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Biomarkers of Diagnostic, Prognostic and Therapeutic Value in HIV-positive Patients: A Review

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Abstract

Despite advancements in treatment, HIV/AIDS remains a global public health challenge, particularly in resource-limited settings. Biomarkers play a crucial role in HIV care by aiding in early diagnosis, predicting disease progression, and guiding therapeutic interventions and as such, this article aim to explore the diagnostic, prognostic, and therapeutic significance of biomarkers in HIV-positive patients. Through a comprehensive examination of existing literature, this review identifies key biomarkers associated with inflammation, immune activation, neurocognitive impairment, and co-infections in HIV-positive individuals. Additionally, it discusses novel biomarkers that hold promise for improving patient outcomes and enhancing HIV management strategies. Through the synthesis of existing evidences, this review aims to provide insights into the evolving field of biomarker-based approaches in HIV care and inform healthcare practitioners, researchers, and policymakers about the potential implications for clinical practice and public health interventions in HIV diagnosis, treatment and management.

Keywords: HIV, AIDS, Biomarkers, Diagnosis, Treatment, Prognostic, Therapeutic

Introduction

AIDS, a condition caused by the transmission of HIV (Human Immunodeficiency Virus), continues to be a major worldwide public health issue [1]. The HIV/AIDS has been effectively mitigated in affluent countries thanks to the collective efforts of Joint United Nations Programme on HIV/AIDS (UNAIDS). However, HIV/AIDS remains a substantial problem in many developing countries that lack sufficient resources, leading to the loss of human life [2]. In the past thirty years, the occurrence of HIV/AIDS has increased dramatically, placing it among the top ten diseases with the greatest worldwide influence [2]. Based on 2017 statistical estimates, approximately 36.9 million people globally now have HIV. In addition, there were 1.8 million new cases of HIV infection and 0.94 million deaths caused by HIV-related diseases [2].

HIV is capable of penetrating the brain, most likely by means of lymphocytes and macrophages generated from monocytes. The penetration of pathogens into the brain tissue causes infection and triggers the activation of macrophages, resulting in ongoing inflammation. Local inflammation plays a substantial role in both untreated patients and maybe in a milder form after successful antiretroviral treatment [3]. The HIV retrovirus can be categorised into two main groups, specifically HIV-1 and HIV-2. The various forms are further classified into several subcategories [1]. The HIV-1 group M is the prevailing and highly contagious variant of the virus, responsible for the widespread AIDS epidemic [1]. HIV targets and inhibits CD4 T-cells, which are crucial

components of the immune system, resulting in the decline of the body's capacity to fight against infections or diseases [1].

Previous research has thoroughly demonstrated a strong association between HIV infection and abnormal immunological activation [4]. HIV-infected patients have heightened levels of biomarkers linked to inflammation, interferon response, T-cell activation, and monocyte and macrophage activation compared to uninfected persons. Persistent elevation of these levels may occur after attaining virologic suppression by antiretroviral therapy (ART) [4]. In addition, the persistent stimulation of the immune system during antiretroviral therapy (ART) to control the virus has been associated with other chronic health problems, including cardiovascular disease, neurocognitive impairment, diabetes, and mortality [4].

Currently, serologic testing algorithms mostly utilise rapid tests in areas with limited resources (RLS) to diagnose HIV infections [5]. Serology-based incidence tests are frequently used to determine the rate of new infections in cross-sectional surveys, along with viral load (VL) evaluation in an algorithm [5]. The innovative rapid incidence assay has generated significant excitement because of its ability to quickly identify locations with a high prevalence of disease when used in programmatic settings [5]. The successful enrolment and retention of patients in antiretroviral therapy (ART) programmes have been considerably influenced by the efficient adoption of straightforward point-of-care (POC) CD4 technologies [5]. These technologies provide patients with test results on the same day. As a result of medical improvements, individuals with HIV/AIDS are living longer, leading to a decrease in death rates [5].

Although, a significant number of people who with HIV/AIDS are currently in a state of stability. Access to HIV/AIDS medication is not uniformly widespread, and the efficacy of medications and vaccines is still uncertain [6]. Medical progress has resulted in increased longevity for individuals with HIV/AIDS, while simultaneously imposing greater obligations and difficulties on families and societies. Furthermore, the weakened immune system produced by HIV/AIDS sometimes leads to the simultaneous presence of other illnesses (such as tuberculosis), and treating these extra diseases might worsen the impact of HIV/AIDS.

The HIV/AIDS epidemic continues to pose significant challenges worldwide, particularly in regions with limited resources. Despite advancements in treatment and prevention, there remains a pressing need for comprehensive approaches to improve the diagnosis, prognosis, and therapeutic management of HIV-positive patients. This review aims to critically examine the role of biomarkers in addressing these challenges and enhancing HIV care. The significance of this review lies in its potential to provide insight into the diagnostic, prognostic, and therapeutic value of biomarkers in HIV care. It achieve this by exploring existing literature and identifying novel biomarkers, this review seeks to contribute to the growing body of knowledge on HIV pathogenesis and treatment outcomes. Moreover, it aims to provide insights into the utility of biomarkers in guiding clinical decision-making and improving patient outcomes.

The review has several objectives, one of which is to evaluate the current landscape of biomarkers used in HIV diagnosis, prognosis, and treatment monitoring. Another one is that it seeks to identify novel biomarkers with potential applications in HIV care. Also, it aims to discuss the clinical significance and practical implications of biomarker-based approaches in HIV management. Lastly, this review strives to inform healthcare practitioners, researchers, and policymakers about

the evolving role of biomarkers in combating the HIV/AIDS epidemic and improving patient care globally.

HIV as a universal burden

The HIV epidemic is characterised by its rapid expansion following the introduction of HIV-1 and later HIV-2 into human populations in the 1920s. Virtually every nation on the planet is affected. According to the 2019 report by the Joint United Nations Programme on HIV/AIDS (UNAIDS), the global population of individuals living with HIV was estimated to be 38 million. Out of the total, 36.2 million individuals were adults, while 1.8 million were children between the ages of 0 and 14. According to Hagengaard et al., there were approximately 1.7 million new cases of HIV/AIDS infection and 690,000 deaths caused by HIV/AIDS-related illnesses [7]. In 2005, the worldwide occurrence of HIV reached its peak, and then decreased over a period of five years. Since 2010, there has been a notable increase in the prevalence of HIV, perhaps due to the increasing effectiveness of antiretroviral medication (ART) in prolonging the survival of individuals with HIV [8]. Presently, the incidence of [particular ailment or issue] is on the rise globally, as well as in countries including South Africa, Portugal, Brazil, Mexico, Peru, Spain, Germany, and the United States. Both the gross and age-standardized rates are rising in these countries, indicating that this surpasses the inherent increase resulting from population growth. According to a study by Romona et al., Portugal experienced a significant rise in the prevalence rate, which increased from 86 to 370 per 100,000 inhabitants between 1990 and 2019 [8]. However, South Africa witnessed a significant surge from 354 to 14,251 per 100,000 during the same period, surpassing the aforementioned comparison by a large margin. Central and southern African countries, namely Lesotho, Mozambique, South Africa, Zimbabwe, and Namibia, have a significantly higher prevalence of HIV/AIDS [8].

HIV incidence rates exhibit a bimodal pattern, with two separate peaks observed in infancy and young adulthood. These peaks represent the instances when the virus is transmitted from a mother to her kid during childbirth, and through sexual contact or the sharing of needles, respectively [8]. The age group that had the highest rate of occurrence, after infancy, was the cohort of individuals aged 20-39 years. According to UNAIDS Data, there are almost 5000 new infections recorded every day, with 500 of these cases specifically impacting children. Adolescent females, specifically those aged 15-24, in sub-Saharan Africa are particularly susceptible to harm. The phenomenon of ageing in individuals who are HIV positive due to improved survival with antiretroviral therapy (ART) was apparent when comparing the prevalence rates between 1990 and 2017 [8]. The median age rose as the age group shifted from 25–30 to 35–40. Globally, females have higher prevalence rates, but males have higher fatality rates. The incidence of new cases is similar among boys and females. This phenomenon is observed in countries such as South Africa and Zimbabwe. However, males in Brazil, Western Europe, and the US have higher rates of prevalence, incidence, and mortality compared to females [8].

The need for quality HIV diagnosis

The diagnosis of HIV-1 infection is based on the detection of specific antibodies, antigens, or a combination of both. There are multiple commercially available tests designed for this purpose.

Serological tests are frequently used for screening purposes. An important advancement has been the increased availability of rapid HIV-1 antibody tests. According to Greenwald et al., these tests are easy to do and provide results within a short time frame of 20 minutes [9]. Assessing the count of CD4+ cells and the viral load is essential for the aim of determining the stage of the condition. Plasma viral load is frequently used to evaluate the efficacy of antiretroviral therapy. Several assays currently on the market provide precise determination of the quantity of HIV-1 RNA copies in the plasma. The latest versions of the Amplicor and Quantiplex assays, created by Roche in Indianapolis, IN, USA, and Bayer Diagnostics in Walpole, MA, USA, respectively, have effectively resolved the initial inadequate performance for non-B subtypes [10]. The viral load determines the rate at which the immune system is damaged, whereas the CD4+ cell count reflects the degree of immunodeficiency and is therefore used to assess the stage of infection. CD4+ cell counts, together with clinical signs such the occurrence of opportunistic infections, are vital criteria utilised to categorise HIV-1 disease. Flow cytometry analysis is the well-established method for measuring the quantity of CD4+ cells [11].

Early identification is essential for efficient control of HIV. Before the implementation of highly active antiretroviral therapy (HAART) in 1996, HIV infection consistently caused a decline in immune function, making individuals vulnerable to opportunistic infections and leading to early death from AIDS. The present conditions have undergone substantial alterations for individuals who have HIV and are receiving Highly Active Antiretroviral Therapy (HAART) [12]. From a medical perspective, individuals who are going through the early stage of HIV infection (PHI) usually have symptoms that are similar to those of influenza. According to Jun et al., there is a direct correlation between higher amounts of viral particles in the bloodstream and more severe and prolonged symptoms [13]. Additionally, without medical intervention, the disease progresses at a faster rate. Commencing antiretroviral medication (ART) at an early stage has been proven to inhibit the reproduction of HIV, hence diminishing the severity of symptoms. HIV viral reservoirs impede the total eradication of HIV, even when antiretroviral therapy (ART) is initiated 10 days after infection. Initiating antiretroviral therapy (ART) at an early stage can contribute to the goal of eradicating HIV by maintaining tiny or undetectable viral reservoirs, while simultaneously reducing immune activation levels [13].

Significance of Biomarkers in HIV care

Biomarkers are highly specific and sensitive biological substances that can be found in physiological fluids such as blood or tissues. They have the ability to signify an atypical or typical procedure, ailment, or state and can furnish data that aids in the identification, prediction, and management of the problem [14]. In order for biomarkers to be valuable in enhancing treatment modalities or obtaining an understanding of a disease, they must possess clinical significance [15]. Prior research has demonstrated a correlation between HIV infection and abnormal immune system activation. HIV-positive individuals exhibit elevated levels of biomarkers associated with inflammation, interferon response, T-cell activation, and monocyte and macrophage activation in comparison to non-infected individuals. It has been observed that certain biomarkers remain elevated even after achieving virologic suppression through antiretroviral therapy (ART) [4]. When quantified, these biomarkers have demonstrated their ability to forecast the progression of the disease in those who are infected, and their concentrations aid in the therapeutic administration of individuals who are HIV-positive.

Considering the blood neurofilament light chain protein (NfL), which is a useful tool for evaluating neuroaxonal damage in the central nervous system without the need for a lumbar puncture, Research by Gisslén et al., has demonstrated a strong correlation between NfL levels in both plasma and cerebrospinal fluid (CSF) samples of HIV patients [16]. This finding has been further supported by the research of Alagaratnam et al. [17] Based on the results of those investigations, Hagberg et al., indicated that blood NfL concentration can be used to track the effects of treatment plans, the progression of the infection, and determine if HIV patients with mild cognitive impairments have active neuronal damage [18].

HIV patients have a higher likelihood of developing cancer due to their reduced immune system, frequent co-infection with cancer-causing viruses, and engagement in risky behaviors such as an unhealthy lifestyle. Nevertheless, the identification and advancement of biomarkers have proven valuable in the screening, diagnosis, prognosis, and treatment of HIV patients who are at risk of getting cancer [14]. One of the most critical biomarkers implicated in cervical cancer are HPV, oncogenes E6 and E7, and Ki-67, among numerous others that are frequently higher in HIV-infected patients [19]. The single biomarker of HIV infection, HIV-1 RNA, facilitated the rapid medication development that turned HIV infection from a deadly illness to a treatable condition [20]. These have reasonably suggested the significance of biomarkers in the care and management of HIV and suggest the necessity for the emergence of new large-scale genomic techniques for the development of novel biomarkers in the studies of HIV infection to better improve treatment and clinical outcomes for patients.

Some Novel Biomarkers in HIV Care

Searching for new biomarkers that could improve patient care and health outcomes is necessary in the vast and significant field of HIV care research. However, it has been established that such biomarkers might be of varied origins, such as those from inflammation and immune activation signals to those linked with viral reservoirs, microbial translocation, and co-infections. More importantly, some of these indicators have been developed to diagnose brain deficits, cardiovascular abnormalities, and metabolic issues in people with HIV. As such, it is crucial to present an in-depth review of such markers, since they hold a promising impact on the management and treatment of patients with HIV.

There are well-documented markers of inflammation linked with HIV infection, such as cytokines including IP-10, interferon-α, IL-6, IL-10, and IL-15 [21]. Lei et al., found that plasma levels of IP-10 are up-regulated following HIV infection and positively correlated with the progression of HIV disease [22]. Keating et al., found that elevated levels of IL-6 are linked to an increased risk of death and are raised in late-stage AIDS but not early in HIV infection [23]. Infected CD4 T cells treated with IFN-α for a brief period of time were shown to significantly inactivate HIV during the early stages of replication [24]. IL-15 increased the survival and proliferation of CCR5+CD4+ T cells isolated from blood and lymphoid tissues. IFN-α was found to limit HIV-1 replication by reducing the formation of late reverse transcriptase products in infected cells. In addition, IL-15 therapy lengthened the lifespan of infected CCR5+CD4+ T cells and enhanced their viral output [25]. HIV-infected patients demonstrate unbalanced immunological abnormalities in distinct cytokine serum levels [26]. Hence, it offers an insight into illness development and therapy possibilities.

CD38 and HLA-DR are further interesting markers of immunological activation in HIV infection since they have been demonstrated to rise with disease progression [27]. A study by Paiardini and Müller-Trutwin, also demonstrated that they are higher on HIV-specific CD8+ T cells when compared with CD8+ T cells specific for other viruses [28]. The measurement of CD38 expression on lymphocytes has become an important technique for monitoring patients during an infection with HIV and has been recommended for use in the follow-up of antiretroviral therapy (ART). CD38 has prognostic significance since it reflects the starting point of the immune response. CD38 is not only an essential prognostic marker but also plays an active role in HIV infection [29]. Human genetic variability, including the HLA-I system, also has a direct impact on virus and immune system interaction. Some HLAs are connected to a slower disease progression to AIDS and elite controllers (EC). These associations can be varied based on the HIV-1 clades and HLAs that are most common in a certain geographic region. HIV and HLA can choose distinct epitopes as immunodominant interactions in a population- or individual-level manner [30].

Inflammation and thrombosis biomarkers are additionally promising biomarkers that may enhance cardiovascular disease (CVD) risk assessment beyond conventional and HIV-specific variables. These biomarkers may also be helpful in assessing CVD prevention tactics for people living with HIV [31]. In HIV infection, increasing rates of CD16+ monocytes and monocyte activation markers, such as sCD14 and sCD, have been reported and linked with disease progression and viral load. The same markers are also connected with the onset of CVD and the advancement of atherosclerosis [32]. In a study conducted by Foster et al., cardiac troponin T (cTnT) was suggested as a biomarker for the presence and size of myocardial plaque in patients with HIV, CKD, or other diseases precluding IV contrast administration [33]. More so, high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and the new cardiac biomarker galectin-3 (Gal-3) were reported to be higher in HIV-infected patients compared with healthy age- and sex-matched persons [34]. Galectin-3 is a potent apoptosis-inducing protein that affects numerous cellular processes and has been hypothesized to potentially contribute to the complete obliteration of HIV-1/SIV-infected macrophages [35]. Understanding the intricate roles of Gal-3 in viral illnesses such as HIV may lead to the development of novel ways for controlling and preventing diverse viral diseases, eventually enhancing patient outcomes and reducing the worldwide burden of viral illnesses [36].

Increases in lipopolysaccharide (LPS) and/or soluble CD14 (sCD14), which indicates LPS-induced monocyte activation, are associated with multiple markers of immune activation in HIV-positive individuals, including type I interferons and activated CD8+ T cells (the latter being one of the strongest predictors of disease progression in HIV infection). Microbial translocation has also been related to lymphoid tissue fibrosis, which may limit CD4+ T cell recovery in patients on antiretroviral medication [37]. These inflammatory biomarkers could provide doctors with additional details on the risk of disease progression, as it was observed by Rodolphe et al., that sCD14 represents a better predictive biomarker of disease progression in HIV-2-infected patients [38]. Additionally, a study by Liu et al., demonstrates that sCD14 is a very accurate biomarker for smear-negative HIV-associated TB [39]. The results imply a role for sCD14 in the early screening or triaging for active TB in HIV-infected persons in order to recognize those individuals who should undergo further TB confirmatory tests. This further demonstrates the relevance of sCD14 measures as a diagnostic biomarker for HIV-associated TB [39]. More so, LPS has been proposed

as a marker of microbial translocation by Vassallo et al., which is associated with chronic immunological activation in HIV-infected patients. Even in effectively treated patients, LPS readings are rarely normal [40]. Several studies suggest a role for LPS as a negative prognostic marker of immunological reconstitution in patients with attenuated CD4 T cell increases. Increased plasma LPS has been found in HIV+ patients with dementia; plasma sCD14, generated by LPS activation in monocytes, is related to neurocognitive impairment in HIV [41]. Plasma, but not CSF sCD14 or sCD163, is a better marker to link with HIV-associated neurocognitive impairment (HAND). A study by Jiang et al., indicated that plasma LPS was directly linked with plasma and CSF levels of serial pro-inflammatory cytokines in all patients and HIV+ subjects, but not in HIV-infected persons [42].

CD2, CD30, and CD32a are yet another key cellular marker of the HIV reservoir that holds promising relevance in the management of persons living with the disease [43]. According to a study by Iglesias-Ussel et al., cells overexpressing CD2 might bind HIV-1 and become infected more rapidly, which might provide a possible target for the eradication of subconsciously infected CD4+ T cells [44]. CD30 was also found by Hogan et al., to be a marker of residual, transcriptionally viable HIV-1-infected cells in the setting of suppressive ART [45]. Given that CD30 is only expressed on a limited number of total mononuclear cells, it is a possible therapeutic target for persistent HIV-1 infection. In addition, infection with other viral infections increases surface CD30 expression on lymphocytes, and higher CD30 expression was actually linked with HIV clinical progression before the onset of ART. Hence, CD30 may be a substitute indication of early replication or viral transcriptional activity before detection by standard peripheral blood sampling [46]. Recently, Descours et al., revealed that CD32a can serve as a marker of latently HIV-infected CD4+ T cells [47]. In that investigation, very little expression of CD32a on bystander cells was observed, and infection frequencies seemed to correspond with the expression of CD32a. These findings have attracted a lot of attention since CD32 (a) might be a possible target for future HIV cure methods [48].

Furthermore, it is significant to note that a number of potential biomarkers for the diagnosis of HIV-HCV/HBV co-infections have been studied, including serum adenosine deaminase activity (ADA), FibroTests, AST-to-Platelet Ratio Index (APRI), Fibrosis-4, HA, and microribonucleic acids (MiR) [49]. Serum ADA was reported to be considerably elevated in HIV-infected patients and has been deemed a valuable diagnostic tool among the other markers in this disease due to its low cost and simplicity to perform [50]. HIV infection promotes the progression of liver fibrosis to a complex disease, making the fibro test a valuable biomarker to identify co-infection in HIV-infected individuals [51]. The diagnostic accuracy of serum HA levels increases steadily with the hepatic fibrosis stage. However, hyaluronic acid (HA) is superior to other simple non-invasive indexes employing parameters easily available in normal clinical practice just for the diagnosis of cirrhosis [52].

Conclusion

In conclusion, this review has provided a comprehensive overview of the diagnostic, prognostic, and therapeutic significance of biomarkers in HIV-positive patients. Despite considerable progress in HIV/AIDS management, the disease continues to impose a significant burden on global health, particularly in resource-constrained settings. Biomarkers serve as invaluable tools in HIV care,

facilitating early diagnosis, predicting disease progression, and guiding therapeutic interventions. Through an extensive examination of existing literature, this review has identified key biomarkers associated with inflammation, immune activation, neurocognitive impairment, and co-infections in HIV-positive individuals. Furthermore, it has highlighted the potential of novel biomarkers to improve patient outcomes and enhance HIV management strategies.

The findings of this review underscore the importance of integrating biomarker-based approaches into clinical practice and public health interventions. Through the use of biomarkers, healthcare practitioners can optimize patient care, tailor treatment regimens, and monitor disease progression more effectively. Moreover, biomarker research holds promise for advancing our understanding of HIV pathogenesis and informing the development of innovative therapeutic interventions. However, several challenges remain in the field of HIV biomarker research, including the need for standardization, validation, and accessibility of biomarker assays, especially in resource-limited settings. Additionally, ongoing efforts are required to identify novel biomarkers and elucidate their clinical significance in HIV care. Lastly, this review emphasizes the significant role of biomarkers in improving the diagnosis, prognosis, and treatment of HIV/AIDS. It is as well important to remind everyone that continued investment in biomarker research and implementation is essential to address the evolving challenges of the HIV epidemic and improve health outcomes for affected individuals worldwide.

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