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Implications of CD4/CD8 ratios in Human Immunodeficiency Virus infections

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Abstract

Human Immunodeficiency Virus (HIV) is a major Public Health burden to the world despite all efforts to eradicate the menace. HIV infection is characterized by profound CD4 T cell destruction, compromised mucosal barrier function and chronic immune activation. In addition, this infection is associated with a marked activation and expansion of HIV-specific and bystander CD8 T cells. The impairment in CD4 T cell regeneration and the persistent elevation of CD8 T cell counts are considered to be a consequence of viral persistence and multiple inflammatory factors including gut microbial translocation, leading to major T cell dysfunction. The ratio of CD4/CD8 is very important in the improvement of the lives of the HIV positive patients and should be carefully monitored and the balance maintained.

Keywords: CD4, CD8, HIV, CD4/CD8 ratios.

Introduction

Human Immunodeficiency Virus (HIV) is a major Public Health burden to the world despite all efforts to eradicate the menace. HIV infection is characterized by profound CD4 T cell destruction, compromised mucosal barrier function and chronic immune activation. In addition, this infection is associated with a marked activation and expansion of HIV-specific and bystander CD8 T cells (Jakheng and Obeagu, 2022). The impairment in CD4 T cell regeneration and the persistent elevation of CD8 T cell counts are considered to be a consequence of viral persistence and multiple inflammatory factors including gut microbial translocation, leading to major T cell dysfunction(Oloro and Obeagu, 2022; Obeagu and Obeagu, 2022; Igwe *et al.,* 2022). Antiretroviral therapy (ART) in a majority of patients suppresses HIV plasma viral load (VL)

and stops the progression to AIDS, allowing progressive CD4 T cell recovery paired with a persistent elevation of CD8 T cells. Such changes on T cell populations over time result in a partial restoration of the CD4:CD8 ratio. Patients on suppressive ART who present with lower CD4:CD8 ratios have a higher risk for non-AIDS morbidity and mortality even with optimal CD4 T cell recovery (Lu *et al.*, 2015).

Over the last three decades, CD4 count monitoring has guided the clinical management of HIV infection. These cell numbers have been used in the clinic to direct diagnostic workups (Obeagu *et al.,* 2022; Obeagu *et al.,* 2023), to decide prophylaxis for opportunistic infections, and to determine initiation of antiretroviral therapy (ART). However, the usefulness of CD4 monitoring has recently raised a vivid debate. It has been shown that in stable patients who achieve complete virological suppression and immunological recovery under ART, CD4 counts exceptionally drop below clinically meaningful thresholds (Serrano-Villa *et al.,* 2015).

Despite long-term viral suppression and CD4 T-cell recovery on effective antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection is still associated with chronic immune activation and inflammation(Caby *et al.,* 2016).

CD4 helper/inducer cells and CD8 cytotoxic/suppressor cells are 2 phenotypes of T lymphocytes, characterized by distinct surface markers and functions that mostly reside in lymph nodes but also circulate in the blood. The normal CD4/CD8 ratio in healthy hosts is poorly defined. Ratios between 1.5 and 2.5 are generally considered normal; however, a wide heterogeneity exists because sex, age, ethnicity, genetics, exposures, and infections may all impact the ratio. Normal ratios can invert through isolated apoptotic or targeted cell death of circulating CD4 cells, expansion of CD8 cells, or a combination of both phenomena (Obeagu *et al.,* 2023; Obeagu2023*;* Obeagu and Obeagu, 2023). A low or inverted CD4/CD8 ratio is an immune risk phenotype and is associated with altered immune function, immune senescence, and chronic inflammation in both HIV-infected and uninfected populations (McBride and Striker, 2017).

The CD4/CD8 T-cell ratio represents an important indicator of HIV disease severity and response to antiretroviral therapy (ART). People with HIV (PWH) with persistent CD4/CD8 T-cell ratio inversion (defined as a ratio <1.0) exhibit elevated biomarkers of T-cell activation, exhaustion, and immunosenescence. Relatedly, prior work using a bioinformatic framework suggests that CD4/CD8 T-cell ratio is a robust biomarker of T-cell pathogenesis among PWH. Persistent CD4/CD8 T-cell ratio inversion has been implicated in inflammatory mechanisms involved in the development of non–AIDS-related health comorbidities that emerge in the context of otherwise successful ART(Paul *et al.,* 2022).

Human Immunodeficiency Virus (HIV)

HIV is one of the most devastating infectious diseases affecting humankind, with an estimated 36.7 million people living with human immunodeficiency virus (HIV) infection as per 2015 estimates. Although the majority of this infection is caused by HIV-1, a closely related viral strain, HIV-2 that is believed to have spread in parallel with HIV-1 is also an etiological agent of this dreadful infection. The two viruses share striking similarities in genetic and biological properties, such as genome structure and mechanisms for transactivation and CD4+ cell depletion, and yet, HIV-2 exhibits much longer clinical latency periods, significantly lower rates of disease progression and transmission and lower viral load in the asymptomatic phase as compared to HIV-1 infection. The distinct differences in pathogenicity provide a unique opportunity to look for protective viral and host immune mechanisms that contribute to viral control (Vijayan *et al.*, 2017).

Human Immunodeficiency Virus (HIV)and CD4

The hall mark of human immunodeficiency virus (HIV) infection is a gradual loss of CD4+ T-cells and imbalance in CD4+ T-cell homeostasis, with

progressive impairment of immunity that leads ultimately to death (Vijayan *et al.,* 2017).

For decades, the CD4 cell count measurement has been used to understand the progression of the human immunodeficiency virus (HIV) disease. HIV is a fatal infection, characterized by the targeting and destruction of CD4 T lymphocytes in the peripheral blood. CD4 T lymphocytes are a part of the human T-lymphocyte cells that are produced in the bone marrow and eventually mature in the thymus. They circulate the body to fight against bacteria, viruses, and other organisms. If HIV goes untreated, the virus enters the cell and replicates, which eventually causes CD4 cells to die. The remaining infected cells release virions, which infect other cells, leading to the progression of the disease. The loss of CD4 T lymphocytes will result in the inability to have a proper immune response.

CD4 cell count is a laboratory test that measures the number of CD4 T-cells. The normal range is between 500 to 1500 cells/mm^3. Clinicians use this test to monitor the destruction of CD4 cells, and it also monitors the effectiveness of the antiretroviral treatment (ART). For a physician, the CD4 cell count has become the best indicator of disease progression and is used to stage disease and guide medical therapy. Per the Center for Disease Control and Prevention (CDC), one of the indications for the diagnosis of AIDS is when CD4 cell count drops below 200 cells/mm^3. The decline of CD4 T cells can lead to opportunistic infections, and it increases mortality(Garcia & Guzman, 2021).

The primary cellular receptor for the human and simian immunodeficiency viruses HIV-1, HIV-2 and SIV is the CD4 antigen. HIV infection of CD4+ cells is initiated by binding of the virus to the cell surface, via a high-affinity interaction between the first domain of CD4 and the HIV outer envelope glycoprotein, gp120 (Sattentau and Moore, 1993).

Given the fact that HIV infection accelerates both the production and the destruction of CD4+ T-cells, in the early stages of the infection, there is constant replacement of dying CD4+ T-cells with native CD4+ T-cells originating from the thymus. It is reported that during the course of HIV infection, about 1 billion of HIV particles are produced per day, resulting in increasing numbers of infected CD4+ T-cells. Subsequently, infection spreads to the memory cells in the thymus and the virus starts to replicate there. Each time a memory CD4+ T-cell is infected by HIV, it is destined to undergo the process of elimination, thus contributing to the progressive decline in CD4+ T-cell numbers(Vijayan *et al.*, 2017).

Human Immunodeficiency Virus and CD8

HIV infection has conflicting effects on circulating CD8 T cells during its natural course. HIV normally causes circulating CD8 cells to increase in response to infection, which results in a low CD4/CD8 ratio before HIV decreases CD4 cells. Some individuals who are on ART will have their CD4 counts increase while their CD8 counts decrease, causing the ratio to normalize. For some people, however, the high numbers of circulating CD8 cells are maintained, and their ratios do not increase despite the virus being suppressed and CD4 levels rising(Appay and Sauce, 2008).

Few studies have focused on the prognostic relevance of CD8 numbers, even though CD4 counts are an important predictor of opportunistic infections and non-AIDS outcomes(Sanchez-Martinez et al., 2019). When CD4 numbers decrease with untreated HIV infection, CD8 counts rise. Some people who achieve CD4 counts over 500 cells/mm3 during ART-mediated viral suppression also suffer a concurrent fall in CD8 counts, which normalizes the CD4/CD8 ratio(Sanchez-Martinez et al., 2019). Others, however, continue to have large quantities of CD8+ T cells in the blood and, as a result, a continuously low CD4/CD8 ratio(Sanchez-Martinez *et al.*, 2019).

(McBride and Striker, 2017) said an infection with the human immunodeficiency virus (HIV) results in significant changes to the adaptive immune system, including the loss of CD4 T cells and the growth of HIV-specific and nonspecific CD8 T cells. These changes indicate a CD4/CD8 ratio inversion that endures even after years of

effective antiretroviral therapy, especially if treatment is started later than recommended(McBride and Striker, 2017).

Modern antiretroviral treatment (ART) should be able to permanently stop HIV replication in people with HIV infection, according to current expectations(Sauter *et al.,* 2016). Those who are on ART have a greater risk of morbidity and death, even though treatment-mediated increases in the peripheral CD4 count are linked to lower rates of morbidity and mortality when compared to age-matched people who are HIV-negative(Serrano-Villar and Deeks, 2015). The on-therapy CD4 count helps forecast this risk, however, reaching a seemingly normal CD4 count may not completely improve health(Serrano-Villar and Deeks, 2015). Similarly, it has been demonstrated that even among treated patients with CD4+ T cell counts above 500 cells/mm3, a further increase in CD4+ T cell count is still correlated with a slender reduction in mortality risk(Serrano-Villar *et al.,* 2014).

A vital part of the cellular immune response and a key player in the management of viral infection are CD8+ T-cells(Sanchez-Martinez *et al.,* 2019). When HIV infection is present, CD8+ T-cells may identify infected cells thanks to an MHC-I-dependent mechanism and can lyse infected cells by secreting perforin and granzymes(Serrano-Villar et al., 2014). By the interaction of death-inducing ligands released by CD8+ T-cells with death receptors on the surface of the infected cell, these cytotoxic T-lymphocytes (CTL) can also kill virally infected cells(Sanchez-Martinez et al., 2019). Furthermore, beta-chemokines and the CD8+ antiviral factor (CAF), which inhibit viral binding and transcription, are secreted by CD8+ CTL(Sanchez-Martinez *et al.,* 2019).

For HIV to withstand the stresses exerted upon it by the immune system, the virus has devised many ways to dodge the CD8+ T-cell response(Rosado-Sánchez *et al.,* 2017). HIV has a high mutation rate, which enables it to suppress infected cells' surface MHC-I expression and avoid being recognized by CD8+ T cells(Serrano-Villar & Deeks, 2015). Additionally, by modifying the pattern of cytokine synthesis and interaction of cellular receptors, HIV affects normal CD8+ T-cell signaling. These cells enter an anergic state as a result of the inappropriate T-cell receptor (TcR) activation that results(Petrovas *et al.,* 2004).HIV is capable of reducing the amount of circulating effector and memory CD8+ T cells that can fight viral infection by interfering with the function of CD4+ T-cells and antigen-presenting cells that are necessary for appropriate CD8+ T-cell maturation. The dysfunction of CD8+ T-cells is ultimately aberrated(Domínguez-Domínguez *et al.,* 2022).

Ratio of CD4/CD8 in Human Immunodeficiency Virus Patients

T lymphocytes may be classified into 2 phenotypes: CD4 helper/inducer cells and CD8 cytotoxic/suppressor cells(Domínguez-Domínguez et al., 2022). Both cell types are mostly found in lymph nodes but can also be found in the blood and are distinguished by different surface markers and functions(Domínguez-Domínguez *et al.,* 2022). In healthy hosts, the ideal CD4/CD8 ratio is not well known. Ratios between 1.5 and 2.5 are often regarded as normal; nevertheless, there is significant variation due to the possibility of the ratio being impacted by sex, age, ethnicity, genetics, exposures, and illnesses(Sauter et al., 2016). Normal ratios can flip as a result of CD4 cell proliferation, targeted or isolated apoptosis, or a combination of these two processes(Sauter et al., 2016). In both HIV-infected and HIV-uninfected populations, a low or inverted CD4/CD8 ratio is a phenotype that raises immunological risk because it is linked to immune dysfunction, immune senescence, and chronic inflammation(Rosado-Sánchez *et al.*, 2017).

With age, the likelihood of having an inverted CD4/CD8 ratio rises(Wikby *et al.,* 2008).In comparison to males, women are less likely to have an inverted ratio across all age groups(McBride and Striker, 2017). It is hypothesized that the variations in populations are caused by thymus atrophy brought on by aging

and hormones. Low plasma estradiol levels, high circulating CD8, and low CD4/CD8 ratios in women with premature ovarian failure are correlated with hormonal effects on the ratio, according to research(McBride & Striker, 2017). Better ratio recovery in HIV therapy is linked to the persistence of the thymus(Rosado-Sánchez *et al.,* 2017).

Measuring the ratio may be a suitable substitute for measuring the HIV reservoir and manipulating it might be a possible target for further HIV treatment strategies(Hadrup *et al.,* 2006). Learning more about the effects of different ART regimens and the concurrent management of coinfections is necessary(Hadrup et al., 2006). However, no systematic reports are made about the effect of immunotherapy on the ratio even though the use of immunotherapy as a treatment for oncologic illnesses is growing(Sanchez-Martinez *et al.,* 2019). While investigating HIV and other chronic illnesses, researchers utilizing human and nonhuman animal models should think about employing the CD4/CD8 ratio as a marker that can be translated into therapeutic practice(Domínguez-Domínguez *et al.,* 2022).

Implications of the ratio of CD4/CD8 in Human Immunodeficiency Virus patients

The CD4/CD8 ratio is improved by early, efficient, and ongoing ART. Early ART has also been found to decrease the HIV reservoir's growth(Sauter *et al.,* 2016). Consequently, it is a notion that merits further research to utilize the CD4/CD8 ratio as a peripheral surrogate of the HIV reservoir. Integral levels of HIV-DNA in peripheral blood cells have been associated by researchers with the CD4/CD8 ratio(Sauter *et al.,* 2016).

Similar to this, it has been shown that the frequency of CD4 T lymphocytes harboring HIV-proviral DNA is inversely correlated with the CD4/CD8 ratio(Serrano-Villar and Deeks, 2015). In addition, despite detectable HIV-RNA reduction, lower ratios during ART are also linked to chronically greater HIV-DNA. Although increasing the ratio over 1.0 is probably a necessary condition or co-occurring phenomenon with reservoir reduction, a high ratio alone is probably insufficient to eliminate the reservoir, especially in older patients who started their therapy later(Domínguez-Domínguez *et al.,* 2022). Therapies designed to shrink the viral reservoir may utilize the ratio to gauge their effectiveness if a stronger association between ratio and reservoir can be demonstrated(Domínguez-Domínguez *et al.,* 2022).

According to previous research, elevated CD8+ T cell counts have been connected to several disorders in PWH, such as myocardial infarction, restenosis after coronary stenting, malignancy, and non-AIDS mortality(Rosado-Sánchez *et al.,* 2017).Poor vaccine response, bacterial infections, myocardial infarctions, cancer cases, frailty instances, non-AIDS fatalities, and cancer cases are only a few of the clinical outcomes that have been associated with the CD4/CD8 ratio(Rosado-Sánchez *et al.,* 2017).

HIV-related diseases have generally been the final manifestation of the disease(Domínguez-Domínguez *et al.,* 2022). Antiretroviral therapy use has been effectively monitored using CD4+ T-cell counts to stave off AIDS. Contrarily, the CD4/CD8 ratio, and CD8+ T cell counts have gained more recognition as new markers in recent years due to their associations with putative mechanisms thought to be in charge of the emergence of AIDS and non-AIDS-related comorbidities, including cumulative toxicities of antiretroviral drugs, immunosenescence, CMV serostatus, HCV coinfection, bacterial translocation chronic inflammation, as well as indicators of HIV persistence(Domínguez-Domínguez *et al.,* 2022; Sanchez-Martinez *et al.,* 2019).

Regardless of the patient's status as a late presenter, a low CD4/CD8 ratio over time is linked to a higher risk of morbidity and death in PLWH(McBride and Striker, 2017). These preliminary results confirm the prognostic value of variation in CD4/CD8 ratio over time in this extremely vulnerable subpopulation and can help identify the subgroup of service users who may

require closer monitoring to prevent comorbidities, thereby optimizing follow-up and resource use in the healthcare system(McBride and Striker, 2017; Serrano-Villar and Deeks, 2015).

Conclusion

The impairment in CD4 T cell regeneration and the persistent elevation of CD8 T cell counts are considered to be a consequence of viral persistence and multiple inflammatory factors including gut microbial translocation, leading to major T cell dysfunction. The ratio of CD4/CD8 is very important in the improvement of the lives of the HIV positive patients and should be carefully monitored and the balance maintained.

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