

HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; IL-2: Interleukin 2; IFN-γ: Interferon-gamma; TNF-α: Tumor Necrosis Factor Alpha; IL-4: Interleukin-4; HTLs: Type 1 Helper T-Lymphocytes; MIP-1β: Macrophage Inflammatory Protein-1beta; GM-CSF: Granulocyte Monocyte Colony Stimulating Factor; NK cells: Natural Killer Cells; PBMCs: Peripheral Blood Mononuclear Cells; IP-10: Interferon-gamma-inducible Protein 10; DHEA; Dehyroepiandrosterone; NF-κB: Nuclear Factor-Kappa Beta; OPC: Oropharyngeal Candidiasis; AZT: Zidovudine; IRD: Immune Restoration Disease.

Background

Infection with HIV results in acquired immunodeficiency syndrome which progressively depletes $CD4^+$ T lymphocytes consequently impairing host immune functions [1]. Contrastingly, unlike the $CD4^+$ cell moiety that gradually declines over time, the $CD8^+$ cytotoxic T lymphocyte (CTLs) expansions persist until far advanced stages of HIV disease, when all T-cell numbers tend to fall [2,3]. Highly active antiretroviral therapy (HAART) is primarily used in controlling HIV replication with successful intervention being measured by an increase in baseline $CD4^+$ T cell counts, reduction of $CD8^+$ T cell numbers and significant decline in HIV viral load [4,5]. HIV viral load remains the preferred clinical parameter to monitor individuals on ART [6,7], arguably because it accurately detects virological failure prior to the manifestation of either immunological or clinical deterioration.

T lymphocytes play a significant role in controlling numerous viral infections [8]. The lymphocyte subset known as Th-1 (T helper 1) is responsible for directing a cytotoxic $CD8^+$ T-lymphocyte response, while the Th-2 (T helper 2) subset diminishes cytotoxic responses while mounting antibody production [9]. A variety of T cell factors are important in enhancing their functional roles. These factors include secretion of cytokines that mediate T cell effector functions as well as supporting the expansion of the immune system [10,11], CD40 expression that provide co-stimulatory signals to both responding B cells and $CD8^+$ T cells [12-14], and capability for proliferation when stimulated by an antigen [15].

Immunologically, infection by HIV results in chronic immune activation subsequently leading towards a dysregulated production of multiple chemokines and cytokines [16], most of which have been used as hallmarks of disease progression as well as in assessment of patient's response to antiretroviral treatment [17]. These cytokines are classified into pro- and anti-inflammatory mediators, with interplay of signals between them conferring either protection from or predicting clinical outcome in both viral and mycobacterial infections [18,19]. For instance, plasma levels of Th-1 associated cytokine profile including; interferon-γ (IFN-γ), interleukin (IL)-2 and interleukin (IL)-12 are highly elevated during acute HIV-1 infection, and gradually decline as disease progresses [20]. On the other hand, Th-2 expressed anti-inflammatory cytokines including interleukin (IL)-4 and interleukin (IL)-10 become significantly elevated during HIV disease advancement [9,21]. In most infections, Th-1 immunity is protective while type 2 responses assist with down-regulation of Th-1 associated inflammatory profiles [22,23], thereby regulating immune balance.

With the growing understanding of their roles during infections and disease progression, cytokines including IFN-γ, IL-10 and tumor necrosis factor alpha (TNF-α) have been assayed in plasma to assess the efficacy of antiretroviral therapy during HIV infection [24,25]. For example, HAART markedly increases plasma IFN-γ levels [26,27], and considerably lowers IL-10 systemic levels during HIV infection [25]. Hence, these actions co-operatively show that antiretroviral treatment markedly influences systemic cytokine levels.

On the whole, concurrent HIV, opportunistic pathogens and antiretroviral treatment subject HIV patients to marked immunological, biochemical and metabolic derangements [28-30], however, assessment of cytokine profiles and clinical biomarkers including $CD4^+$ and $CD8^+$ T cells as immunological correlates of disease progression and therapeutic outcomes among HIV infected cohorts exposed to antiretroviral therapy or naive for treatment remains less defined. As such this review has gathered information from various studies with the goal of describing derangement in cytokine profiles during ongoing HIV infection while evaluating the influence of antiretroviral treatment towards cytokine expression.

Methods

Relevant sources comprising of Medline, PubMed, Hinary, Cochrane, Embase, DynaMed Plus, CINAHL database and Google scholarly articles were systematically searched for crucial articles and reports on cytokine profiles among ART-experienced HIV infected subjects bearing opportunistic infections or not. Additionally, conference abstracts were also inspected for potential material before being included for review. The inclusion criteria was confined to English only articles lying within January 1990 to March 2016, with major emphasis being focused on research papers describing cytokine expression particularly in relation to HAART. Reference lists of potential studies that met our search criteria were also thoroughly inspected. Studies that characterized patients as having HIV co-morbidities including Tuberculosis (TB), hepatitis B and C were excluded. Similarly, those articles primarily dealing with ART-naive subjects were also not considered for review. Terms employed in the study search included; "cytokine expression in HIV", "ART and cytokine interactions", "opportunistic infections and HIV", "HAART and opportunistic infections", "impact of HAART on cytokine profiles".

Results

Based on our general research criteria, the initial search identified 849 potential articles. However, final articles selected after assessing the eligibility of the full-text (if available) and whether relevant to the review objectives comprised 19 articles. Final articles selected for review had a total of 5927 participants and were conducted in various countries comprising; Japan, Iran, Brazil, Norway, Italy, London, China, Rwanda, California, New Orleans, Texas and South Africa. Age groups (years) identified varied but majority of studies reported participants lying between ages 18-60 years.

Among the research articles that satisfied the criteria for inclusion, 4 were cross-sectional based in nature [5,21,31,32], 8 were longitudinal studies [27,33-39], 5 were prospective cohort studies [40-44] whereas 2 studies involved use of both cross-sectional and longitudinal study designs [26,45]. Table 1 presents the types of studies, population among other variables included in our review.

Discussion

Based on previous research it is apparent that various plasma cytokines are expressed within the body during HIV disease progression [27,46]. Similarly, antiretroviral treatment has been shown to cause a dysregulation in cytokine expression profiles [26,31]. However, this has not been fully interrogated, more specifically the contribution of each specific antiretroviral agent towards circulating plasma cytokine levels. To add further, the presence of opportunistic infections including oropharyngeal candidiasis (OPC) stemming from HIV associated immunosuppression have been shown to contribute towards cytokine derangement [32,40]. Based upon these critical observations, the current review summarizes data from multiple studies with the objective of understanding alterations in immune activation profiles during underlying HIV disease, while evaluating the role of antiretroviral treatment towards cytokine expression.

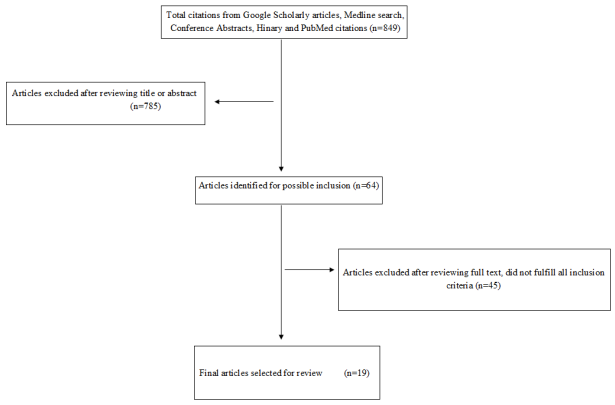

Figure 1: Search strategy and results.

Author/year	Title	Year of Study	Study country	Age group studied (Yrs)	Sample Size	Study type
Reuben et al. [27]	Magnitude of IFN-γ production in HIV-1-infected children is associated with virus suppression.	2002	Houston, Texas, USA)	Children	21	Longitudinal
Klein et al. [21]	Demonstration of the Th1 to Th2 cytokine shift during the course of HIV-1 infection using cytoplasmic cytokine detection on single cell level by flow cytometry.	1997	Frankfurt, Germany.	Adults	48	Cross-sectional based
Malherbe et al. [31]	Circulating biomarkers of immune activation distinguish viral suppression from nonsuppression in HAART-treated patients with advanced HIV-1 subtype C infection	2014	Pretoria, South Africa.	Adults (≥ 18 yrs)	58	Cross-sectional based
Watanabe et al. [26]	Sustained high levels of serum interferon-γ during HIV-1 infection: a specific trend different from other cytokines.	2010	Japan	Adults	35	Cross-sectional based
					18	Longitudinal study
Lilly et al. [40]	Tissue-associated cytokine expression in HIV positive persons with oropharyngeal candidiasis	2004	Louisiana, New Orleans	Adults	67	Prospective cohort
Imami et al. [33]	Assessment of type 1 and type 2 cytokines in HIV type 1-infected individuals: impact of highly active antiretroviral therapy.	1999	London, United Kingdom	Adults	9	Longitudinal study
Stylianou et al. [45]	IL10 in HIV infection: increasing serum IL10 levels with disease progression-downregulatory effect of potent antiretroviral therapy.	1999	Oslo, Norway	Adults	74	Cross-sectional based
					32	Longitudinal study
Jones et al. [39]	Cytokine profiles in human immunodeficiency virus-infected children treated with highly active antiretroviral therapy.	2005	Hong Kong, China	Children	12	Longitudinal

Mousavi et al. [32]	Plasma Levels of IFN-γ, IL-4, IL-6 and IL-17 in HIV-Positive Patients With Oral Candidiasis.	2016	Kerman, Iran	18-50	98	Cross-sectional based
Kranzer et al. [5]	Community viral load and CD4 count distribution among people living with HIV in a South African township: implications for treatment as prevention.	2013	Cape Town, South Africa	Adults	1300	Cross-Sectional Survey
Keating et al. [41]	The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of US women.	2011	Interagency HIV study (USA)	Adults	3766	Prospective cohort
Meira et al. [44]	Correlation between cytokine serum levels, number of $CD4^+$ T cells/mm^3 and viral load in HIV-1 infected individuals with or without antiretroviral therapy.	2004	Sao Paulo, Brazil	18-63	99	Prospective cohort
Graziosi et al. [43]	Kinetics of cytokine expression during primary human immunodeficiency virus type 1 infection	1996	Birmingham, Bethesda & Baltomore, USA	Adults	9	Prospective cohort
Norris et al. [34]	Elevations in IL-10, TNF-α, and IFN-γ from the earliest point of HIV type 1 infection.	2006	San Francisco, California	Adults	40	Longitudinal study
Aukrust et al. [42]	Tumor Necrosis Factor (TNF) System Levels in Human Immunodeficiency Virus—Infected Patients during Highly Active Antiretroviral Therapy: Persistent TNF Activation Is Associated with Virologic and Immunologic Treatment Failure.	1999	Olso, Norway	16-60	60	Prospective cohort
Twizerimana et al. [38]	Immunological profiles in HIV positive patients following Haart initiation in Kigali, Rwanda.	2014	Kigali, Rwanda	Adults	33	Longitudinal study
Stylianou et al. [35]	Interferons and interferon (IFN)inducible protein 10 during highly active antiretroviral therapy (HAART)-possible immunosuppressive role of IFNα in HIV infection.	2000	Oslo, Norway	15-64 yrs	60	Longitudinal study
Vecchiet et al. [36]	Interleukin-4 and interferon-gamma production during HIV-1 infection and changes induced by antiretroviral therapy.	2003	Chieti, Italy	Adults	52	Longitudinal study
Hardy et al., [37]	Reconstitution of $CD4^+$ T cell responses in HIV1 infected individuals initiating highly active antiretroviral therapy (HAART) is associated with renewed interleukin2 production and responsiveness.	2003	London, United Kingdom	Adults	36	Longitudinal

Note: IFN-γ: Interferon-gamma; TNF-α: Tumor Necrosis Factor alpha; IL-2: Interleukin-2; HIV: Human Immunodeficiency Virus; HAART: Highly Active Antiretroviral Therapy; IL-10: Interleukin-10; IP-10: Interferon Inducible Protein-10; IL-17: Interleukin-17; IL-4: Interleukin-4; IFN-α: Interferon Alpha; IL-6: Interleukin-6; Th 2: T-helper 2 cells.

Table 1: Studies/articles included in the review.

Cytokines in HIV

A repertoire of cytokines is produced by $CD4^+$ and $CD8^+$ T cells during HIV infection [16]. Observed changes in these cytokine levels during the course of HIV have the potential to either enhance or suppress viral replication [20]. Among these key cytokines includes; IFN-γ which has been identified to induce cellular antiviral proteins as well as activate macrophages [47]. Tumor necrosis factor alpha has been shown to inhibit viral gene replication and expression [48]. On the other hand, macrophage inflammatory protein (MIP)-1beta (β) is a

chemokine known to suppress HIV infection by competing for the HIV co-receptor chemokine receptor 5 (CXCR-5) [49]. Lastly, perforin forms pores through cell membranes resulting in cell death [50]. The soluble factors above are produced when there is contact between a viral specific antigen and the $CD8^+$ T cells.

Decline in $CD4^+$ T cell counts during HIV infection is associated with the loss of T cell mediated responses, which has direct correlation with elevated HIV viral load [5,51]. T cell functional defects are seen during the early phase of infection, which is accompanied by the production of type 1 cytokines including; IFN-γ and IL-2 and thereafter persistence of type 2 cytokines mainly IL-4 and IL-10 [21,22]. Enhanced expression of type 2 cytokines is associated with HIV disease progression [33]. Additionally, types 1 helper T-lymphocytes (HTLs) synthesizes IL-2 and IFN-γ that are essential in enabling effector virus-specific $CD8^+$ cytotoxic T lymphocyte responses [52]. These effector cells suppress HIV-1 by direct target cell lysis or by the secretion of soluble mediators such as a $CD8^+$-antiviral factor (CAF) and C-C chemokines, which contribute toward CD4 (HTLs) resistance to HIV-1 infection [53,54].

During viral infection, virus-specific $CD4^+$ and $CD8^+$ T cells have been observed to secrete a repertoire of cytokines including; IFN-γ, IL-2, TNF-α, GM-CSF, RANTES, and MIP-1β [55]. However, the distribution of cytokine secreting subsets is dissimilar as cytokine secreting $CD8^+$ T lymphocytes dominate during advanced infection [56]. In the course of HIV progression, mononuclear cells lose the capacity to secrete pro-inflammatory IL-2, IL-12, and IFN-γ while producing increased levels of anti-inflammatory mediators IL-4 and IL-10 [57]. The loss of IL-2 secretion leads to the loss of the ability of T lymphocytes to proliferate when stimulated by common antigens during HIV infection [57].

Among the many cytokines, IL-12 is one of the most critical since it enhances natural killer (NK) and Th-1 functions while also inducing production of other cytokines, particularly IFN-γ and IL-2 besides generation of cytotoxic lymphocytes [58,59]. It has been reported that IL-12 production is suppressed in HIV-1 infected patients [41]. This down-regulation of IL-12 responses is one mechanism used by HIV to counter type 1 associated immunity.

On the other hand, loss of testosterone derivatives in serum has been reported among HIV subjects and leads to lean-muscle-mass wasting [60,61]. Reduced expression of dehyroepiandrosterone (DHEA) during AIDS progression has been linearly correlated to losses in $CD4^+$ T cells leading to faster progression to AIDS [62]. This advancement of disease with the loss of $CD4^+$ T lymphocytes are inversely correlated with the serum cortisol levels [60,62]. As such, HIV/AIDS leads to low DHEA and high glucocorticoid levels that in turn cause suppression of IL-2, IFN- γ, and IL-12 production while stimulating the production of IL-4 and IL-10 [63]. The above factors result in the suppression of type 1 immune responses while stimulating type 2 responses in addition to killing $CD4^+$ T lymphocytes [57]. Overall, this range of activities proves not effective in clearing a broad range of pathogens [57].

The inflammatory mediator IL-7 has a role in different stages of T cell development from precursors at bone marrow level to mature T cells in the peripheral blood stream [64]. However, its role in HIV-1 disease progression has yet to be understood. *In vitro* studies show that IL-7 induces HIV replication and raises the virus DNA levels in infected $CD8^+$ peripheral blood mononuclear cell (PBMC) cultures [64,65]. Additionally, studies reveal IL-7 to be effective in enhancing HIV-1 proviral reactivation when compared to IL-2 alone or in combination with phytohaemagglutinin (PHA) in $CD8^+$ depleted peripheral blood mononuclear cells (PBMCs) [65]. Among HIV subjects on ART, stromal IL-7 levels decline with an increase in $CD4^+$ levels.

Like other soluble markers of immune activation, IL-15 a novel cytokine with IL-2 like activity is described to be involved in development and activation of naive and memory effector T cells [23,66]. This cytokine plays a role in the survival and expansion of naive as well as memory $CD8^+$ T cells [67]. Additionally, IL-15 increases effector function, proliferation and survival of NK cells [68,69], which are imperative in the control of HIV replication. Among ART naive patients, IL-15 production is decreased while in individuals with a good response to HAART, the levels of IL-15 are comparable to those of healthy subjects [70].

The secretory cytokine IL-2 that is produced by activated T cells exerts an array of immunological roles including T cell proliferation, differentiation and survival [71]. Among HIV infected individuals cytokine trial interventions have shown that introduction of exogenous recombinant IL-2 restores the ability of the immune system to induce T cell expansions especially the $CD4^+$ moiety [72]. As such, the degree of HIV-associated immune activation that is mirrored by T-cell turnover is reduced among recombinant IL-2 recipients [73]. These events show that IL-2 functions to control deleterious immune effects of HIV.

Normally, TNF-α, a potent cell signaling protein is identified for its crucial role in immunoregulation [74]. During HIV disease the cytokine is able to induce viral expression in severely infected cells [75]. Various studies document an initial burst of TNF-α levels during primary HIV infection [34], although much higher frequency and concentration is observed during progressive disease [42,76], that may be linked to continuous TNF-α activation. Therefore, in as much as HIV causes marked dysregulation of TNF-α production, the cytokine also contributes towards pathogenesis of HIV.

Heightened levels of immune activation resulting from HIV pathogenesis accelerates cytokine shift towards Th-2 responses. Based upon this, IL-10 a Th-2 expressed cytokine is significantly elevated during chronic HIV disease, which is correlated with HIV viral load [45]. Interleukin-10 extends HIV pathogenesis by crippling effector T cell responses [77,78]. However, in as much as the cytokine has been implicated in poor disease outcomes, it also partly confers immune protection. For instance, IL-10 suppresses replication of HIV within macrophages [79], which reduces risk of TB development among HIV infected persons. Interestingly, IL-10 may also inhibit expression of Th-1 associated cytokines including IFN-γ for immune regulation purposes [80].

Interferon-gamma being among the critical Th-1 cytokines and secreted predominantly by $CD4^+$, $CD8^+$ (CTLs) and NK cells exerts both antiviral and immuno-stimulatory functions [81]. As such, the inflammatory mediator is highly expressed during acute phase of HIV and confers protection until advanced stages of disease where Th-2 responses override [45,82,83]. This elevation in systemic levels of the cytokine during acute disease stage has been linked with peak HIV viraemia [84] that is partly responsible for excessive immune activation experienced in HIV. It is also key to note that deficiencies in NK cell responses among HIV patients independent of $CD4^+$ T cell depletion directs IFN-γ secretion [85], hence signifying the role of IFN-γ as a primary cytokine against HIV disease.

The chemokine marker IFN-γ-inducible protein 10 (IP-10) of the innate immune system mediates a number of immunological functions [86]. For instance, elevated levels of this chemokine have been reported in different viral infections such as severe influenza infection [2,87], West Nile virus infection [88], acute and chronic Hepatitis C [89], showcasing its involvement in immune responses during viral infections. However, during HIV mono-infection, levels of IP-10 are upregulated compared to healthy individuals [35,90,91]. More importantly, the raised IP-10 levels during HIV are inversely correlated with $CD4^+$ T cell counts and directly with viral load thus promoting HIV replication [41,92]. These findings clearly highlight the role of IP-10 in HIV pathogenesis and disease progression.

Finally, exosomes from HIV infected cells are capable of stimulating the secretion of pro-inflammatory cytokines via trans-activation response (TAR) ribonucleic acid (RNA). Incubation of macrophages with exosomes retrieved from HIV-1 infected cells has been shown to result in dramatic elevations of pro-inflammatory cytokines tumor necrosis factor-beta (TNF-β) and Interleukin (IL)-6 hence indicating that exosomes with TAR RNA can play a role in controlling cytokine gene expression [93]. Toll like receptor binding via TAR RNA or TAR microRNA has the potential to activate nuclear factor-kappa beta (NF-κB) pathway thereby regulating cytokine expression. This explains a possible inflammation mechanism that is normally observed in patients infected with HIV who are under combination ART [93].

HIV-1 Controllers but not non-controllers maintain $CD4^+$ T cells co-expressing various cytokines

In a study to evaluate the cytokine co-expression profiles of HIV-1 specific $CD4^+$ T lymphocytes expressing; IFN-γ, IL-2 and TNF-α, it was found that $CD4^+$ T cells secreting two to three cytokines had over 50% response while in non-controllers over 75% of the cells were single producers (secreted one cytokine) of mainly IFN-γ [49]. Functional superiority belonged to those cells producing more than two cytokines [49]. The HIV-1 controllers were defined as ART naive individuals with plasma viremia of 1000 HIV RNA copies per ml after one year of medical follow up while non-controllers were ART naive subjects with plasma viremia of 7000 HIV 7000 HIV RNA copies per ml. The double and triple cytokine producers secreted higher levels of cytokines per cell than single producers while triple producers expressed more superior cytokine levels per cell compared to IL-2 and IFN-γ double producers. These observed differences were not much pronounced in cells producing single cytokines [49].

Effect of HIV on expression of cytokines in tissues of patients with oropharyngeal candidiasis

Oropharyngeal candidiasis (OPC), caused primarily by Candida albicans, remains the most common fungal lesion among HIV positive individuals despite the invention of HAART [94,95]. A study by Lilly et al. [40] evaluated the effects of HIV on tissue cytokine and chemokine expression among infected subjects with and without OPC. Changes were documented in chemokines and cytokines of both the Th-1 and Th-2 arms of the immune system. There was notable rise in chemokines (MCP-1, RANTES, IP-10) and cytokine levels of (IFN-γ, IL-12, IL-2 IL-15, IL-6) and significant reduction in TNF-α levels compared to controls [40]. This observed trend generally indicates an enhanced pro-inflammatory type host immune responsiveness towards HIV in the presence of OPC.

In yet another study by Mousavi et al. [32] on immunological interaction between OPC and HIV, there were marked differences in expression of cytokines assessed. Individuals co-infected with HIV and OPC exhibited significantly higher IFN-γ and IL-17 production compared to HIV/OPC mono-infected and uninfected control population. The increase in IFN-γ levels is suggestive of improved type 1 immunological outcomes. Similarly, elevation in IL-17 levels is directed towards fungal pathogens. Previous studies reveal that deficiency in IL-17 cytokine levels highly predisposes disseminated candidiasis [96,97].

Similarly, in addition to IL-17, expression of IL-22 and TNF-α also confers immune integrity against *C. albicans* [98,99]. The two cytokines are reported to synergistically trigger an innate immune response involving release of various immune-modulatory molecules including chemokines CXCL-9/-10/-11; antimicrobial peptides human β defensin 2 (HBD-2) and S100 proteins; and initial complement factors C1r and C1s which all confer protection in human primary keratinocytes [99-101], that maintains *C. albicans* infections at bay.

With the onset of HAART, incidences of OPC in HIV co-infected subjected have steadily declined [102]. This activity is hypothesized to result from immune reconstitution and $CD4^+$ T cell recovery associated with various antiretroviral agents [103,104], and/or unusually as a result of immunologic hyper-activation against underlying fungal challenge [105,106].

Altogether, infection with HIV highly interferes with oral mucosal immune cell populations that are critical in host defence against *C. albicans* [107]. The cytokine expression profiles observed during HIV and OPC reflect upon changes in $CD4^+$ and CD8 CTLs as they are the chief producers of these inflammatory mediators [108]. For instance, IL-2, TNF-α and IL-15 are CD8 cell associated cytokines [109], whereas IFN-γ a key Th-1 expressed cytokine is produced by both $CD4^+$ and $CD8^+$ subsets of the immune system [81]. There only difference is identified by the relative systemic distribution at specific time-points. The interplay of signals and kinetics of production between these immune regulators confers resistance or increases susceptibility towards diseases including OPC and HIV.

Cytokine profiles in HIV patients on HAART

Derangements in cytokine production during both acute and chronic stages of HIV have initially been addressed [43,110]. Similarly, the contribution of antiretroviral treatment towards expression of multiple plasma cytokines during HIV has previously been described, though not well elucidated [35]. Standard antiretroviral treatment for management of HIV comprises of at least three antiretroviral drugs that suppress HIV replication. Selection of these therapeutic agents is performed from among Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs) [111].

Studies have documented the effects of HAART in HIV patients immune reconstitution and subsequent viral suppression [33]. IFN-γ earlier shown to be crucial in regulating HIV replication [45], yields discordant results during antiretroviral treatment. Various studies describe a steady raise in IFN-γ levels during acute HIV-1 infection, which markedly increases during HAART [26,27]. This may be related to immune restoration following viral suppression. Contrastingly, more recent studies document significant decline of plasma IFN-γ levels with HAART administration among previously untreated HIV-1 infected subjects [31] that may be related to down-regulation of

inflammation and immune activation by antiretroviral drug intervention. Collectively, these reported contradictory findings may be attributed to distinct mechanisms of immune activation that are differentially affected by antiretroviral therapy.

Successful antiretroviral therapy has previously been reported to lower plasma IL-10 levels [25], which is paralleled by a reduction in viral load among HIV-1 infected individuals [33]. This indicates that high HIV viral load may be the main driver of high plasma IL-10 levels, which significantly reduce upon effective treatment with antiretroviral therapy. Furthermore a lack of decline in plasma IL-10 levels following HAART administration has been associated with virological treatment failure [45], which further reinforces the above argument.

The chemokine IP-10 and cytokine IFN-α have previously been shown to have a pathogenic role in HIV by enhancing viral replication [92], that complicates antiretroviral treatment outcomes. A study by Stylianou et al. [35] involving HIV positive cohorts, revealed elevated IP-10 and IFN-α levels in HIV subjects relative to healthy controls prior to HAART initiation. Upon therapeutic intervention, levels of both cytokines significantly declined although not to normal concentrations [35]. This observation may be an indication of host immune recovery that regulates inflammatory episodes associated with these cytokines.

The pro-inflammatory mediator TNF-α has initially been implicated in HIV pathogenesis by inducing virus transcription-activating factors [112]. Previous studies conducted by Meira et al. [44] documented lower TNF-α, IL-4 and IL-10 serum level among HIV-1 mono-infected ART-experienced compared to their ART-naive counterparts. Similarly, elevated levels of TNF-α have been reported in mononuclear phagocytes during HIV, and which significantly decline during HAART [42]. A heightened level of the three cytokines hastens HIV replication and has been associated with poor HIV outcomes [113,114]. Thus the observed findings above delineate HAART to induce immunological recuperation while down-regulating cytokine associated inflammation and immune activation.

Interleukin-4 a definer of Th-2 subset exerting dominant antiproliferative effects is identified among the critical cytokines promoting HIV immunopathology [115]. However, with HAART commencement, expressed levels of this cytokine gradually decline to those comparable with healthy controls [36]. This may be linked to marked reduction in HIV viral load with subsequent suppression of inflammatory episodes resulting from combined antiretroviral therapy.

In contrast to IL-4 cytokine expression profile, IL-2 a potent pro-inflammatory mediator bears immune protective effects including infection with HIV [37]. The absolute values of IL-2 increase substantially in HAART patients [38,44], with the lowest values recorded in non-treated patients [33]. This observation may be due to immune recovery with subsequent proliferation of naive $CD4^+$ and $CD8^+$ T cells [116,117] that enhances expression of this inflammatory marker. Interestingly, it has been shown that IL-2 secretion is transiently enhanced during zidovudine (AZT) monotherapy [118]. This may be an indication that various ART regimen enhance more responses of specific immune effector cells, however, additional studies are warranted to reinforce this assumption.

The primary role of the regulatory cytokine IL-12 in antiviral cell-mediated immunity has extensively been investigated [119]. Previous studies show that untreated HIV-1 infected subjects with progressive disease have suppressed serum IL-12 levels compared to HIV uninfected controls [41]. Similarly, studies on HIV infected children enrolled on HAART demonstrated up-regulation in IL-12 production following treatment with antiretroviral agents, which was positively correlated with $CD4^+$ T cell counts [39]. These findings reveal that HAART not only restores immune integrity but also induces a significant CD4 cell rescue and IL-12 proliferation that are required for proper immune effector functions.

IL-6 a B-cell stimulatory cytokine is involved in IgH class switching and possesses anti-apoptotic properties on B cells which heighten development of various tumors [120]. Elevated IL-6 levels that remain persistently high have the ability to cause B-cell hyper-activation that promotes development of lymphoma [120]. Similar pattern of IL-6 mediated immune deterioration is experienced during HIV. Studies document elevated systemic IL-6 levels that is directly associated with residual levels of HIV viraemia [121], which indicates that IL-6 may contribute towards advancement of disease. Apparently, during HAART the circulating levels of this cytokine are reported to remain unchanged [122]. The paradoxical finding may be attributable to transmitted drug resistance prior to HAART initiation. Levels of this cytokine have also been described to remain steadily high in patients who develop immune restoration disease (IRD) despite being on ART, which may be owed to persistent immune activation associated with asymptomatic opportunistic infections [123].

Conclusions and Future Perspectives

Based on review from multiple studies, it is clear that HIV induces a cascade of host inflammatory cytokine responses at magnitudes greater than those observed with most other infectious agents. Additionally, an observed alteration in cytokine profiles has been shown to be associated with adverse clinical events and disease advancement. Similarly, notable changes in systemic cytokine levels observed during HAART initiation are suggestive of declining immune activation and chronic inflammation subsequent to $CD4^+$ T cell recovery and HIV viral load reduction. Interestingly, though, cytokine profiles have been documented to variate among individual HIV patients, which may be attributed to distinct mechanisms of immune activation that are differentially affected by antiretroviral treatment. On the whole, more investigations on inflammatory and regulatory profiles are warranted in order to potentiate their utility as predictors of HIV disease progression and response to treatment among HIV infected cohorts.

Competing Interests

The authors declare no relevant conflicts of interest to disclose.

Authors Contributions

JWR and NGK conceived the idea. All authors conducted the search and reviewed the articles and reports against the inclusion criteria. In addition, all authors revised and edited the manuscript. Final version of the manuscript was approved by all stakeholders.

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