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Review Article

Effect of Highly Active Antiretroviral Therapy on T-Cell Sub-population Profile in Human Immunodeficiency Virus-1 Infected Patients

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Abstract: The range of T cell abnormalities in advanced HIV-1 infection treatment is broad. The defects are both quantitative and qualitative and affect virtually every limb of the immune system. Beyond the precise measurement of naive T cells ($CD45RA^+CCR7^+CD27^+CD28^+$), the differential expression of different molecules on T cell allows the distinction between numerous subsets of resting or antigen-experienced T cells on the treatment. However, in spite of intense investigation, the mechanisms underlying highly active antiretroviral therapy (HAART) –induce immune reconstitution remain to be fully characterized. HAART treatment induced changes in the peripheral distribution of naïve ($CD45RA^+$ $CD62L^+$) and memory $CD45RA^-$ $CD62L^+$) cells, CCR5, $CXCR4^-$, $CD95^-$ expressing T cells, T-reg cells and on gamma delta (ϒδ) T cells. As a concluding remark prolonged suppression of plasma viral load (pVL) by HAART improves not only αβ T-cell function but also ϒδ T-cell reactivity, and it is strongly recommended that once started the treatment, sever immunocompromized patient should continue the treatment for long time.

Keywords: T-lymphocytes, HIV-1 Infection, Highly Active Antiretroviral Therapy

1. Introduction

Progressive human immunodeficiency virus type 1 (HIV-1) infection is often associated with high plasma virus load (pVL) and impaired $CD8^+$ T-cell function; in contrast, $CD8^+$ T cells remain poly functional in long-term non progressors (LTNs). However, it is still unclear whether T-cell dysfunction is because of high pVLs [1,2] and in spite of intense investigation, the mechanisms underlying HAART-induced immune reconstitution remain to be fully characterized. Initial studies performed on HIV-1 infected patients with advanced disease suggested that HAART-induced T cell repopulation was mainly due to an early recirculation of memory cells from lymphoid tissues to blood, accompanied by a slow production of newly generated naïve T cells. However that, recently, a correlation between the size of thymic tissue and the magnitude of naïve T cells recovery after HAART has been demonstrated, suggesting a critical role for the thymus in lymphocyte restoration, also it has been demonstrated that HAART normalizes the function of progenitor cells, induces changes in T cell subsets, reverses $CD4^+$ T cell defects, and restores the production of IL-2 and the IL-2 reactivity of lymphocytes [3]. Thus remarkable importance considering that an effective immune reconstitution is possible only if new naïve cells, with wider repertoire, are generated [4]. So, the objective of reviewing is to see effect of

highly active antiretroviral therapy (HAART) on T-Cell Sub-Population profile in HIV-1 infected patients.

1.1. T Lymphocytes Development and Maturation

During the prethymic phase, pluripotent stem cells develop into lymphoid progenitor cells capable of becoming T cells. Such progenitors initially appear in the liver by about six weeks of gestation, and then shift by about five months of gestation to the bone marrow, which is the major source of T cell progenitors throughout the remainder of life. Progenitor cells reach the thymus via the blood, entering into the thymus through venules near the cortico medullary junction and then migrating to the outer cortex [5,6]. Interaction of the T cell receptor (TCR) with cognate ligands in the thymus may result in either maturation (positive selection) or death (negative selection) [7] and critical parameter that controls the fate of a thymocytes seems to be the number of TCRs engaged with complexes of peptide and major histocompatibility complex [8]. In the late thymic phase, cells that fail to interact with self-major histocompatablity complex (MHC) die by apoptosis. Following positive selection, the T cells become double positive (DP) cells. DP cells are the targets of the selective processes that establish the repertoire of TCR specificities. In the final phase of thymic T cell development, cells become single-positive (SP) [9,10] (Fig1).

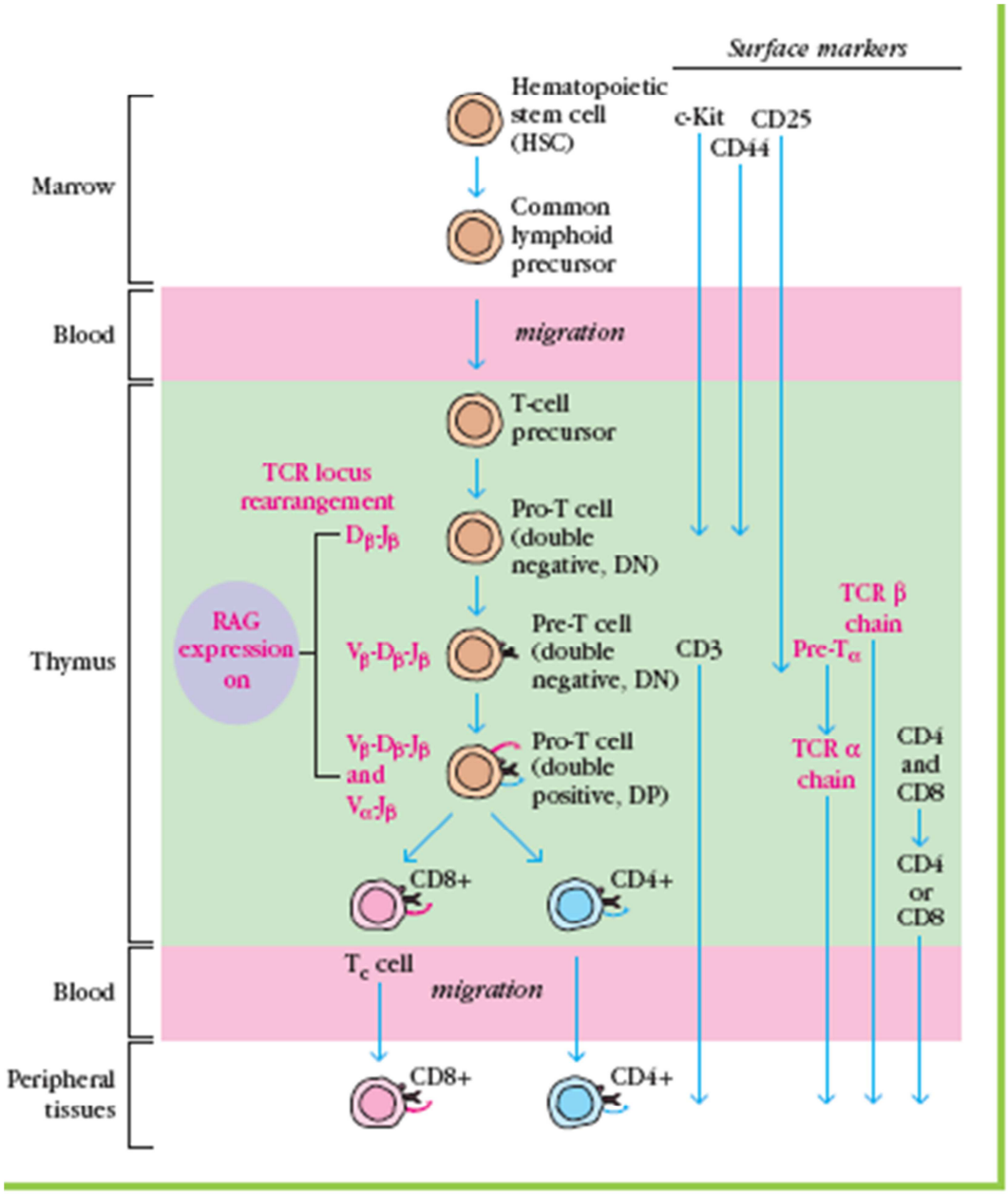

Figure 1. *Development of αβ T cells in the mouse. T-cell precursors arrive at the thymus from bone marrow via the bloodstream, undergo development to mature T cells, and are exported to the periphery where they can undergo antigen-induced activation and differentiation into effector cells and memory cells. Each stage of development is characterized by stage- specific intracellular events and the display of distinctive cell-surface markers. Source:- cuby immunology.*

Two principal categories of T cells based on their functions have been defined: most regulatory T cells express $CD4^+$, and most cytotoxic T cells express $CD8^+$ molecules, but exceptions exist. Cytotoxic T cells expressing $CD4^+$ are prominent in graft rejection and have also been observed in tumor immune responses. Cytokine producing cells expressing $CD8^+$ may also be seen in certain normal or pathological immune responses [11]. Thymocytes undergo a series of differentiation and selection steps to become mature $CD4^+8^-$ or $CD4^-8^+$ (single positive) T cells [12]. Υδ T cells population are minor constituents in the peripheral blood but provide a high contribution to the immune compartment of the gastrointestinal mucosa [13], likely representing the first defense against pathogens crossing this surface. In the mucosa, they constitute up to 50% of all lymphocytes population and approximately 10% of lymphocytes in the lamina propria [14–16].

1.2. Pathophysiology and Pathogenesis of HIV/AIDS

In primary HIV infection, virus replication in $CD4^+$ T cells intensifies prior to the initiation of an HIV-specific immune response [17], with a burst of viremia resulting from the rapid replication of virus in susceptible cells in lymphoid organs (particularly the gut-associated lymphoid tissue), with subsequent dissemination of virus to the brain and other tissues [18,19]. The events associated with primary HIV infection are likely critical determinants of the subsequent course of HIV disease [20], and the pathogenesis of HIV infection is a function of the virus life cycle, host cellular environment, and quantity of viruses in the infected individual. After entering the body, the viral particle is attracted to a cell with the appropriate CD4 receptor molecules where it attaches by fusion to a susceptible cell membrane or by endocytosis and then enters the cell. The probability of infection is a function of both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells available at the site of contact that have appropriate CD4 receptor. Host cells infected with HIV have a shortened life span as a result of the virus's using them as "factories" to produce multiple copies of new HIV. Thus, HIV continuously uses new host cells to replicate itself [21–23].

HIV uses two major co-receptors for fusion and entry; these co-receptors are also the primary receptors for certain chemo attractive cytokines termed chemokines. CCR5 and CXCR4 are the major co-receptors used by HIV [24]. A number of mechanisms responsible for cellular depletion and/or immune dysfunction of $CD4^+$ T cells have been demonstrated in vitro; these include direct infection and destruction of these cells by HIV and immune clearance of infected cells, as well as indirect effects such as immune exhaustion due to aberrant cellular activation and activation-induced cell death. The combination of viral pathogenic and immunopathogenic events that occurs during the course of HIV disease from the moment of initial (primary) infection through the development of advanced-stage disease is complex and varied [24, 25].

The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as helper T cells. This subset of T cells is defined phenotypically by the presence on its surface of the $CD4^+$ molecule, which serves as the primary cellular receptor for HIV. A co-receptor must also be present together with $CD4^+$ molecules for efficient fusion and entry of HIV-1 into its target cells [26, 27].

1.3. Highly Active Anti Retro Viral Therapy (HAART)

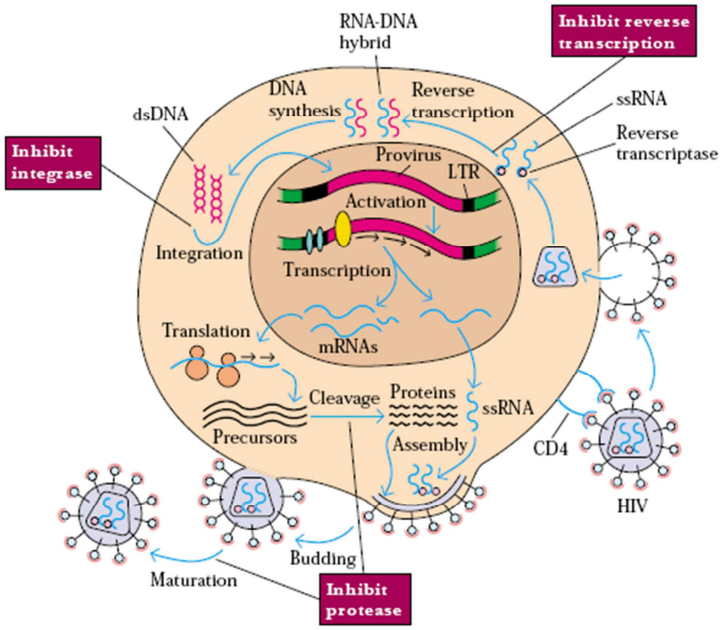

Figure 2. *Stages in the viral replication cycle that provide targets for therapeutic antiretroviral drugs. At present, the licensed drugs with anti-HIV activity block the step of reverse transcription of viral RNA to cDNA or inhibit the viral protease necessary to cleave viral precursor proteins into the proteins needed to assemble a new virion and complete its maturation to infectious virus. Source: - cuby-immunology.*

Highly active antiretroviral therapy (HAART), two or more nucleoside analogues (NRTIs) in combination with at least one protease inhibitors (PI) or one non-nucleoside reverse transcriptase inhibitors(NNRTI); one NRTI in combination with at least one PI and at least one NNRTI; tenofovir containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs classified as HAART [28]; greatly decreases plasma HIV-1 viral RNA concentrations and increases $CD4^+$ T cell counts even in patients at advanced stages of the disease [29–31]. The lower rates of morbidity and mortality associated with such treatments suggest that immune responses in the host against opportunistic pathogens may be improved, though this is still a controversial topic [30]. Currently available drugs for the treatment of HIV infection fall into four categories: those that inhibit the viral reverse transcriptase enzyme, those that inhibit the viral protease enzyme, those that inhibit the viral integrase enzyme, and those that interfere with viral entry [32] (Fig. 2).

Since immunological factors as a whole and T cell sub-population in particular influencing the decision to start and to continue the therapy are still debated [33], it would be great clinical importance to see whether a more complete immune reconstitution of T cell subpopulation might be achieved in patients starting HAART [34].

2. Phenotypic and Cytokine Profile of T Lymphocytes Before the Therapy

There is a lack of information about the stability of these responses over time in subjects experiencing differences in HIV disease progression. As indicated by one study, the functional profile of HIV-specific $CD8^+$ T-cell responses may evolve in different ways depending of the targeted HIV protein and the ability to control virus replication [35].

2.1. Phenotype Profiles T lymphocytes

The characterization of the HIV-1-specific T-cell responses has been the objective of a very large number of studies [35–37] and any type of phenotypic and functional abnormalities have been described [9], the process by which lymphocytes of specific subsets, such as helper, cytotoxic or memory T cells, migrate to the appropriate site is important [38]. For these reasons, it is important to provide some general background on the phenotypic markers and functions that are generally used to define populations of antigen (Ag) -specific T cells at different stages of differentiation prior to address in details the abnormalities observed in HIV infection [6, 30].

The T cell population can be divided into distinct subsets based on their phenotype, i.e. the expression of diverse cell surface receptors. The most-commonly used markers are CD45RA (or CD45RO), CCR7, CD27, and CD28. $CD4^+$ T cells have helper T (Th) cell function and include two major functional subsets, Th1 and Th2 [40]. By using seven or eight-color flow cytometric analysis, we can investigate the subsets classified by four markers, CD27, CD28, CD45RA and CCR7. These subsets showed different patterns of cytokine production after they were stimulated with phorbol myristate acetate and ionomycin. Therefore, there is a good correlation between the phenotypic profiles of both virus-specific $CD4^+$ and $CD8^+$ T cells and the control of virus replication [9].

Cytokine production suggested that $CCR7^+CD45RA^+CD27^+CD28^+$, $CCR7^+CD45RA^-CD27^+CD28^+$ and $CCR7^-CD45RA^-CD27^+CD28^+$ subsets were naive, central memory and effectors memory T cells [10], respectively, whereas $CCR7^-$, $CD45RA^-$, $CD27^-$, $CD28^+$ and $CCR7^-$, $CD45RA^-$, $CD27^-$, $CD28^-$ subsets included Th1 and Th2 cells [41] but one study done on china categorized phenotypically as based on the expression of CD45RA and CCR7 only. According to its observation, $CD4^+$ T cells were subdivided into naive, central memory and effect memory cell subsets (CD4 Naïve, CD4 CM and CD4 EM, respectively). Naive cells have the phenotype of $CD45RA^+CCR7^+$; CM cells are characterized as $CD45RA^-CCR7^+$; EM cells are defined as $CD45RA^-CCR7^-$ [42].

Concerning about ϒδ T cells, there are two main ϒδ T -cell subsets that express either the first variable region (Vϒδ1) or the second variable region (Vϒδ 2) of the delta locus from the T-cell receptor (TCR) [16]. The Vδ1 ϒδ T cells are found predominately at mucosal sites and can respond to nonclassical major histocompatibility complex molecules expressed on stressed cells, while V δ2 ϒδ T cells are predominately in the peripheral circulation and respond to non peptide phosphor antigens [14].

2.2. Cytokine Profiles of T Lymphocytes

2.2.1. Cytokine Profiles of $CD4^+$ T-Cells

Mature $CD4^+$ helper T lymphocytes have been categorized into two major functional phenotypes, TH_1 and TH_2, which produce distinct arrays of lymphokines and which are thought to arise from a pluripotential precursor cell termed TH_0 [43]. IFN-gamma is the major cytokine secreted by Th1 cells [41], IL-4 is the cardinal marker of Th2 cells [44], and secretion of IL-17 defines Th17 cells [45]. T_H-17 cells are a distinct lineage of proinflammatory T helper cells that are essential for autoimmune disease [46]. Initially it was thought that IL-2 was produced exclusively by Th1 cells. Evidence suggests that IL-2 may be important in the maintenance of Th2 cells, expansion of memory Th17 cells, and induction of T reg as well. Th subsets also may be differentiated by their chemokine receptors. Specific chemokine receptors are expressed on the three Th subsets [25].

2.2.2. Cytokine Profiles of $CD8^+$T-Cells

After stimulation by specific peptide antigen, secretion of interferon (IFN)-γ, tumor necrosis factor (TNF)-α, macrophage inflammatory protein (MIP)-1β, and perforin produced by antigen-specific $CD8^+$ T cells ex vivo [47]. Thus, Alloantigen-stimulated $CD8^+$ mouse spleen cells, spontaneously or in the presence of IL-12 or IFNγ plus anti-IL-4, differentiate into $CD8^+$ T cells secreting a Th1-like cytokine pattern (IL-2 and IFNγ). IL-4 induced differentiation

into $CD8^+$ T cells secreting Th2 cytokines (IL-4, IL-5, IL-6, and IL-10) [48]. According to Thailand's diversity of $CD8^+$ T cells study, they demonstrated the presence of four different subsets of $CD8^+$ T cells, which expressed different combinations of cytolytic molecules. They also identified seven different subsets of cytokine producing cells based on different combination of IFN-gamma, TNF-alpha, and IL-2 (Fig.3).

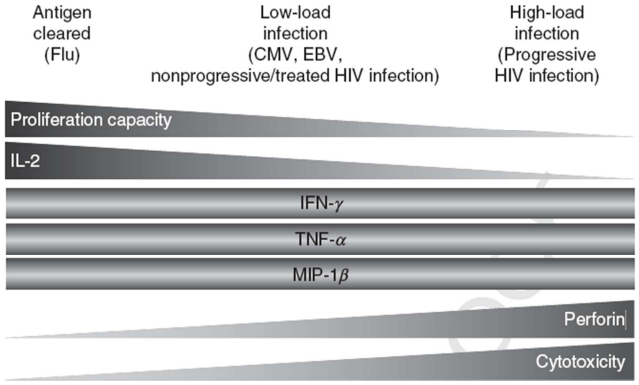

Figure 3. *Schematic representation of the functional profile of virus - specific CD4+ and CD8+ T cells based on the level/duration of antigen exposure/load. All functions are relevant for both CD4+ and CD8+ T cells with the exception of perforin expression and cytotoxicity which pertain to CD8+T cells. Source:- Alexander Harari and Giuseppe Pantaleo. HIV - 1 - Specific Immune Response.*

Their results showed significant alterations of these cell subsets that expressed different combination of cytolytic effector molecules or cytokines in HIV infected patients [49].

2.2.3. Cytokine Profiles of Υδ T-Cells

Υδ T cells demonstrate a variety of functions which include the production of cytokines to augment the adaptive immune response at the sites of infection or tumors. The comparative study done on following pathogenic human immunodeficiency virus (HIV) infection of humans and nonpathogenic simian immunodeficiency virus (SIV) infection of sooty mangabeys also shows that the levels of the production of the two sub population of Υδ T cells cytokines did vary [14]. For example, when Vδ2 Υδ T cells from uninfected donors were stimulated with protease inhibitor (PI) antigen, nearly 90% of the cells expressed TNF-α compared to 60% expressing IFN-γ. The increased expression of TNF-α suggests that Υδ T cells may preferentially express this cytokine for the potential killing of HIV/SIV-infected cells or modulating the immune system in response to opportunistic pathogens [14].

3. Immunity of T-Lymphocyte During HIV-1 Infection

$CD4^+$ T-lymphocytes play a vital role in maintaining the integrity of the human immune system. They are also the primary target cells for HIV [50]. Certain functional profiles of HIV-1-specific $CD4^+$ and $CD8^+$ T-cell responses have been shown to correlate with more effective control of virus replication and stable disease [51,52]. With regard to $CD4^+$ T cells, vigorous HIV-1-specific $CD4^+$ T -cell proliferative responses correlate with lower levels of viral load and more effective control of virus replication following primary infection [51]. The phenotype of HIV-1-specific $CD4^+$ T cells during primary infection is typical of effector cells and thus $CD45RA^-$ $CCR7^-$ $CD127^-$. The phenotype of HIV-1-specific $CD4^+$ T cells remain unchanged in chronic infection compared with primary infection [26].

Furthermore, it has been also shown that a critical component of protective HIV-1-specific $CD4^+$ T cell response is represented by the presence of IL-2 secreting $CD4^+$ T cells [53]. The evidences for a protective role of HIV-1-specific T-cell responses are even stronger for $CD8^+$ T cells [54]. In particular, there are several observations supporting the protective role of HIV-1-specific $CD8^+$ T -cell responses [55,56]; vigorous HIV-1-specific $CD8^+$ T -cell responses composed of cytotoxic, proliferating, and IL-2 secreting cells are found in long-term nonprogressors (LTNPs) [57]. HIV-1 specific $CD8^+$ T -cell responses are found in subjects repetitively exposed to HIV-1 but remaining uninfected [56].

The initially expanded HIV-1-specific $CD8^+$ T -cell population progressively reduces as viremia levels decline. Therefore, it is clear that this initial $CD8^+$ T -cell response is very powerful, and it is likely that this response exerts high selective pressure as indicated by viral sequence diversification and eventually emergence of virus escape mutants [58]. However, after the transition to the chronic phase of infection, the magnitude of the HIV-1-specific $CD8^+$ T -cell response is generally lower compared to primary infection [59]. Similar considerations like $CD4^+$Tcells can be made for the phenotypic profile of HIV specific $CD8^+$ T cells during primary and chronic infection. Therefore, there is a good correlation between the phenotypic profiles of both virus-specific $CD4^+$ and $CD8^+$ T cells and the control of virus replication [59]. Exceedingly high viral loads and rapid loss of $CD4^+$ T cells in all tissue compartments is a hallmark of acute HIV-1 infection, which is often accompanied by clinical symptoms, such as fever, maculopapular rash and/or lymphadenopathy. The resolution of the clinical symptoms and the subsequent decrease of plasma viremia are associated with the emergence of HIV-1-specific $CD4^+$ and $CD8^+$ T cell responses [60]. Viral antigen has been associated with both the development and expansion of virus-specific $CD8^+$ T cells during acute infection and their functional impairment in the setting of persistent antigenemia during chronic viral infection. Data suggest that persistence of antigen can be the cause, rather than the consequence, of the functional impairment of virus-specific T cell responses observed during chronic HIV-1 infection [61]. The study done in New York, HIV-1 induce persistent changes of mucosal and blood ΥδT cells, results demonstrate that HIV-1 infection is associated with significant expansion of Vδ1 and contraction of Vδ 2 cell populations in both the mucosa and peripheral blood. Such changes were observed during acute HIV-1 infection and persisted throughout the chronic phase.

3.1. Effectors Function of T-Cells in HIV-1 Infection

On the basis of the analysis of IL-2 and IFN-γ, three functionally distinct populations of antigen-specific $CD4^+$ T cells (single IL-2, dual IL-2/IFN-γ, and single IFN-γ have been identified) [54]. Furthermore, the presence of IL-2 secreting T cells is consistently associated with the antigen-specific proliferation capacity. Single IL-2 and dual IL-2/IFN-γ antigen-specific $CD4^+$ T-cell populations have intrinsic proliferation capacity while single IFN-γ have poor proliferation capacity that can be promoted in the presence of an exogenous source of IL-2 (53,54). A large percentage (>60%) of antigen-specific $CD4^+$ T cells secrete TNF-α and, based on the secretion of IFN-γ, two equally represented cell populations of single IFN-γ and dual IFN-γ/TNF-α can be identified [59].

With regard to $CD8^+$ T cells, two cell populations of antigen-specific CD8 T cells (dual IL-2/IFNγ and single IFN-γ) can be defined based on the ability to secrete IL-2 and IFN-γ [53]. $CD8^+$ T-cell populations are cytotoxic as measured by the expression of perforin & granzyme B or by the degranulation activity following antigen-specific stimulation. Recently, the term polyfunctional has been used to define $CD4^+$ and $CD8^+$ T-cell responses that, in addition to typical effector functions such as secretion of IFN-γ, TNF-α, MIP-1b, and cytotoxic activity, comprise distinct T-cell populations also able to secrete IL-2 and retaining antigen-specific proliferation capacity. The term "only effectors" defines T-cell responses populations able to secrete cytokines such as IFN-γ, TNF-α, and MIP-1b, and endowed with cytotoxic activity but lacking IL-2 and proliferation capacity [1,22].

Study conducted in New York, once activated ϒδT cells, they exert cytotoxicity via the perforin-granzyme pathway or through induction of apoptosis via Fas/Fas-ligand interactions. These cells can also produce a variety of cytokines and chemokines, depending on the stimulatory signal [62].

T-regulatory cells (T-regs) are a critical T-cell population that profoundly inhibits T-cell activation, proliferation and effector functions. But when we see the involvement of T-reg cells in HIV^+ subjects, the total T-reg percentage is inversely correlated with the lymphocyte proliferative responses as compared to tetanus ($r=-0.45$, $p=0.002$) and Candida ($r=-0.43$, $p=0.003$) antigens [63]. Similar correlations were seen between memory T-reg percentages and the lymphocyte proliferative response to tetanus and Candida in HIV^+ subjects. T-reg percentages did not correlate consistently with markers of immune activation. T-reg percentages are increased in the older HIV^+ population and may play a role in the accelerated disease progression seen in older HIV-infected persons [64].

3.2. Specificity and Breadth of HIV-1-Specific T-Cell Responses

Extensive characterization of the specificity and the breadth of HIV-1- specific T-cell responses have been performed particularly for $CD8^+$ T cells [61]. HIV-1-specific $CD8^+$ T cells recognize a large number of epitopes within the different HIV-1 proteins including structural, regulatory, and accessory proteins. In this regard, a recent study has shown an association between the presence of gag-specific $CD8^+$ T-cell responses and lower levels of viremia. In contrast, $CD8^+$ T-cell responses against Env and accessory/regulatory proteins were associated with higher viremia levels [65]. These observations are of interest and indicate the possibility that immune responses targeting certain regions of HIV-1 may be more protective than others and eventually influence the clinical course of chronic HIV-1 infection [59].

4. T- Lymphocytes Depletion after Infection of HIV-1

T cells actively undergoing thymopoiesis show moderate $CD3^+$ expression. $CD3^+$ expression is a hallmark of mature T cells which are either preparing to emigrate or are residing in the per vascular space of the thymus [66]. $CD4^+$ T-lymphocytes play a vital role in maintaining the integrity of the human immune system. They are also the primary target cells for HIV [34]. The progressive depletion of these cells eventually results in weakening of the host's immune ability to fight against any pathogen, thus rendering the host susceptible to infections and leading ultimately death of patients in the terminal stage AIDS [67]. Although the degree to which a host adaptive immune response contributes to this steady state remains controversial, a number of reports suggest an important role for HIV-specific $CD4^+$ and $CD8^+$ T-cell responses [68]. However, even in untreated individuals with strong and broad HIV-specific T-cell responses, increased viral replication and accelerated $CD4^+$ T-cell loss eventually occur [51]. Several mechanisms likely contribute to this failure of the adaptive immune system to control viral replication on a durable basis, including abnormal signaling of $CD8^+$ T cells through co stimulatory molecules, decreased stores of perforin, impaired antigen presentation, abnormal T-cell differentiation, the emergence of immunologic escape mutations, and/or impaired $CD4^+$ T-cell help [39]. Compared to HIV-uninfected individuals, HIV-infected subjects had lower levels of $CD4^+CD8^+$ double positive cells (CD3-low DP HIV^+ 33.5%; HIV^- 50.5%; CD3bright DP HIV^+ 23%; HIV^- 31.05%) [69]. In evaluating single positive cells, they found lower expressions of $CD4^+$ single positive cells in HIV-infected patients in comparison to HIV^- negative subjects (HIV^+ 13.9%; HIV^- 37.7%). Conversely, HIV^+ subjects displayed higher levels of $CD8^+$ single positive ells than uninfected controls (HIV^+ 46%; HIV^- 22.5%) [27]. In $CD4^+$ depletion and immune activation one study found that thymuses of HIV infected individuals were characterized by a relative depletion of $CD4^+$ single positive T cells and a corresponding enrichment of $CD8^+$ single positive T cells. The analysis also revealed a decreased expression of interleukin-7 receptor in early thymocytes from HIV-infected individuals [27]. Frequency of regulatory T cells ($CD25^+FoxP3^+$) was significantly increased in HIV-infected thymuses, particularly in priory-committed $CD4^+$ single positive cells [27]. However, Subjects in the long term survivors with no evidence of

immune suppression (LTS-NS) group had significantly higher frequencies of naive ($CCR7^+CD45RA^+$) and central memory ($CCR7^+CD45RA^-$) $CD4^+$ T cells compared to with severe immune suppression (LTS-SS) subjects (p = 0.0005 and, 0.0001, respectively). It is also observed that a highly significant increase in the frequency of naive $CD8^+$ T cells (T NAIVE) in the LTS-NS subjects (p = 0.0066), compared to the LTS-SS subjects and differentiation profiles of Gag-specific $CD8^+$ T cells were similar between the progression groups [70].

Depletion of $CD4^+$ T cells from the gut occurs rapidly during acute HIV-1 infection. Therefore there is the association between this defect in gut homing and any weakness in the gut mucosal barrier, microbial translocation, and increased T cell activation in HIV-infected individuals [17]. HIV-1 infection is associated with a significant increase in mucosal but not peripheral ϒδ T-cell populations. HIV-1 infection was associated with a significant increase in the percentage of mucosal T cells that express the ϒδ TCR (23.3% + 15.6% for HIV-1-seropositive subjects versus 13.2% +5.2% for HIV-1-seronegative subjects; P= 0.03) [62]. Polyclonally activated Vδ1 cells from HIV-infected donors were also cytotoxic for normal $CD4^+$ T cells. The Vδ1 subset is often expanded in HIV-infected individuals, which inverts the Vδ2:Vδ1 cell ratio, possibly due to microbial products that accumulate in blood when mucosal boundaries fail and allow microbial translocation [71]. In the study of T-reg cells groups, older HIV^+ subjects had a total T-reg percent that is 2.8% (p=0.02) higher than among younger HIV^+, older HIV^- and younger HIV^- subjects. In HIV^+ subjects, the total T-reg percentage is inversely correlated with the lymphocyte proliferative responses to tetanus (r=−0.45, p=0.002) and Candida (r=−0.43, p=0.003) antigens [72]. But one study done on naive T-cell dynamics in HIV-1 Infection showed that both naive $CD4^+$ and naive $CD8^+$ T cells are depleted in individuals with HIV-1 infection by unknown mechanisms. At baseline, naive $CD4^+$T-cell numbers were lower than naive $CD8^+$ T-cell numbers; after HAART, a greater increase in naive $CD4^+$T cells than naive $CD8^+$T cells was observed [73].

5. T-Cells After Highly Active Antiretroviral Therapy (HAART)

5.1. Naïve and Effectors T- Cells Changes

Antigen KI-67 is a nuclear protein that is associated with and may be necessary for cellular proliferation [74]. More than 10-fold increase in the percentage of dividing naive $CD4^+$ T cells in the blood was found when the number of these cells was below 100 per ml. In the $CD8^+$ T-cell compartment, the number of dividing cells was elevated 20- to 25-fold. This increase was most notable in the $CD27^+$ CD 45RO^+ and $CD27^-$ $CD45RO^+$ memory $CD8^+$T-cell pool, corresponding with the degree of expansion of these subsets [75].

The study on Naïve T cells dynamics, analyzed the relationship between T-cell turnover, thymic function, and immune activation in HIV-1-infected patients showed at baseline, naive T-cell numbers were lower in the $CD4^+$pool compared to the $CD8^+$ pool, but no difference between the two groups was observed in the percentages of proliferating naïve T cells or in the number of T-cell receptor excision circle (TRECs) [73]. Even though a dramatic decrease in proliferation was observed for both naive $CD4^+$and $CD8^+$ T cells after the first 6 months of therapy, they found that naive $CD4^+$T-cell numbers significantly increased after initiation of HAART, but naive $CD8^+$ T-cell numbers were only marginally affected [73]. In the case of long lasting recovering of $CD4^+$T cells function studying, immunological response occurred in both the naïve and previously treated groups [30], however, the proportion of immunological responders was higher among naïve than among previously treated patients. Beside this, loss of $CD4^+$ T-cell reactivity recall antigens was shown to be reversible with HAART in severely immunosuppressed or previously treated patients, though the restoration of reactivity was seen in a larger proportion of naïve than of previously treated patients [76]. The $CD4^+$ cell counts significantly increased from baseline only in immunological responders, with a median gain of 65 $CD4^+$ cells/μL at month 1 and a median gain of 102 $CD4^+$ cells/μl at month 12. By contrast, non-responders had only a slight increase in $CD4^+$ cell count above baseline at any particular time. The memory ($CD4^+$, $CD45RA^-$) T-cell subset showed a significant expansion in immunological responders only, with a rapid increase at month 1 (gain 55/μL, p<0·01) and a plateau until month 12 [30]. But the study done in Rural Burkina Faso, greater improvement of $CD4^+$T cells count observed; median $CD4^+$ T-cell counts increased from 174 (10^{th}-90^{th} percentile: 33-314) cells/ μL at baseline to 300 (114-505) cells/ μL after 3 months and 360 (169-562) cells/ μL after 12 months of HAART [77]. Early $CD4^+$ T-cell recovery was accompanied by a reduction of the expression levels of $CD95^+$ and $CD38^+$ on T-cells and immunological response occurred in both the naïve and previously treated groups. However, the proportion of immunological responders was higher among naïve than previously treated patients (6 of 7 *vs.* 4 of 13; p<0·05) [30].

T cell responses to HAART, the result also shows HAART-induced changes in the peripheral distribution of naïve ($CD45RA^+$ $CD62L^+$) and memory $CD45RA^-$ $CD62L^+$) cells, $CCR5^-$ $CXCR4^-$ and $CD95^-$ expressing T cells [4]. HAART induced suppression of viremia and associated with an increase in $CD4^+$ T cell proliferative responses [78]. The analysis of cytokine production after 12 months of HAART showed an increased number of interleukin (IL-2), but not IL-4 and (IFN)-γ producing T cells and a decreased percentage of $CD8^+$ IFN γ^+ cells. The analysis of IFN γ producing T cells, the frequency of $CD4^+$ and $CD8^+$ INF γ producing T cells before and after HAART, a significant decrease in the percentage of $CD4^+$ IFN γ expressing T cells was observed in HIV infected patients as compared to controls after taking HAART. As opposite, within the $CD8^+$ subset, the peripheral distribution of INF γ expressing cells was comparable to control [3,4]. The percentage of IL-2

expressing $CD4^+$ and $CD8^+$T cells was similar in HIV infected patients after taking HAART and in controls [4] and supported by other study as HAART was associated with cytokine profiles that more closely resembled to those of HIV-uninfected women [79].

5.2. Helper ($CD4^+$) T Cell

Treatment with highly active antiretroviral therapy (HAART), Combining HIV protease inhibitors (PI) and reverse transcriptase inhibitors (RTI) [30], can suppress HIV replication both in the circulation and in lymphoid tissues and improve $CD4^+$T cells count and function [80,81]. Current treatment for HIV/AIDS is a combination therapy, using regimens designated on combination antiretroviral therapy (ART), or highly active antiretroviral therapy (HAART), is the cornerstone of management of patients with HIV infection. In most cases, this combines the use of two nucleoside analogs and one protease inhibitor [82].

The combination strategy appears to overcome the ability of the virus to rapidly produce mutants that are drug resistant [83]. In many cases, HAART has lowered viral load to levels that are not detectable by current methods and has improved the health of AIDS patients to the point that they can again function at a normal level [84]. The success of HAART in treating AIDS has opened discussion of whether it might be possible to eradicate all viruses from an infected individual and thus actually cure AIDS. Most AIDS experts are not convinced that this is possible, mainly because of the persistence of latently infected $CD4^+$ T cells and macrophages, which can serve as a reservoir of infectious virus if the provirus should be activated [84,85]. Even with a viral load beneath the level of detection by PCR assays, the immune system may not recover sufficiently to clear virus. In addition, virus may persist in sites such as the brain, not readily penetrated by the drugs, even though the virus in circulation. The use of immune modulators, such as recombinant IL-2, in conjunction with HAART is being examined as a strategy to help reconstitute the immune system and restore normal immune function [32,70,82,86].

Among HAART treated and untreated patients, durable control of HIV replication is associated with high levels of HIV-specific IL-2^+ and IFN-γ^+ $CD4^+$ T cells, low levels of T-cell activation, and preservation of an expanded population of HIV-specific T cells with a less differentiated immunophenotype. This suggests that control of HIV in the setting of chronic disease may require durable maintenance of HIV-specific memory T cells and the absence of generalized immune activation [39]. In the study conducted in Switzerland, on emergence of poly functional $CD8^+$T cells after prolonged suppression of HIV replication by HAART, the result shows after the initiation of drug, $CD4^+$ T-cell counts increased from a median of 185 cells/µl at week 0 to 315 cells/ µl at week 24 and to 508 cells/ µl at the late time point in the study group [1]. In the control group, $CD4^+$ T-cell counts decreased from 336 cells/ µl at week 0 to 275 cells/ µl at week 24 and reached a nadir of 208 cells/ µl at the later time points. One study done in china indicates that central memory $CD4^+$ cells are as an early indicator of immune reconstitution in HIV/AIDS patients with anti-retroviral treatment (ART). The number of central memory cells among the $CD4^+$ T cells and the of activation of $CD8^+$ T cells is believed to be a better indicator of immune restoration in patients on antiretroviral therapy (ART) than the absolute numbers of $CD4^+$ and $CD8^+$ T cells alone [42]. In the same study done on France, HAART can induce sustained recovery of $CD4^+$ T-cell reactivity against opportunistic pathogens in severely immunosuppressed patients. This recovery depends not on baseline values but on the amplitude and duration of viral-load reduction and the increase of memory $CD4^+$ T cells [30]. Compared to the baseline, $CD4^+$ T cells and CD4 CM numbers increased significantly after HAART. On the other hand, the CD4 EM cells and CD4 naïve cells did not undergo a significant change in number after HAART [42] but for nearly 30 years, $CD4^+$ cell counts have been used as the primary indicator for HIV-1 disease progression, and are instrumental in determining start of antiretroviral therapy or vaccine development [51]. Poly functional $CD4^+$ T-cell populations accounted for more than 50% of the total response in both cohorts (61% in LTTS and 64% in LTNPs; P= 0.39). In particular, the mean percentage of the 'triple positive' population, i.e. the cells producing simultaneously IFN-γ, IL-2 and TNF-α, was 30% (range 11%–49%) and 33% (range 3%-69%) in LTTS and LTNPs, respectively (P =0.32). Therefore, They able to demonstrate robust and poly functional HIV-1-Gag-specific CD4+T-cell responses of similar intensity and functional profile in both cohorts [56]. In conclusion restoration of CD4+ T lymphocyte responsiveness to recall antigen is achieved during HAART [87].

5.3. Cytotoxic ($CD8^+$) T Cell

The other T cell sub population profile is the cytotoxic activity [88]. *Env-specific CTLs are positively correlated with $CD8^+$ cell counts* [89*] however, as t*he frequencies of HIV Gag-Pol- specific CTLp were estimated by limiting dilution assay before and during HAART in 7 patients randomly selected among the 20 HIV-1 infected individuals, their result showed no meaningful correlations were observed between the number of CTLp, viral load, $CD4^+$ and $CD8^+$ counts [4]. The study done in Thailand, on alteration of $CD8^+$ T cell effector diversity during HIV-1 Infection with discordant normalization in effective antiretroviral therapy, the mean percentage of triple positives (perforin, granzyme A, granzyme B expressing cells) and double positives (only granzyme A and B co expressed cells) in untreated HIV infected patients was higher than healthy individuals ($P < 0.0001$ and $P < 0.0001$, respectively) whereas the mean percentage of single positive (only granzyme A expression) cells and triple negative cells in untreated HIV infected patients were lower than healthy individuals (P= 0.0024 and $P < 0.0001$, respectively). When the frequency of total granzyme A positive cells and total granzyme B positive cells were determined, untreated HIV infected patients showed a higher percentage of both populations than those from the healthy individuals($P<0.0001$) [49] (table1).

Table 1. *Comparison of HAART-Induced Changes on Immunological Parameters in HIV-1 Patients at Baseline and After 3, 6, 9 and 12 Months of Therapy and HIV-1 Negative Healthy Adult Control Subjects from Nouna. Median Values are shown with the 10th - 90th Percentile in Parentheses. ND= Not Determined, NA= Not Applicable.*

Parameter	At base line (A)	At 3 Months (B)	At 6 Months (C)	At 9 Months (D)	At 12 Months (E)	Control (F)
$CD4^+$T-Cells/µl						
N=	61	56	55	51	48	26
CD4 count	174(33-314)	300(114-505)	353(128-500)	330(150-541)	360(169-562)	ND
Naive $CD4^+$ T-cells						
N=	50	42	38	22	36	26
Activated $CD4^+$T-cells						
N=	53	49	41	45	36	26
% of $CD95^+$T-cells	97(85-100)	95(89-99)	95 (89-99)	87 (73-98)	88 (72-98)	91 (77-98)
%$CD38^+$T cells	91(81-96)	83(71-92)	78 (73-93)	75 (66-84)	76(67-86)	59(34-96)
$CD8^+$T-Cells/µl						
N=	61	56	55	51	48	26
Naïve $CD8^+$T-cells						
N=	61	56	55	47	43	26
Activated CD8+T-cells						
N=	53	49	41	45	36	26
%$CD38^+CD8^+$Tcells	98(90-99)	92(81-99)	88(71-94)	85(65-95)	85(63-95)	83(63-95)
HIV-1plasma viral load						
Log_{10} copies per ml	5.8(4.6-6.6)	2.1(1.6-2.8)	1.6(1.6-2.4)	1.6(1.6-2.1)	1.6(1.6-2.3)	NA

Source:- Tiba F, Nauwelaers F, Traoré S, et al. Immune Reconstitution During the First Year of Antiretroviral Therapy of HIV-1-Infected Adults in Rural Burkina Faso. Open AIDS J. 2012 Feb 24; 6:16–25.

In the study conducted in Switzerland, the result shows after the initiation of drug, the percentages of $CD8^+$ T cells in the study and control groups were stable (approximately 44% of lymphocytes) over the period of analysis [1]. And their dynamics of cytokine secretion by $CD8^+$ T cells after onset of the drug indicate that after antigenic stimulation, a median of 35.8% of $CD107a^+$ $CD8^+$ T cells secreted IFN-ϒ in HIV-infected patients at week 0, followed by TNF-α (median, 12.1%) and finally IL-2 (median, 8.3%). In healthy donors, however, these frequencies were of equal magnitude (IL-2, 28.7%; IFN-ϒ, 27.1%; and TNF-α, 22.4%). After initiation of HAART, a significant recovery of cytokine (IL-2 and TNF-α) secretion capacity within degranulating $CD8^+$ T cells was observed, while IFN-ϒ secretion capacity remained constant. $CD8^+$ T cells from viremic study group patients predominantly secreted IFN-ϒ (median, 5.8%) before initiation of the treatment (week 0), followed by TNF-α (median, 2.2%) and finally IL-2 (median, 1.4%), which is concordant with previous findings. On the contrary healthy donors exhibited similar frequencies of $CD8^+$T cells that were able to secrete IL-2 (median, 4.2%), TNF-α (median, 4.1%), and IFN-ϒ (median, 3.3%). Upon initiation of HAART, the frequencies of IL-2- and TNF-α-secreting $CD8^+$ T cells increased continuously, leading to a statistically significant increase for the latest time point of analysis compared to baseline [1].

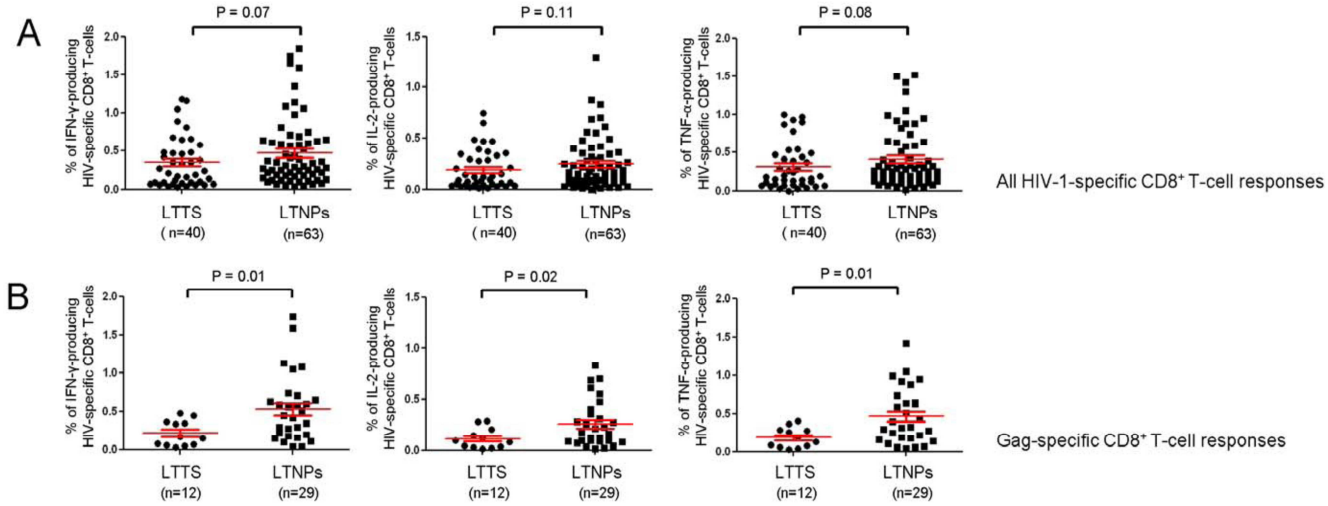

Figure 4. *Comparison of the magnitude of HIV-1-specific CD8+ T-cell responses between LTTS and LTNPs. Cumulative data (mean+/-SE) of the percentage of IFN-γ-, IL-2- and TNF-α-producing HIV-1 specific CD8+ T-cells following 6 hours of in vitro stimulation with optimal CD8+ T-cell HIV-1 peptides (A) or with optimal CD8+ T-cell Gag-derived peptides (B) LTTS: long-term treated HIV-1 seroconverters; LTNPs: HIV-1 long-term nonprogressors. Source:-Cellerai C, et al. Early and Prolonged Antiretroviral Therapy Is Associated with an HIV-1-Specific T-Cell Profile Comparable to That of Long-Term Non-Progressors.*

Therefore they assessed the simultaneous ability of $CD8^+$T cells to execute four different effectors functions: degranulation, IFN-ϒ, TNF-α, and IL-2 secretion. Prolonged suppression of pVL by HAART allows for the development of poly functional $CD8^+$ T cells as assessed after HIV-specific antigen stimulation. In particular, prolonged HAART was associated with the appearance of $CD8^+$T cells exhibiting three or four simultaneous functions increased clonal turnover, and superior functional avidity [90]. In one study, comparison of early and prolonged antiretroviral therapy association with T-cell profile between long terms treated HIV-1 seroconvert (LTTS) and to that of long-term non-progressors (LTNs), the expression of CD38 on HIV-1specific $CD8^+$ T-cells has been shown to be low in LTNP cohorts and similar to that found in successfully treated patients. However, comparative data between LTTS and LTNPs for $CD8^+/CD38^+$ T-cells are not available and this marker could be an indicator of the extent of immune reconstitution which is taking place with prolonged HAART initiated at seroconversion [56] (Fig4).

5.4. T-regulatory Cell Frequency in HIV Infection After HAART Therapy

T-regs are characterized by the expression of the forkhead transcription factor ($FoxP^3$) (91), which is critical to their regulatory function [92]. FoxP3 is a transcriptional repressor of nuclear factor of activated T-cells (NFAT) and nuclear factor-kappa B (NFκB), which leads to the suppression of interleukin (IL)-2 secretions [93]. Deficiency in T-reg number or function is associated with autoimmune disease, while increased T-reg frequency is seen in certain cancers and chronic infections [94]. Frequency of regulatory T cells ($CD25^+FoxP3^+$) was increased in HIV-infection and with aging[63], particularly in priory-committed $CD4^+$ single positive cells. On the other hand data suggest that HIV infection is associated with a complex set of changes in the immunophenotype of thymocytes, including a reduction of intrathymic $CD4^+$ T cell precursors, increased expression of activation markers, changes in the expression pattern of IL-7R and enrichment of T regulatory cells generation [27,95]. Studies showed that thymocytes obtained from HIV-infected and uninfected controls, expression of CD25 and $FoxP^3$ on $CD4^+$ SP cells was significantly increased in thymuses of HIV-infected individuals compared to uninfected controls (HIV^+ 4.3%, HIV^- 1.3%, p = 0.05), while the expression of CD25 and $FoxP^3$ on $CD4^+CD8^+$ DP cells was comparable (HIV^+ 0.22%, HIV^- 0.19%). Those data demonstrate that HIV induces an increase in T-reg frequency, particularly in committed $CD4^+$ single positive cells [96,97]. Whereas, the study conducted in Uganda show, T-reg number is strongly correlated with both $CD4^+$ and $CD8^+$ T cell activation. And in the multivariate modeling, this relationship between T-reg depletion and $CD4^+$ T cell activation was stronger than any other clinical factor examined [98]. Other study demonstrate that the continuous loss of Th17 cells was accompanied by a concomitant rise in the frequency of T-reg cells, resulting in a loss of Th17/T(reg) balance during the progressive HIV infection. Meanwhile, the T-reg levels, Th17 levels and Th17/T-reg ratios of the elite controller group were comparable to those of the HIV-1 negative controls in the follow-up study [99]. Possibly, this is a result of enhanced Treg survival and function caused by direct infection [27] (Fig. 5)

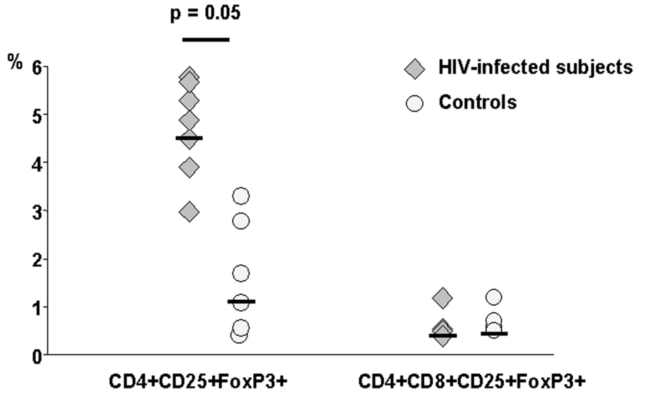

Figure 5. *Expression of CD25 and FoxP3 on $CD4^+$ SP and $CD3^+$DP thymocytes in HIV-infected (grey triangles) and uninfected controls (white circles). The expression of CD25 and FoxP3 on $CD4^+$ SP cells was significantly increased in thymuses of HIV-infected individuals compared to uninfected controls (HIV^+ 4.3%, HIV^- 1.3%, p = 0.05), whereas the expression of CD25 and FoxP3 on $CD4^+CD8^+$ DP cells was comparable in the two groups of subjects (HIV^+ 0.22%, HIV^- 0.19%). Source: - Alessandra Bandera et al. $CD4^+$ T cell Depletion, Immune Activation and Increased Production of Regulatory T Cells in the Thymus of HIV-Infected Individuals.*

Damage of the immune system by HIV infection is more pronounced in association with older age and indicated a positive association between age and the plasma HIV-1-RNA copy number at the time of identification of HIV-1 serostatus among recently diagnosed older HIV-1- positive individuals [100]. Naive and total $CD4^+$ T-cell regeneration in response to highly active antiretroviral therapy (HAART) is less robust in older compared to younger HIV infected (HIV^+) patients, and older age at HAART initiation is associated with a higher risk of HIV disease progression or death despite HAART [72]. The proportion of T-regs also correlated positively with HIV-1 plasma viraemia, but correlated inversely with $CD4^+$ cells, thus suggesting a selective expansion along with increased viraemia and $CD4^+$ depletion. Interestingly, a positive correlation was found between the levels of T-regs and $CD8^+CD38^+$ T cells thus T-regs efficiently controlled residual immune activation in patients with viral suppression in ART, but failed to control the hyper activation resulting from viral replication after ART interruption [101].

5.5. ϒδ T - Cell Response in HIV Infection and HAART

HIV^+ patients exhibited a decreased percentage of ϒδT cells expressing Th1 cytokines following stimulation [102]. This dysfunction is primarily within the Vδ2 ϒδ T-cell subset which decreased overall level in the blood and a reduced Th1 cytokine production but significant expansion of Vδ1 cells observed [13]. Infection with human immunodeficiency virus (HIV) disrupts the balance among ϒδT cell subsets, with

increasing Vδ1$^+$ T cells and substantial depletion of circulating Vδ2 T cells [15,103]. Patients treated with HAART exhibited a partial restoration in their ϒδT-cell Th1 cytokine response that was intermediate between the responses of the uninfected and HIV$^+$ patients [14,104]. On the contrary, HIV$^+$ patients on HAART only tended to have a lower ratio of ϒδ intraepithelial lymphocytes (IEL) (median 12.8%) than those receiving no treatment (median 14.3%) [105]. Significant suppression of HIV-1 replication, (plasma level of HIV-1 RNA, fewer than 50 copies/ml) for a mean duration of 16.4 months, the gastrointestinal mucosa and blood of treated HIV-1infected subjects contained a predominance of Vδ1 cells, while Vδ2ϒδ T cells represented a minority [106]. With regard to the percentage of Vδ2-expressing ϒδ T cells in the blood, there was no significant difference between effectively treated (5.1% ± 5.1%) and untreated (5.0% ±4.3%) HIV-1seropositive subjects (P= 0.993) but the blood of subjects in both groups contained a significantly reduced percentage of Vδ2 cells compared with that of HIV-1seronegative subjects (42.2% ± 20.7%; P= 0.001 for each comparison) [107,108]. ϒδ T-cell reactivity was markedly increased after only 3 months of HAART. The immunosuppressive peptide isopentenyl pyrophosphate (IPP), induced cytokine levels were compared before and after 6 months of HAART. IFN-γ production was essentially unchanged in the HIV-asymptomatic group before and after HAART [109]. However, a potentially harmful increase in TNF-α production was observed. HAART has been reported to be associated with a number of side effects in human immunodeficiency virus (HIV) positive persons [110], however, monitoring HIV disease progression, deciding the time to initiate HAART requires evaluation of T-cell population like total CD4+ (TCD4+) [111] and other T- cell subpopulation counts and also HIV/RNA viral load at regular intervals, altogether, their observations suggest that HAART improves not only αβ T-cell function but also ϒδ T-cell reactivity, and demonstrate that ϒδ T-cell activation depends on IL-2 provided by CD45RA helper cells. Interestingly, the HAART induced recovery of naive T cells can extend its effects on ϒδ T-cell responsiveness to non-peptidic microbial antigens. Thus, analysis of ϒδ T cell reactivity may be useful for evaluating changes in immune function during HAART [109].

6. Conclusion

Two major principal categories of T cells based on their functions have been defined: T cells that modulate the activity of B cells and other T cells, and effector cells mediating cellular immune responses (cytotoxic cells). T-cell immune activation is known to play an important role in HIV pathogenesis and is linked to CD4$^+$ T-cell decline and disease progression. Prolonged suppression of pVL by HAART allows for the development of poly functional CD8$^+$ T cells. In particular, prolonged HAART was associated with the appearance of CD8$^+$T cells exhibiting three or four simultaneous functions. Suppression of viral replication by HAART may result in a substantially decreased antigenic stimulus, reduced inflammatory cytokine expression, reduced adhesion molecule expression, and redistribution of lymphocytes from those previously inflamed tissues into the blood. The number of CD4$^+$T cells, CD4 naïve and CD4CM subsets all increased gradually after HAART in a biphasic way, showing a rapid increase before week 4 and a gradual increase after week 4. The increase in the number of CD4$^+$ central memory cells was greater than CD4$^+$ naïve cells, and was most likely the major contributing factor in the overall increase of CD4$^+$ T cells. The HAART induced recovery of naive T cells can extend its effects on γδ T-cell responsiveness to non-peptidic microbial antigens.

Recommendation

HAART induce sustained recovery of CD4$^+$T-cell reactivity against opportunistic pathogens in severely immunosuppressed patients. This recovery depends not on baseline values but on the amplitude and duration of viral-load reduction and the increase of memory CD4$^+$ T cells, so once started the treatment sever immunocompromized patient should continue the treatment for long time. In addition, the number of central memory cells among the CD4$^+$ T cells and activation of CD8$^+$ T cells is believed to be a better indicator of immune restoration in patients on HAART than the absolute numbers of CD4$^+$ & CD8$^+$ T cells alone, leads to phenotypic determination of lymphocytes is necessary to continue prolong time the treatment.

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