Markers of HIV-1 Disease Progression and Treatment Response in Highly Active Antiretroviral Therapy (HAART) Era: A Review

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Abstract After the discovery of human immunodeficiency virus 1 (HIV-1) infection more than three decades ago, there has been a significant development in the laboratory diagnosis, treatment and management of patients on highly active antiretroviral therapy (HAART). Initially HIV-1 infection was implicated to cause various cancerous conditions (Kaposi’s sarcoma), and infectious diseases (tuberculosis, other bacterial, viral, parasitic and fungal infections). Studies have demonstrated that HIV-1 infection and the disease course is complex and that many HIV infected patients do not progress to acquired immune deficiency syndrome (AIDS) even after 10-15 years (late/non progressors). Introduction of HAART has significantly reduced the morbidity and mortality in HIV-1 infected patients resulting in extended life on par with HIV non infected individuals. Late research has revealed that HIV-1 infected individuals are at greater risks of developing non infectious complications (liver disease, cardiovascular disease (CVD)) that may precipitate with the initiation of HAART. With the increased availability and affordability of HAART, the focus now is on developing effective strategies to monitor HIV-1 disease progression and treatment response.

Keywords: human immunodeficiency virus (HIV), highly active antiretroviral therapy (HAART), disease progression, treatment response

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1. Introduction

Human immunodeficiency virus (HIV), since its discovery in 1983 has been a cause of great concern to the medical community [1]. Disease diagnosis and management have been plagued by social and economic limitations. As evidenced from the available literature, Asia and African regions bear the majority of the burden of HIV infected population [2]. From the time when HIV-1 was first discovered, there have been many studies on the pathogenesis and progression of the disease. HIV-1 disease progression is complex and is different in infected population [3]. Though sexual route is the most common means of transmission, needle stick injury, contact with blood and blood products and intrauterine infections also contribute to HIV-1 infection. HIV-1 disease appears to be complex, with infected population being susceptible to various infections (bacterial, fungal, parasitic and viruses), malignancies (Kaposi’s sarcoma, Burkitt’s lymphoma and many others) and chronic inflammatory conditions related to HIV-1 replication in various systems of the human body. HIV infection results in the development of Acquired ImmunoDeficiency Syndrome (AIDS), due to depletion of CD4+ T cells. AIDS development after HIV-1 infection has been noted to occur within 5 years after being infected (early progressors), later than 10 years (intermediate progressors) and some infected individuals do not develop AIDS symptoms even after 15 years (late progressors) [4]. CD4+ T cell decline < 200 cells/mm³ indicates AIDS development with corresponding rise in the HIV/RNA viral load. With the introduction of highly active antiretroviral therapy (HAART), the disease progression is slowed and the HIV infected population can live a normal life; however, one cause of concern remains the monitoring of patients on HAART therapy, who are susceptible to toxic drug reactions of HAART [5]. Since the poor and economically weak third world nations cannot afford regular CD4+ T cell counts and HIV-1/RNA viral load testing, cheaper and alternative markers of HIV disease progression are needed [6,7]. HIV-1 disease progression is monitored using various markers including viral markers (plasma HIV RNA load, serum p24 Ag, serum anti p24 antibodies), surrogate markers(antibodies against p17, gp 120, gp 41 and nef gene product) and nonspecific markers including CD4+ T-cell counts, CD8+ T-cell counts and Delayed Type Hypersensitivity test (DTH). Elevated serum β2 microglobulin, neopterin (D-erythro-1',2',3'-trihydropyrrtrim), Dehydroepiandrosterone (DHEAS), serum cortisol, CRP, ESR, Tumor Necrosis Factor (TNF), Interferon-γ, Interleukin-2 (IL-2) and IL-4
are also considered as alternate biomarkers [8]. Some studies have also suggested the utility of biochemical parameters including serum albumin, Globulin, Serum Glutamate Oxaloacetate Transaminase (SGOT), Total protein, Total cholesterol, High density Lipoproteins (HDL), Low density Lipoprotein(LDL), Lactate Dehydrogenase (LDH), Creatine Kinase (CK/MB) and Gamma Glutamyl transpeptidase (GGT) as useful markers of HIV-1 disease progression and treatment response [9,10].

2. HIV and Markers of Hematological Abnormalities

HIV-1 infection alone or in combination with HAART therapy, has been shown to influence the hematological parameters including blood hemoglobin (HB), total leukocyte count (TLC), erythrocyte sedimentation rate (ESR) and absolute eosinophilic count (AEC). Studies performed in the past have reported that there was a need to perform tests for hematological abnormalities in HIV infected individuals before initiating HAART therapy [8,11]. This was suggested taking into consideration the adverse effect of HAART. Anemia is well documented in HIV infected population, and initiation of HAART may worsen the condition of the patients or there may be rise in the Hemoglobin numbers following HAART indicating a better prognosis as observed in our study (Figure 1). Performing total leukocyte count (TLC) before initiation of HAART will enable the physician treating HIV-1 infected patients to use it for the prognosis of the treatment and disease management. Studies have also demonstrated the significance of TLC as an alternate marker to CD4+ T cell counts [12,13,14,15]. Considering the fact that rise in erythrocyte sedimentation rate (ESR) indicates inflammatory condition and that HIV-1 infected patients suffer from various infections and inflammatory conditions, use of ESR in disease management and treatment response has been a subject of debate for a long time [16]. Our study which was carried out in patients attending integrated counseling and testing center (ICTC), Area hospital, Siddipet, Andhrapradesh, India and which included HIV-1 infected population as well as patients on HAART (3-6 months) has demonstrated that levels of ESR may be raised in HIV-1 infected population who are antiretroviral therapy naïve (Figure 2) and that after initiation of HAART a further rise in ESR indicates poor prognosis and may contribute to severe morbidity and mortality. A decrease in ESR may indicate better prognosis and an increase may suggest development of immune reactivation inflammatory syndrome (IRIS), a consequence that results after initiation of HAART in a group of patients resulting in worsening the condition of patients [17,18,19]. In our study we included 56 HIV-1 seropositive patients and evaluated the blood levels of ESR and HB and compared the results with HIV-1 infected population those who were HAART naïve with patients initiated on HAART (3-6 months). The results revealed a significantly positive correlation of the tested parameters before and after antiretroviral therapy as shown in Table 1 indicating their prognostic value in the management of HIV-1 infected patients on HAART.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HAART –ve (Mean±SD)</th>
<th>HAART +ve (Mean±SD)</th>
<th>Correlation co-efficient (r)</th>
<th>Student t-test (p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (HB) (gm%)</td>
<td>10.6605±1.981</td>
<td>10.8361±2.224</td>
<td>0.904*</td>
<td>0.237</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation Rate (ESR) (mm Hg)</td>
<td>16.369±8.946</td>
<td>13.083±7.262</td>
<td>0.726*</td>
<td>0.0089*</td>
</tr>
</tbody>
</table>

*Statistically significant

Figure 1. Graph depicting Hemoglobin (HB) levels before and after therapy
These results emphasize the interest of peripheral blood constituents as a complement to CD4+ T cell counts and HIV/RNA viral load in the HIV-1 disease and antiretroviral therapy management. It should be noted that measurement of CD4+ T cell counts < 200 cells/mm³ in HIV infected population do not always indicate AIDS condition as revealed from previous report documented in women; thus, alternatives to CD4+ T cell counts may help in evaluating the real condition of the HIV-1 infected patient [12,20]. It has been observed that though WHO guidelines recommend using immunological failure criteria to guide switches in antiretroviral therapy, CD4+ T cell count and clinical response alone lack sufficient sensitivity and specificity as surrogates for virological response. Management of patients on HAART requires drug substitutions to prevent serious anemia or drug (i.e., rifampicin) interactions and competent clinical monitoring is warranted [21,22].

3. HIV, HAART and Markers of Liver Injury

Human Immunodeficiency Virus-1 (HIV-1) infection and its role in the initiation of liver destruction can be attributed to apoptosis, mitochondrial dysfunction either by decreasing mitochondrial DNA in various cells or by alteration in mitochondrial membrane by HIV-1 proteins that in turn stimulate inflammatory response [23,24]. HIV-1 infection results in cytopathic effect on cells carrying CD4 receptors including helper T cells, macrophages of various organs, microglial cells, B-lymphocytes, hematopoietic stem cells, rectal mucosal cells and liver sinusoidal epithelial cells [25]. Hepatomegaly was seen as a common feature in both HIV-1 infected asymptomatic patients and AIDS cases. HAART related drug reactions, hepatotoxicity, dyslipidemia and disturbed metabolism should be considered as host factors that may determine and influence HIV-1 disease progression [26]. A recent study that we performed showed that HIV-1 infections result in liver disease and those patients on HAART must be carefully monitored for possible hepatic destruction by measuring serum GGT, ALT and AST, all non invasive methods which are cost effective and easily performed [27, 28 29 and 30]. Existing literature suggests that in HIV-1 infected and HAART naive patients there was a positive correlation between AST (or ALT) levels and HIV/RNA viral load and that in HIV-1 infected patients without HBV or HCV infection, chronic elevated ALT levels were associated with high HIV-1-RNA levels [27]. The strong and consistent association between higher fibrosis scores at baseline and the risk of liver fibrosis in HIV-1 infected population may be clinically relevant and more proactive interventions may be required in older patients and alcohol abused patients [28]. HIV-1 infected population should also be screened for other hepatotrophic viruses including Hepatitis B virus (HBV) and Hepatitis C Virus (HCV) as co-infection because these viruses may increase the liver injury/damage and thereby accelerate disease progression resulting in severe morbidity and mortality [31,32,33].

4. HIV, HAART and Cardiovascular Complications

Among the conditions that contribute to morbidity in HIV-1 infected population, non-HIV-related cardiovascular risk factors and metabolic disorders resulting from chronic inflammatory response and antiretroviral therapy (insulin resistance, lipodystrophy and hypertension) should be considered as significant. Recent studies have emphasized the significance of HIV-1 infection in coronary heart disease (CHD) and showed that the risk of CHD increases after initiation of HAART. Rise of inflammatory markers including C-reactive protein (CRP) and coagulation markers are associated with increased mortality, and possibly Cardio Vascular Disease (CVD), in HIV-1 infection. Antiretroviral therapy in HIV-1 infected population is attributed to initiate pro atherogenic effects and increased risk of Coronary artery disease (CAD). Initiation of HAART has considerably reduced the mortality in HIV infected individuals and the
patients live long enough similarly to the HIV-1 non-infected group and are at increased risk of acquiring CVD/CAD, although a recent study has noted that there was an improved endothelial function initially after starting HAART [34,35,36]. Management of dyslipidemia and other metabolic disorders in people living with HIV-1 requires awareness of the effects of antiretroviral agents on fatty acid and lipid parameters, effect of co-morbidities including age, sex, race, nutrition and related causes, and interactions between lipid-modifying agents and antiretroviral agents.

5. Significance of Alternate Biomarkers in HIV Disease Monitoring and Treatment Response

From the time when HIV epidemic was prevalent and when the number of people being detected for HIV-1 positivity was on the rise, CD4+ T cell count and HIV/RNA viral load were used to assess their immunological status and infectivity based on virological load. HIV-infected patients were screened for various opportunistic infections depending on the CD4+ T cell counts and clinical examination and prophylactic therapy were initiated where and when necessary [37]. HIV/AIDS, after introduction of HAART, has taken a different course in which people infected with HIV are considerably living longer due to reduced incidence of opportunistic infections and other AIDS-related conditions. HIV-infected individuals are bothered by noninfectious complications that need emergency medical attention and care. Even if HIV-1 disease pathogenesis is complicated, significant research has been done to show that HIV-1 has the ability to disturb the cell metabolism. Oxidative stress and programmed cell death (apoptosis) can result in accumulation of free radicals and in turn be responsible for prolonged inflammatory activity. HAART has worsened the situation by adding adverse drug reactions to already significant HIV-1 disease pathogenesis. From being a life-threatening infection, HIV-1 has now emerged as a chronic infection that can influence most of the human systems. Cardiovascular complications, gastrointestinal infections, hepatic emergencies, pulmonary infections (tuberculosis, cryptococcosis), psychiatric ailments, hematological malignancies/abnormalities, renal and other oncological complications have been on the rise among HIV-infected patients more so after initiation of HAART therapy. Physicians treating HIV-1 seropositive patients should think beyond opportunistic infections and consider other factors including the nutrition, the toxic effects of HAART, the nutrition, age, and other demographic causes. Risk of IRIS after initiation of HAART, which can exacerbate underlying infectious or inflammatory condition, should be considered as a cause of serious concern [38,39,40,41,42].

6. Conclusions and Future Perspectives

From the available literature, it is evident that the HIV-1 disease pathogenesis is complex and that the HIV-1 infection, disease progression, treatment and management of HIV-1 infected population given HAART therapy should be considered based on all factors including the infectious and non-infectious complications. Physicians treating HIV infected patients should consider specific assessment for co-morbidities (physiological, immunological, infectious diseases, lifestyle, alcoholism and smoking, drug use) and other related factors that could influence disease progression. Large scale HIV screening programmes, economically viable strategies and analysis studies of antiretroviral therapy and treatment response, and genotypic resistance testing would be effective in future for making decisions on policies to be initiated for HIV-1 disease management. HIV primary care should include wide range of prevention and treatment programmes including vaccination/prophylactic treatment for Hepatitis A, B, parasitic infestation/infection/fungal infections and others. Currently in India more than 3 lakh HIV seropositive individuals have access to HAART and the number of HIV-1 infected patients put on HAART is on the rise each day through antiretroviral therapy (ART) centers located in peripheral regions [37]. Success in the HIV disease management can only be achieved with improved laboratory diagnosis and effective management strategies of patients on HAART therapy.

7. Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max). Pearson’s correlation co-efficient test is performed to investigate the difference between the sample groups. Analysis of variance (ANOVA) has been used to find the significance of study parameters between different groups of patients. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

References


