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AIDS Rev. 2017;19:81-8

The Revival of an "Old" Marker: CD4/CD8 Ratio

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Abstract

The effectiveness of modern antiretroviral therapies transformed HIV infection into a chronic disease characterized by a persistent condition of inflammation and immune activation. For this reason, even though AIDS-related mortality has been reduced with an increased life expectancy, patients living with HIV infection are more likely to develop non-AIDS events despite the achievement of complete suppression of HIV replication. Hence, the scientific community feels the need to find new biomarkers, which would be suitable in clinical practice for identifying patients who require close monitoring because of an increased risk of developing comorbidities. A renewed interest has emerged about the usefulness of the CD4/CD8 ratio as a marker of immune activation and immune senescence. Recently, many studies have underlined that the CD4/CD8 ratio might represent a good predictor of AIDS and non-AIDS events. Herein, the potential role of the CD4/CD8 ratio for monitoring of HIV patients in different clinical settings is reviewed.

(AIDS Rev. 2017;19:81-8)

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Key words

CD4/CD8 ratio. AIDS. ART. Chronic inflammation. Immune activation. Immune senescence.

Introduction

Nowadays, antiretroviral therapy (ART) leads to excellent virological results in HIV-infected subjects. In fact, an undetectable HIV viral load is reached in the majority of treated patients. ART has also markedly reduced AIDS-related mortality, improving health and life expectancy. However, while on the one hand, the progression to AIDS has been dramatically reduced as a result of efficient ART, on the other hand HIV disease has changed its face, becoming a chronic infection that is characterized by persistent inflammation, immune activation, and immune senescence[1,2].

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Moreover, the incidence of non-AIDS events (including malignancies, end-stage renal disease, liver failure, pancreatitis, cardiovascular disease, and diabetes) is significantly increased in the HIV population, despite effective ART, compared to uninfected individuals[3]. For this reason, the scientific community currently feels the need to find new markers that might be useful in clinical practice for identifying patients who require close monitoring because of an increased risk of developing non-AIDS related diseases. The HIV viral load and CD4 cell count are still the most used markers to monitor HIV-positive patients. However, the CD4/CD8 ratio is increasingly becoming a valuable marker of immune activation and immune senescence and is considered an accurate predictor of non-AIDS events[4-6]. Nonetheless, the CD4/CD8 ratio is also considered a surrogate marker of immune senescence in the general population. In fact, a CD4/CD8 ratio < 1.0 is not only a peculiar hallmark of HIV infection, but is also found in the elderly and in about 5% of the healthy population[7]. In addition, in the OCTO Immune Longitudinal Study

including Swedish octogenarians and nonagenarians, an inverted CD4/CD8 ratio was associated with short-term mortality[8].

Furthermore, it is still debated which is the better cut-off of CD4/CD8 ratio that can be considered as altered and possibly associated with the occurrence of diseases [5,6].

Based on this renewed scientific interest, this review aims to analyze the different settings in which the CD4/CD8 ratio could be taken into account by HIV physicians.

CD4/CD8 ratio and the natural history of HIV infection

The natural history of HIV infection is characterized by a progressive depletion of CD4 lymphocytes, an increase of CD8 cells, and a concomitant inversion of the CD4/CD8 ratio. Low CD4/CD8 ratios are observed earlier after HIV infection, particularly in patients with prolonged symptoms of acute infection[9], and generally within less than one year after seroconversion[10]. Time from HIV seroconversion to the CD4/CD8 ratio inversion has shown to independently predict the time to AIDS occurrence[11]. In fact, the depletion of CD4 cells and the persistent expansion of CD8 cells, in particular memory CD8 cells, is responsible for immune dysregulation, resulting in high rates of overall morbidity and mortality. Therefore, the CD4/CD8 ratio is an overall prognostic marker of HIV disease progression, as reported by several authors since the beginning of the AIDS epidemics[10,11].

CD4/CD8 ratio and response to antiretroviral therapy

Currently, CD4+ T-cell recovery over time is a goal achieved by the majority of patients on ART. However, in some patients a rise of CD4 T-cell count is not obtained despite full plasma viral load suppression. A partial immune reconstitution may depend on several factors, including previous treatment failure or interruptions, duration of ART, low CD4+ T-cell count at the time of ART initiation, advanced stage of disease, and low adherence to ART[12]. It is documented that early initiation of ART may contribute to immune reconstitution and to a reduction of immune dysfunction with lower onset of serious clinical events[13]. Nevertheless, the CD4/CD8 ratio normalization occurs rarely in HIV-infected people even after several years of effective ART[6,14]. In a large Canadian observational cohort of 4,206 HIV-positive treatment-naive patients initiating ART, only 7.2% of subjects achieved a normal CD4/CD8 ratio within a median of three years after the initiation of modern ART[14].

This observation is in agreement with Mussini, et al. who showed, in a cohort of 3,236 HIV patients initiating ART with a median CD4/CD8 ratio of 0.39, that about 12% of patients reached a normalized ratio in a similar (two-year) time period[6]. The probability of achieving a normalized CD4/CD8 ratio was only 4.4% by one year from baseline, 11.5% by two years, and 29.4% by five years. High pre-ART CD4 cell counts and CD4/CD8 ratio at baseline and a negative cytomegalovirus (CMV) serology were associated with a normalized ratio. However, it is currently expected that HIV-infected individuals might achieve higher rates of CD4/CD8 ratio normalization because of early ART initiation, regardless of CD4 count, compared with old cohorts of patients initiating ART at CD4 counts < 250 cells/mm^3 as in the previously cited Canadian cohort[14].

Our group assessed the prevalence of an inverted CD4/CD8 ratio in a group of 112 patients with very long-term follow-up (more than 15 years) for HIV infection and extended ART treatment (median duration 16 years)[15]. The proportion of patients who normalized the CD4/CD8 ratio over time was 37%, even though most patients (> 80%) had a recovery of their CD4 count (> 350). Similarly to previous observations[16] and also in our experience, a progressive increase of the CD4/CD8 ratio could be observed even after several years of ART without reaching a plateau. Older age, low nadir CD4, and detectable HIV viral load were associated with an inverted CD4/CD8 ratio[15].

This is consistent with the study of Leung, et al. where the failure to normalize the CD4/CD8 ratio over time in patients initiating ART was not associated with a higher risk of AIDS-defining illness or death[14]. On the contrary, older age, baseline CD4+ T-cell count < 200 cells/mm^3, higher pretreatment CD8 T-cells, and time-updated HIV-RNA suppression demonstrated to be associated with AIDS-defining illness/death[14]. Based on these data, Leung, et al. suggested that the CD4/CD8 ratio did not seem to show any additional short-term predictive value as a prognostic marker for improved health outcomes with respect to developing AIDS-defining illness.

More recently, by evaluating a large cohort of patients with long-term viral suppression, Caby, et al. reported that factors associated with a persistent CD4/CD8 ratio < 1 were: lower nadir CD4+, chronic CMV infection, a long history of ART (initiation before 1997), and a shorter time of viral suppression[17].

All the evidence suggests that most of successfully treated HIV-positive patients continue to have immunological impairment, probably because of persistent immune activation[1]. Whether the type of ART may influence the CD4/CD8 ratio evolution is still under investigation[18-20]. The impact of ART regimens on the CD4/CD8 ratio normalization was investigated in an observational cohort of 567 treatment-naive patients who initiated ART with a CD4/CD8 ratio < 1[19]. In agreement with previous studies[6,14], only 10.9% of patients achieved a normalized CD4/CD8 ratio in the first year of ART[19]. Nonetheless, in this population, initiating ART with raltegravir-containing regimens was an independent predictor of CD4/CD8 ratio normalization within the first year of treatment, thereby suggesting a potential role of integrase strand transfer inhibitors in reverting the ratio and, consequently, in reducing the immune dysfunction in HIV patients who started ART. This is similar to what was observed by a post hoc analysis of the STARTMRK study, where the authors reported that patients receiving raltegravir showed faster CD4/CD8 ratio normalization compared with those treated with efavirenz[18].

In another recent study, different ART regimens, consisting of two nucleoside/nucleotide analogs plus "a third agent" (a nonnucleoside reverse transcriptase inhibitor [NNRTI], a protease inhibitor [PI], or an integrase strand transfer inhibitor) were compared in a population of 570 patients achieving long-term (at least six month duration) virological suppression[20]. The authors found that NNRTI-based regimens were associated with a higher CD4/CD8 ratio increase compared with PI-based regimens, which other authors supported, to induce a proinflammatory state[21], thus resulting in CD8 expansion[20]; however, this observation might be misleading and should be confirmed in prospective randomized clinical trials.

Of note, if the association between the CD4/CD8 ratio and HIV viremia is well established, the role of residual viremia in influencing the CD4/CD8 ratio is still pending. However, in a recent study, HIV patients on long-term therapy with residual HIV viremia (51-200 copies/ml) and lower concurrent CD4/CD8 ratio were more likely to show CD8 T-cell activation[22]. Moreover, some studies found an inverse correlation between the CD4/CD8 ratio and HIV reservoir size measured as proviral DNA load[23-25].

Early initiation of ART is currently recommended by all international guidelines for HIV treatment[26,27]. It is demonstrated that the CD4/CD8 ratio is affected by the time of ART initiation. In a retrospective study including 352 patients on long-term suppressive ART, Torti, et al. evaluated factors associated with normalization of the absolute CD4 T-cell counts, CD4 T-cell percentage, and CD4/CD8 ratio[16]. Patients with higher CD4 T-cell percentages, lower CD8 T-cell percentages or higher CD4/CD8 ratio at baseline were more likely to have a multiple T-cell marker recovery, i.e. to reach CD4 T-cells > 500/mm^3 with high percentage (defined as > 29%) in addition to a CD4/CD8 ratio > 1, thus suggesting that an early initiation of ART is associated with a higher probability of a complete immune restoration[16].

Similar to previous observations[28], a recent study using data from the SPARTAC trial and the UK HIV Seroconverters Cohort demonstrated that the earlier ART is started in individuals with primary HIV infection (defined as within six months of estimated date of infection), the greater the probability of obtaining a normal CD4/CD8 ratio[29]. In fact, even though in most individuals with primary HIV infection an inverted CD4/CD8 ratio was observed at HIV infection diagnosis, prompt initiation of ART may determine an immunological recovery, resulting in normalization of the CD4/CD8 ratio and an overall reduction of AIDS and non-AIDS related events.

CD4/CD8 ratio and the "inflamm-aging" process

Currently, it is widely accepted that HIV infection causes a state of chronic immune activation and inflammation through several direct and indirect mechanisms[30]. In recent studies, the CD4/CD8 ratio has proven to be an excellent marker of immune activation[28,31]. In a population of vertically infected children, a Spanish group[31] verified an association between an inverted CD4/CD8 ratio and immune-activated (CD38+ HLA-DR+) and senescent (CD28-CD57+) CD4 and CD8 T-cells. Likewise, the same group, using data from four distinct clinical cohorts and three clinical trials, reported that HIV patients with a low CD4/CD8 ratio, although effectively treated with ART, showed altered T-cell subsets and elevated CD8 T-cell activation and presented an increased risk of non-AIDS morbidity and mortality[28].

In addition, a body of evidence suggests that a decline of the CD4/CD8 ratio is linked to immune dysfunction, leading to a poor response to immunization and consequently to a major risk of severe infections and malignancies, in both elderly populations[8,32] and HIV-infected individuals[33-35].

Several studies demonstrated that HIV-infected individuals share with older uninfected subjects increased

levels of inflammation and coagulopathy markers. In particular, aging of the immune function is characterized by an increased proportion of CD28- CD57+ memory CD8+ T-cells, with reduced capacity to produce interleukin 2 (IL-2), increased production of IL-6, high-sensitivity C-reactive protein (hs-CRP), and D-dimer[36,37], resistance to apoptosis, and shortened telomeres[38]. All these findings have been associated with morbidity and mortality in both HIV infection and elderly populations[39,40]. Therefore, HIV infection and aging can be considered as two similar conditions in which immune senescence and immune activation are widely expressed[30]. A slight association of the CD4/CD8 ratio with inflammation biomarkers, such as IL-6, D-dimers and high-sensitivity polymerase chain reaction (hs-PCR), has been described in a recent study[28], suggesting that HIV individuals with a low CD4/CD8 ratio may exhibit an "inflammaging" profile, even if this correlation deserves further investigation. On the contrary, in our cohort of individuals with long-term histories of HIV infection, no association between CD4/CD8 ratio slopes over time and increased levels of chronic inflammation and immune activation was observed[15], as confirmed in another study[41].

Furthermore, other latent viral infections including Epstein-Barr virus infection and chronic CMV infection have been linked to immune activation and immune senescence in HIV-positive patients and in elderly populations[42-44]. In a recent study on 6,111 HIV-positive patients from the ICONA cohort, CMV IgG seropositivity was found to be a risk factor to develop serious non-AIDS-defining events or non-AIDS-related death, in particular cardiovascular and cerebrovascular disease[45]. Finally, HIV/CMV coinfection may further alter the CD4/CD8 ratio as a result of increased CMV-specific T-cell responses and promote inflammation and immune dysfunction[46,47], as also described in the paper by Mussini, et al.[6].

CD4/CD8 ratio and non-AIDS-related clinical events

A large number of comorbidities, including cardiovascular disease, malignancies, neurocognitive impairment, and overall mortality, may occur earlier in HIV-infected individuals compared to uninfected people[48,49]. Several studies have shown that the incidence of non-AIDS-related diseases is constantly growing despite an optimal control of HIV replication. These severe events may occur both in ART-treated patients with low-CD4 restoration[50,51] and in those with a good immune recovery[52,53], and they appear to be related to the previously described immune activation and immune senescence phenomena[54]. Moreover, several studies found that the CD4/CD8 ratio can be considered a good predictor of non-AIDS-related diseases in the HIV population[6,41]. In an observational, cross-sectional study including 132 HIV-treated patients with good immunological and virological response, Serrano-Villar, et al. demonstrated an association between the CD4/CD8 ratio and some markers of age-associated disease. In fact, patients with a low CD4/CD8 ratio were more likely to have higher intima media thickness, higher arterial stiffness, and low estimated glomerular filtration rate[41]. In a case-control study performed on ART-treated HIV-infected patients, the same research team reported a consistent connection between a low CD4/CD8 ratio and the occurrence of severe non-AIDS-related events; the CD4/CD8 ratio performed better than the CD4 cell count, CD8 cell count, or nadir CD4 in identifying persons with a major risk of serious non-AIDS diseases[52].

In a previous study[15], we found that patients with an inverted CD4/CD8 ratio showed a trend for a higher frequency of diabetes and hypertriglyceridemia compared to patients with a normalized ratio, even if they did not significantly differ in IL-6, hs-PCR, and D-dimer levels or in frequency of severe non-AIDS-associated events. Moreover, we did not observe any association between the CD4/CD8 ratio and HIV subtype, coreceptor tropism, CMV infection, and HBV and HCV coinfections.

Of note, the study of Mussini, et al. has clearly defined the importance of the CD4/CD8 ratio as a significant hallmark of non-AIDS events in a large cohort. In this population, a lower CD4/CD8 ratio was associated with the incidence of non-AIDS-defining events and, in particular, patients with a CD4/CD8 ratio < 0.3 were more likely to develop severe non-AIDS events. Therefore, the authors proposed the CD4/CD8 ratio as a suitable tool for identifying individuals who are more likely to have severe non-AIDS-related diseases over time, and for whom closer clinical monitoring would be extremely useful[6].

Recently, some authors have evaluated the role of the CD4/CD8 ratio on the onset of serious non-AIDS-related diseases[49,55,56]. Notably, Castilho, et al. found that the CD4/CD8 ratio was inversely associated with risk of cardiovascular disease events in HIV-infected individuals, particularly in those under age 50 years compared with those over age 50[49]. Moreover, other recent studies have underlined the importance of the

CD8 count on the occurrence of myocardial infarction in HIV-infected individuals[55,56]. In detail, Lang, et al. reported an association between a high current CD8 T-cell and an increased risk of acute myocardial infarction (AMI) in HIV-infected patients[54].

In addition, Badejo, et al. evidenced that the effect of CD8+ T-cells on AMI risk could depend on the CD4+ T-cell level: HIV-infected people with CD4+ T-cell counts ≥ 200 cells/mm^3 had an increased AMI risk with high CD8+ T-cell count than uninfected people, whereas those with CD4+ T-cell counts < 200 cells/mm^3 showed an AMI risk with low CD8+ T-cell count, thus suggesting that CD8+ T-cell counts might be useful information to stratify myocardial infarction risk beyond that provided by only CD4+ T-cell counts[56]. This is consistent with another study where marked elevations in CD8+ T-cell counts were associated with increased non-AIDS-related mortality in a large cohort of long-term ART-treated HIV-infected individuals[57].

Importantly, recent studies have evaluated the impact of the CD4/CD8 ratio on other conditions[57,58]. In fact, Triplette, et al. found an association between a low CD4/CD8 ratio and pulmonary emphysema in HIV-infected individuals, regardless of other risk factors and clinical markers of HIV infection[58]. Furthermore, a low CD4/CD8 ratio has been associated with peripheral fat[59], thus increasing the interest on this marker, which can be clinically useful in a risk stratification of non-AIDS-related diseases in HIV-infected subjects.

CD4/CD8 ratio and HIV/HCV coinfection

Chronic HCV infection also determines CD8 T-cell dysfunction and supports an expansion of the CD8 cells, resulting in a chronic state of immune activation and senescence[60]. HIV/HCV coinfection is characterized by a higher level of T-cell activation and exhaustion compared to HCV or HIV mono-infection, suggesting that HIV and HCV have a complementary role on T-cell activation[61].

Consequently, HCV infection may further alter the CD4/CD8 ratio in individuals with HIV infection. In fact, a lower CD4/CD8 ratio was found in a large cohort of HIV RNA suppressed women with HCV infection compared with HIV-infected women without HCV antibodies[62]. However, a persistent inverted ratio was described even in women who had cleared HCV. The authors hypothesized that the expansion of CD8 count could be explained as a result of immune activation due to previous HCV infection and injection drug use history.

Moreover, chronic HCV infection is also associated with an overall poor immunological recovery in HIV individuals receiving ART. In a large meta-analysis involving HIV/HCV-coinfected patients, a reduced immune reconstitution, as defined by the CD4 cell count after 48 weeks of ART, was observed compared to patients with HIV infection alone[63]. Potter, et al. found that the CD4 cell count recovery is negatively affected by the presence of ongoing HCV replication in HIV/HCV-coinfected individuals initiating ART, and suggested that an active HCV infection impacts immune restoration even after years of ART exposure[64]. In particular, a worse immune recovery has been described in a study from the MASTER cohort in HIV/HCV patients with genotype 3 HCV[65]. To date, two studies reported that HIV/HCV-coinfected individuals, despite long-term effective ART, were more likely to have an inverted CD4/CD8 ratio than subjects with HIV infection alone[66,67].

Recent studies have focused their attention on the CD4 recovery in HIV/HCV patients achieving sustained virological response (SVR)[68,69]. Both studies showed that the clearance of HCV infection was not significantly associated with changes in the CD4 count slope in HIV/HCV-coinfected patients. Even though these studies assessed CD4 slopes after effective anti-HCV therapy, CD4/CD8 ratio modifications were not evaluated. Our group has recently investigated whether the CD4 and CD4/CD8 ratio slopes improved in a cohort of HIV/HCV-coinfected patients with a long history of ART after pegylated-interferon and ribavirin based-treatment[70]. Fifty-five (47%) of 116 HIV/HCV-coinfected patients reached SVR; despite a beneficial impact of SVR in terms of liver-related mortality and fibrosis regression assessed with FIB-4 score, the eradication of HCV infection did not appear to alter either the slope of CD4 gain in the long term or the CD4/CD8 ratio evolution in this ART-treated HIV/HCV-coinfected population. As previously supported[62], a possible explanation for the lack of correlation between HCV clearance and CD4/CD8 ratio normalization relies on the persistent state of immune activation and chronic inflammation of HIV patients that is only partially reverted when HCV infection is eradicated; therefore, the role of HCV itself can easily pass by unnoticed.

Conclusions

The CD4/CD8 ratio is a hallmark of significant clinical impact in HIV patients. In addition to being a recognized biomarker of immune activation and immune

Table 1. Studies evaluating factors associated with normalization of CD4/CD8 ratio and correlations between CD4/CD8 ratio and immune activation, chronic inflammation, and occurrence of non-AIDS events

Reference	(n)	ART treatment	Time on ART (median)	CD4/CD8 ratio cut-off	% normalization CD4/CD8 ratio	Factors associated with normalization of CD4/CD8 ratio	Notes
Mussini, et al.[6]	3,236	Yes	2.6 years	≥ 1	4.4 by 1 year from baseline, 11.5 by 2 years and 29.4 by 5 years	Positive correlation with high pre-ART CD4 count, high CD4/CD8 ratio at baseline, and CMV seronegativity	Association between low CD4/CD8 ratio and occurrence of non-AIDS events
Leung, et al.[14]	4,206	Yes	2.7 years	≥ 1.2	7.2	Positive correlation with baseline CD4 count > 350, CD8 < 500, and CD4/CD8 > 0.5	No association between CD4/CD8 ratio and occurrence of non-AIDS events. Achieving a normal CD4:CD8 ratio was not associated with time to ADI/death.
Saracino, et al.[15]	112	Yes	> 15 years	≥ 0.9	37	Negative correlation with older age, low nadir CD4 count, and detectable HIV viremia	No association between CD4/CD8 ratio with chronic inflammation and non-AIDS events; a trend for diabetes and hypertriglyceridemia in pts. with low CD4/CD8 ratio
Caby, et al.[17]	719	Yes	> 5 years	≥ 1	34	Negative correlation with CMV seropositivity, ART initiation before 1997, low CD4 cell nadir, and shorter HIV RNA suppression	Study evaluating determinants of a low CD4/CD8 ratio in long-term suppressed individuals.
Serrano-Villar, et al.[28]		Yes	NA	0.4 defined as low	NA	Positive correlation with naive T-cells, central memory T-cells and transitional memory T-cells, and negative correlation with effector memory T- cells	Association between a low CD4/CD8 CD8+ with CD8 T cell activation (HLADR+CD38+) and immune senescence (CD28- and CD57+CD28-) and higher risk of morbidity/mortality. Data from four cohorts and two clinical trials
Thornhill, et al.[29]	482*	Yes	< 1 year	≥ 1	46.6 by 1 year in patients starting ART within 6 months from PHI; 12.6 % at 1 year in the group ≥ 6 months	Positive correlation with earlier ART initiation (within 6 months from HIV diagnosis) and CD4/CD8 ratio normalization	Of the 573 patients with PHI from SPARTAC trial and the UK HIV Seroconverters Cohort, 482 had abnormal CD4/CD8 ratio before starting ART.ART initiation within 6 months from seroconversion was significantly more likely to normalize CD4/CD8 ratio than those initiating later
Castilho, et al.[49]	2,006	Yes	> 1.3 years	≥ 0.7	NA	Negative correlation with older age and low nadir CD4 count	Association between a low CD4/CD8 ratio with CAD (coronary artery disease).
Serrano-Villar, et al.[52]	407	Yes	4 years	0.4 defined as low	NA	NA	Association between low CD4/CD8 ratio and non-AIDS events

*All patients had PHI with abnormal CD4/CD8 ratio before starting ART.
ART: antiretroviral treatment; CMV: cytomegalovirus; NA: not applicable; PHI: primary HIV infection, defined as within 6 months from estimated date of diagnosis.

senescence, the CD4/CD8 ratio may be considered a predictor of severe AIDS and non-AIDS associated events. Therefore, it may be useful in clinical practice in monitoring HIV patients and identifying individuals who would benefit from more frequent clinical controls.

Declaration of interest

The authors declare that they have no conflict of interests in publishing this paper.

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