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Editorial

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CD4:CD8 Ratio and Non-AIDS Defining Events in Virally Suppressed HIV Infected Patients: Need to Look Beyond CD4+ T-Cell Counts

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ISSUE

CD4 Count and CD4:CD8 Ratio

Antiretroviral therapy has led to improvement in life-expectancy through viral suppression and improved immune status. This brings in the concern about the non-AIDS defining illnesses which are mostly age associated such as cardiovascular disease, stroke, renal disease, liver disease, neurocognitive disorders, and non-AIDS malignancies.[1-6] These are reported to be present at comparatively younger ages in HIV-infected patients.[7] It also raises questions on the usefulness of CD4 T cell counts in patients with full HIV RNA suppression.[2,8] CD4 count remains the most important predictor of clinical progression in people with HIV infection, but it does not predict immune activation in chronic HIV infection and non-AIDS illnesses.[9] Several immunological alterations characteristic of HIV infection, such as immune activation and inflammation, are similar to the immunological alterations associated with normal aging. This finding has led to an intersection of the fields of aging and HIV disease, especially with regard to immune alterations. Inversion of the CD4:CD8 ratio (<1) has been identified as a hallmark of immunosenescence and an independent predictor of all-cause mortality in the general population.[10,11] This information has prompted the evaluation of the CD4:CD8 ratio as a surrogate marker for the risk of morbidity and mortality in HIV-positive people in the current era of Antiretroviral therapy (ART).

Immune Activation and CD4:CD8 Ratio

Immune activation in HIV infected, marked by levels of circulating markers of innate immune activation is widely accepted as the major driving factor of immunosenescence. Immunosenescence, an observed age-associated decline in immune competence that ultimately yields to disease progression and adverse outcomes, including age-associated disease. Independent association has been found between CD4 and CD8 activation and senescence and between CD4:CD8 ratio and circulating markers of innate immune activation.[12-14] Since persistent immune activation in treated HIV infection drives non-AIDS-associated diseases, CD4:CD8 could be a marker for long lasting immune activation despite ART.[12]

To measure CD4 and CD8+ T cell activation, biomarkers such as Ki67, HLA-DR, cytokines IL-6 and TNF-α and analysis of expression of CD14, CD163, CD28 and CD38 on T cell subsets are employed.[6] Evidence points to the fact that expression of inflammatory markers correlate strongly with risk of mortality and cardiovascular events. For example, biomarkers showing the greatest relative risks in outcome for all cause mortality were D-dimer and Interleukin (IL)-6.[15] Studies so far have found merely association between these activated T cell phenotypes and markers of age related dysfunctions. But the cause effect relationship predicting the events is still not evaluated, limiting its clinical application. Whereas, CD4:CD8 ratio is

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an easily available cost effective investigation that could instruct the clinical care of HIV infected on ART.

Non AIDS Defining Event (NADE)

A large European study of over 12000 HIV patients reported NADE incidence of 1.77 per 100 person-years of follow-up and almost a 7-fold increased risk of death after a non-AIDS event.[16] Other than the infection itself, NADEs are one of the most important factors affecting the prognosis of HIV patients. It is still not clear whether HIV infected are at higher risk of NADEs. The raised risk could be due to life style of the individuals such as IV drug use or HIV infection itself. It is assumed to be fuelled by residual HIV replication in HIV reservoirs or asymptomatic multiplication of co-infecting pathogens or Cytomegalovirus (CMV) specifc immune stimulation and damage to gut mucosal immunity.[1,2,6]

CD4:CD8 Ratio Normalization and NADE

Recently published two longitudinal studies with large sample size from Spain and Italy, have established that CD4:CD8 ratio was significantly lower in those with NADEs including NADE deaths independent of CD4 count through rigorous statistical analysis.[1-2] The CD4:CD8 ratio reflects the health of the immune system and a normal ratio is between 1 and 4. In people with HIV, the CD4:CD8 ratio has been linked to T cell activation, the CD4 cell death due to HIV and the bystander CD4 cells death by HIV mediated apoptosis.[1,17,18] CD4 count decreases by about 30% and CD8 count may increase by about 40%, thus inverting the ratio that is generally less than 1, within six months of seroconversion. The ratio may revert toward normal after initiating antiretroviral therapy. It has been observed that CD4:CD8 ratio remains low in substantial proportion of patients with CD4 T cell immune recovery and viral suppression following ART. Fewer than 15% in an Italian cohort, attained a normal CD4:CD8 ratio after reaching an undetectable viral load with Antiretroviral therapy (ART).[1] The estimated probability of normalization was 4.4% at 1 year, 11.5% at 2 years, and 29.4% at 5 years of ART initiation among those whose CD4:CD8 ratio normalized after ART initiation. Median time to a normal ratio was reported to be 10.1 years.[1,19,20]

Factors described to be associated with normalization include high CD4:CD8 ratio at ART initiation, high pre ART CD4 and negative cytomegalovirus cytology. Those less likely to achieve normalization were older, route of HIV transmission was through homosexual contact or intravenous drug use, longer interval between ART initiation and first viral suppression and more likely to have been treated with zidoviduine and lamivudine, didanosine and stavudine as compared to emtricitabine and tenofovir.[1,12,19,20] Tenofovir and emtricitabine which have lesser toxicity on bone marrow could contribute to early normalization of the ratio.[1] Moreover positive correlation of higher CD4 count at ART initiation with CD4:CD8 recovery supports early initiation of ART. Early ART initiation may contribute to more rapid and robust CD4:CD8 ratio normalization, and the ratio may be a useful clinical endpoint to be used in evaluating novel therapies for ongoing immune dysfunction during treated infection and for HIV eradication.[12] It has been suggested that MSM might have higher prevalence of bacterial and viral infections such as CMV which could increase the activation of the immune system resulting in persistent expansion of CD8 cell population leading to low CD4:CD8 ratio.

Studies have explored CD4:CD8 ratio cutoff with greatest clinical significance to predict clinical progression in terms of occurrence of NADE or death due to NADE. The Madrid study, found that the most accurate cutoff of the CD4:CD8 ratio for the detection of non-AIDS events in a sensitivity/specificity plot was 0.4, with a sensitivity of 0.83 and a specificity of 0.45.[2,12] Whereas, the Italian study used CD4:CD8 ratio as continuous and as categorical variables with the cutoff of less than 0.30, 0.30-0.45 and more than 0.45. It showed that a ratio below 0.30 raised the incidence rate a non-AIDS defining event by double when compared with a ratio above 0.45 and between 0.3 to 0.45.[19] These findings suggest that complete reversion of HIV induced immunological dysfunction is rare. Chronic inflammatory status occurs in HIV infection and can persist despite supressive ART. Despite recovery of CD4, persisting imbalance between CD4 and CD8 cell population leading to low CD4:CD8 ratio identify patients with worse prognosis.[1]

Role of Immune-Modulators

As it has been established that persistent immune activation in treated HIV infection is the driver of NADEs, role of immunomodulators aimed at reduction of inflammation is being studied. Adjuvant therapy such as recombinant human IL-7, rifaximin for controlling translocation for deaccelerating senescence, SB-728-T, a gene therapy, TAT2 (cycloastragenol) are being investigated.[21-24] Broad non-specific immunomodulators such as statins, chloroquine, hydroxychloroquine, aspirin, methotrexate, and several other anti-inflammatory drugs are also being developed as possible adjuncts to standard antiretroviral drugs.[6] Currently, such approaches are limited to *in vitro* studies and early phases of clinical trials, though these provide a glimpse of future possibilities.

Implications

Though CD4 T cell counts are used to assess clinical progression to AIDS in HIV infected individuals, these do not predict immune activation and risk of non-AID events.[9] Low CD4:CD8 ratio is a risk for clinical progression in virally suppressed indivduals on ART therapy. It is an easy to obtain marker for clinicians to predict the risk of serious non-AIDS defining events and death independently of CD4 restoration.

As authors suggest, these findings have potential implications for, one, targeting immune dysfunction in chronically treated HIV-infected individuals, in particular those with

persistent expansion of CD8+ T cells despite adequate CD4+ T cell recovery. Two, CD4:CD8 ratio may be useful in monitoring response to therapies aimed at reducing residual immune activation, and HIV persistence. Finally, ART-suppressed HIV-infected individuals who do not have an increase in the CD4:CD8 ratio might benefit from screening programs or aggressive management of concomitant risk factors for aging-associated disease.[2,12]

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