

Advantages of Alternate Biomarkers in the Management of Human Immunodeficiency Virus with Highly Active Antiretroviral Therapy

Venkataramana Kandi^{1,*}, Adnan Bashir Bhatti²

¹Prathima Inst. of Medical Sciences, Karimnagar, Telangana, India

²Department of Medicine, Capital Development Authority Hospital, Islamabad, Pakistan

*Corresponding author: ramana_200221@rediffmail.com

Abstract The disease burden of human immunodeficiency virus (HIV) is substantially more prevalent among residents of the sub-Saharan Africa and Asia. The availability and affordability of highly active antiretroviral therapy (HAART) have significantly reduced the mortality among HIV-1 infected population, increase their life expectancy and quality of life. However, the poor financial conditions and lack of costly infrastructure in the developing countries hinder regular monitoring of HIV-1 RNA (viral load) and CD4+ T-lymphocyte cell count (TCD4+ cell count). Under these circumstances, there is an increasing need for alternate biomarkers for monitoring the progression of the disease and patient management. Albumin, hemoglobin (Hb), dehydroepiandrosterone sulfate (DHEA-S), red blood cell (RBC) count, erythrocyte sedimentation rate (ESR), plasma highly-sensitive C-reactive protein (hs-CRP), hematocrit (Hct), total lymphocyte count (TLC) are some of the alternate biomarkers with proven utility in the assessment of disease progression.

Keywords: human immunodeficiency virus, highly active antiretroviral therapy, alternate biomarkers, HIV disease progression

Cite This Article: Venkataramana Kandi, and Adnan Bashir Bhatti, "Advantages of Alternate Biomarkers in the Management of Human Immunodeficiency Virus with Highly Active Antiretroviral Therapy." *American Journal of Infectious Diseases and Microbiology*, vol. 4, no. 2 (2016): 32-34. doi: 10.12691/ajidm-4-2-2.

1. Editorial

Chronic exposure of the immune system to human immunodeficiency virus (HIV) leads to the progressive decline of CD4+ T-lymphocyte cell count (TCD4 + cell count) in HIV-1 infected patients. Although the TCD4+ cell count provides important prognostic details, evaluation of lymphocyte subsets often demand resources and laboratory expertise that are not readily available in developing countries, such as sub-Saharan African countries where approximately 67% of the world's total HIV-1 positive patients resides. In these countries using cost-effective alternate biomarkers for monitoring the progression of HIV-1 disease is very useful alternative tool. Alternate biomarkers also tremendously enhance the performance of the physicians to examine the progression of the disease accurately among patients on highly active antiretroviral therapy (HAART).

Early and accurate identification of mortality risk factors in HIV-1 infected population is of paramount importance in lowering the mortality rates in endemic regions like Asia and Africa. The mortality rates among infected patients receiving HAART in African sub-continent have been found to range between 8 and 16 per 100 people per year. The major risk factors for high mortality in low-income developing countries include low

TCD4+ cell count, low hemoglobin (Hb) level, low body mass index (BMI), progression to clinical stage 4 and development of opportunistic infections (e.g., tuberculosis). Several interventions like the promotion of earlier and voluntarily HIV testing, education about prevention, counseling to prompt initiation and compliance to HAART, screening, and treatment of opportunistic infections have been proposed to lower the AIDS-associated mortality in low-income developing countries [1].

Higher TCD4+ cell count (>50 cells/mm³) with decreased level of albumin have better prognostic value for predicting mortality, while low TCD4+ cell counts (<50 cells/mm³) with same decreased level of albumin has no predictive value for mortality; showed by study conducted in the United States and London to find the risk factor for mortality during the first year of HAART among women. This may be due to the plateau effect in patients with a low TCD4+ cell count who already have a higher risk of mortality (20%). The cause of decreased level of albumin in HIV-1 infected patients could be related to many factors including malnutrition, chronic inflammation caused by advanced HIV-1 infection, wasting syndrome, enteropathy or liver disease (e.g., chronic hepatitis B virus co-infection).

It has also been reported that serum albumin below 3.5mg/ml in acute infection indicates faster HIV-1 disease progression. A group of researchers have reported a significant difference in the level of albumin before and after

initiation of HAART ($P < 0.05$), while the differences in other alternative biomarkers such as dehydroepiandrosterone sulfate (DHEA-S) and plasma highly-sensitivity C-reactive protein (hs-CRP) were found to be insignificant ($P > 0.05$). Other studies have reported an increase in the activities of both DHEA-S and hs-CRP with the HIV-1 disease progression. The study revealed that albumin level and to a lesser degree DHEA-S can be used as biomarkers for monitoring HIV-1 disease progression and response to treatment [2].

The association of total lymphocyte count (TLC), hemoglobin (Hb), erythrocyte sedimentation rate (ESR) with CD4 count and the progression of the disease has also been reported. A recent study from India on 215 HAART-naive HIV-1 infected patients measured TCD4+ cell count along with TLC, Hb, and ESR. Statistical tools like correlation and receiver operating characteristic (ROC) curves were used to estimate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of various alternate biomarkers. The study emphasized the need for large-scale, multi-centric studies in India and other developing countries to investigate the usefulness of cheaper and alternate laboratory biomarkers [3].

The level of Hb could independently be used to predict prognosis across demographically distinct populations. The decrease in Hb levels were found to correlate positively with TCD4+ cell count. Studies have reported the incidence of anemia among HIV-1 seropositive people. Anemia is therefore considered as an independent predictor of the progression of the disease and death among HIV-positive patients. It has also been observed that HAART improves anemia in HIV-positive patients. While the adverse effects of antiretroviral drugs including zidovudine on patient's bone marrow requires serious consideration. Monitoring Hb level is thus useful in predicting the progression of the disease before and after initiation of HAART [4]. Serum electrolyte, albumin, and other cost-effective biomarkers inclusion to monitor the progression of the disease would benefit the HIV-1 patients [5].

The World Health Organization (WHO) advocates TLC as an alternative biomarker to TCD4+ cell count in resource-constrained countries. Several studies demonstrated an association between TLC lower than 1200 cells/mm³ and advancement of disease and mortality. A study involving 131 HIV-1 seropositive patients correlated the results of clinical assessment and TLC with different cut-point values of TCD4+ cell count to decide the sensitivity, specificity, PPV, and NPV. The results revealed a significant association between TLC and TCD4+ cell count ($r = 0.73$, $p < 0.0001$). However, the limitation of the study was that WHO recommended criteria for TLC cut-off of 1200 cells/mm³ did not recognize the majority of patients in WHO stage 2 and 3 having CD4 counts < 200 cells/mm³. It means that the more rational use of TLC is necessary for the management of all patients with WHO stage 2 and 3, who have the TLC less than 1200 cells/mm³ and limit TCD4+ cell count testing to patients who are symptomatic but have TLC more than 1200 cells/mm³ [6].

The cost of testing TCD4+ cell count, viral load, and other alternate biomarkers vary considerably. Therefore, countries with low-income economies and insufficient healthcare resources, the alternate biomarkers testing can

prolong the interval of testing between TCD4+ cell count and the viral load that is more cost-effective for patients on HAART.

Sustainability of laboratory assays (cost constraints, transport of reagents and kits, kit shelf-life, access to instruments service, and QA/QC program) must also be taken into consideration, and low-cost TCD4+ cell count testing must also be performed to monitor disease progression. As the TCD4+ cell count tend to vary between standard assay and alternative methodologies, the normal reference ranges should be established on the local population under study for any particular cost-effective assay [7].

Viral load indicate the extent of viral replication and the TCD4+ cell count indicate the result end-organ damage or immunodeficiency. Another significant part of pathogenesis is immune system dysregulation. To assess the prognostic value of each of these elements in disease progression, complete and retrospective marker confirmation studies must be carried out among HAART-naive population [8].

WHO recommendation on using TCD4+ cell count and clinical staging to guide changes in treatment has less sensitivity and specificity. It has been noted that switches in therapy will not be easy if physicians only had TCD4+ cell count data. This will result in switches in therapy that are unnecessary or delayed. Alternative drug options, basic laboratory testing before initiating HAART and competent clinical monitoring of alternative biomarkers will thus be highly helpful under these circumstances [9].

The HIV-1 disease progression starting from the entry of first viral particle into a TCD4+ cell to the later development of AIDS and subsequent death is subjective to many factors. Host factors remain significant in evaluating the progress of treatment in patients on HAART. In-depth studies on host-virus interactions will be highly helpful in the development of new therapeutic approaches. Regular monitoring of viral load and emergence of drug resistance will continue to play a significant role in the management of HIV-1 infection. Successful management of HIV patients requires thorough monitoring of several factors. Alternate biomarkers such as albumin, Hct, Hb, TLC, Hs-CRP, RBC count and ESR were observed to show similar utility to that of TCD4+ cell count and viral load [10].

Many HIV-1 seropositive patients have learned adaptive and coping techniques that have allowed them to survive HIV-1 infection as a chronic but controllable disease. It is also possible that they have made proactive changes in their lives to cope with fatigue and other morbid conditions. As effective HAART allows HIV-infected people to live a longer life. There should be more studies done to try to find ways to monitor HAART treatment to ensure the efficacy and reaping maximum benefits [11-19].

In conclusion it should be noted that the presence of co-infections may negatively influence the efficacy of alternate biomarkers in monitoring and management of HIV disease progression and therefore physicians caring HIV patients should consider all aspects while interpreting alternate biomarkers. Furthermore, it should also be noted that none of the alternative biomarkers that have been discussed here have the sensitivity and specificity that is equivalent to RNA viral load and TCD4+ cell count. Therefore, acquisition of infrastructure to perform viral

load and CD4 count should always be the top priority of health care sector in developing and underdeveloped nations.

References

- [1] Kannangai R, Kandathil AJ, Ebenezer DL, et al: Usefulness of Alternate Prognostic Serum and Plasma Markers for Antiretroviral Therapy for Human Immunodeficiency Virus Type 1 Infection . *Clinical. and Vaccine Immunology*. 2008, 15:154-158.
- [2] Kapiga SH, Mwakagile D, Spiegelman D, Msamanga GI, Hunter D, Fawzi WW: Predictors of CD4+ lymphocyte count among HIV-seropositive and HIV-seronegative pregnant women in Dar es Salaam, Tanzania. *East Afr Med J*. 2000, 77:206-211.
- [3] Sen S, Vyas A, Sanghi S, Shanmuganandan K, et al: Correlation of CD4+ T cell Count with Total Lymphocyte Count, Haemoglobin and Erythrocyte Sedimentation Rate Levels in Human Immunodeficiency Virus Type-1 Disease. *MJAFI*. 2011, 67:15-20.
- [4] Shah S, Smith CJ, Lampe F, Youle M, Johnson MA, Phillips AN, Sabin CA: Haemoglobin and albumin as markers of HIV disease progression in the highly active antiretroviral therapy era: relationships with gender. *HIV Med*. 2007, 8:38-45.
- [5] Dao CN, Peters PJ, Kiarie JN, et al: Hyponatremia, hypochloremia, and hypoalbuminemia predict an increased risk of mortality during the first year of antiretroviral therapy among HIV-infected Zambian and Kenyan women. *AIDS Res Hum Retroviruses*. 2011, 27:1149-55.
- [6] Kanya MR, Semitala FC, Quinn TC, et al: Total lymphocyte count of 1200 is not a sensitive predictor of CD4 lymphocyte count among patients with HIV disease in Kampala, Uganda. *African Health Sciences*. 2004, 4:94-101.
- [7] Balakrishnan P, Solomon S, Kumarasamy N, Mayer KH: Low-cost monitoring of HIV infected individuals on highly active antiretroviral therapy (HAART) in developing countries. *Indian J Med Res*. 2005, 121:345-355.
- [8] Mildvan D, Spritzler J, Grossberg SE, Fahey JL, Johnston DM, Schock BR, Kagan J: Serum neopterin, an immune activation marker, independently predicts disease progression in advanced HIV-1 infection. *Clin Infect Dis*. 2005, 40:853-8.
- [9] Collini P, Schwab U, Sarfo S, Obeng-Baah J, Norman B, Chadwick D, Bibby D, Bedu-Addo G: Sustained immunological responses to highly active antiretroviral therapy at 36 months in a Ghanaian HIV cohort. *Clin Infect Dis*. 2009, 48:988-91.
- [10] Langford SE, Ananworanich J, Cooper DA: Predictors of disease progression in HIV infection: A review. *AIDS Res Ther*. 2007, 4:11.
- [11] Ramana KV: HIV: Disease Management in the Highly Active Antiretroviral Therapy (HAART) Era. *J Medical Microbiol Diagnosis*. 2012, 1:101.
- [12] Venkataramana K: A Study of Biological Markers in HIV Disease Progression and Management in the Highly Active Antiretroviral Therapy (HAART) Era. *American Journal of Bioscience and bioengineering*. 2013, 1:24-37.
- [13] Ramana KV: Are we Close Enough to get rid of. *International Journal of Molecular Medical Science*. 2013, 3:25-29.
- [14] Ramana KV, Sabitha V, Rao R: A: Study of Alternate Biomarkers in HIV Disease and Evaluating their Efficacy in Predicting T CD4+ Cell Counts and Disease Progression in Resource Poor Settings in Highly Active Antiretroviral Therapy (HAART) Era. *J Clin Diagn Res*. 2013, 7:1332-5.
- [15] Ramana KV, Rao R: Human immunodeficiency virus disease management in highly active antiretroviral therapy era: A comprehensive review. *Ann Trop Med Public Health*. 2013, 6:5-9.
- [16] Ramana KV, Rao R, Kandi S, Singh PA, Kumar VP: Elevated activities of serum lactate dehydrogenase in human immunodeficiency virus sero-positive patients in highly active antiretroviral therapy era. *J Dr NTR Univ Health Sci*. 2013, 2: 162-6.
- [17] Ramana KV: Markers of HIV-1 Disease Progression. *American Journal of Infectious Diseases and Microbiology*. 2013, 1:96-100.
- [18] Ramana KV: Effect of Highly Active Antiretroviral Therapy (HAART) on Human Immunodeficiency Virus Disease Pathogenesis. and Progression. *American Journal of Public Health*. 2014, 2:68-74.
- [19] Kandi V: Effect of co-morbidities on disease course in human immunodeficiency virus-infected illicit drug users in the era of highly active antiretroviral therapy. *Epidemiol Health*. 2015, 37:2015008.