Impact of HIV Co-infection and Antiretroviral Therapy on Tumor Necrosis Factor-Alpha (TNF-α), Fibrinogen, and Haptoglobin Markers in Hepatitis B and C Subjects

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Abstract

Chronic hepatitis B virus (HBV) infection, when co-occurring with human immunodeficiency virus (HIV), significantly exacerbates liver inflammation and disease progression. This study assessed the impact of HIV co-infection and antiretroviral therapy (ART) on key inflammatory and acute phase markers—tumor necrosis factor-alpha (TNF-α), fibrinogen, and haptoglobin—in HBV-infected individuals.In the first analysis, levels of these biomarkers were compared between HBV/HIV co-infected subjects and healthy controls. The TNF-α level was significantly elevated in co-infected individuals (206.15 ± 21.43 pg/ml) compared to controls (190.15 ± 21.99 pg/ml) with a t-value of 3.769 and a p-value of 0.044, indicating heightened systemic inflammation. Conversely, fibrinogen levels were significantly lower in the co-infected group (8.2 ± 0.69 g/L) than in controls (9.33 ± 4.26 g/L), with a t-value of 3.391 and p-value of 0.037, suggesting altered acute phase protein synthesis. Haptoglobin levels were markedly higher in co-infected subjects (3.05 ± 1.0 g/L) versus controls (1.08 ± 0.09 g/L), with a statistically significant difference ($t = 3.054$; $p = 0.040$). Further analysis explored the effect of ART by comparing untreated HBV/HIV co-infected subjects with those on therapy. TNF-α levels were lower in the treated group (191.10 ± 19.45 pg/ml) compared to the untreated group (206.15 ± 21.43 pg/ml), with a statistically significant p-value of 0.040. Fibrinogen levels declined substantially in those on therapy (3.37 ± 4.15 g/L) versus untreated individuals (8.2 ± 0.69 g/L), showing a significant reduction ($p = 0.030$). Similarly, haptoglobin levels decreased in treated subjects (2.05 ± 0.03 g/L) compared to untreated (3.05 ± 1.0 g/L), with a p-value of 0.040. These findings demonstrate that HBV/HIV co-infection significantly alters inflammatory and acute phase responses, as reflected by elevated TNF-α and haptoglobin levels and reduced fibrinogen. Importantly, antiretroviral therapy appears to mitigate these effects, reducing TNF-α, fibrinogen, and haptoglobin concentrations, though levels remain abnormal relative to healthy controls. This underscores the importance of early HIV diagnosis and initiation of ART in co-infected patients to manage inflammation and reduce the risk of liver-related complications.

Keywords

HIV Co-infection, Antiretroviral Therapy, Inflammatory, Acute Phase Markers, Hepatitis B and C

1. Introduction

Infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) continue to pose serious public health issues, impacting hundreds of millions globally and substantially contributing to global morbidity and mortality rates. Chronic infection with these hepatotropic viruses is a primary contributor to enduring liver damage, resulting in progressive diseases such as fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The burden is especially severe in places with few resources, where screening, vaccination (for HBV), and antiviral treatment are still not very good. This keeps the cycle of transmission and chronic disease progression going. In addition to the direct cytopathic effects of viral replication, the immunological response of the host is a key factor in how the disease develops. The immune system tries to get rid of viral infections by using both innate and adaptive methods, but these responses often cause long-lasting inflammation in the liver. This kind of inflammation is important for getting rid of viruses, but it can also cause damage to liver cells, fibrogenesis, and long-term structural damage. Pro-inflammatory cytokines, chemokines, and immune effector cells play a role in maintaining the fragile equilibrium between viral suppression and unintended tissue damage. The immunopathology of HBV and HCV infections is a dual process: one aspect involves immune-mediated defence against viral persistence, while the other entails increasing inflammatory damage that contributes to the chronic consequences of infection [1].

Tumour necrosis factor-alpha (TNF-α), fibrinogen, and haptoglobin are important players in the coordination of inflammation and acute phase responses. They operate as both indicators and agents of immune action. TNF-α, a pro-inflammatory cytokine mostly generated by activated macrophages and T lymphocytes, is integral to the initiation and amplification of the inflammatory cascade. It encourages immune cells to move to places where there is an infection or injury, makes adhesion molecules work, and makes other cytokines and chemokines work, which connects innate and adaptive immunity. However, too much or too long of TNF-α activity can hurt tissues, cause fibrosis, and cause problems throughout the body. This shows that it can be both a protective and harmful mediator.

Fibrinogen is an acute phase glycoprotein made by the liver that is important for more than only blood clotting and stopping bleeding. It is also important for inflammation. It creates a temporary extracellular matrix that helps wounds heal, encourages the growth of new blood vessels, and makes it easier for white blood cells to stick to and move through the body. High levels of fibrinogen are a sign of systemic inflammation, but they are also linked to a higher risk of thrombosis and problems with blood vessels, especially in those with chronic viral infections and other health problems.

Haptoglobin is another acute phase protein made by liver cells. Its main job is to bind free haemoglobin that is released during haemolysis. This stops oxidative damage and saves iron. In addition to its role as a scavenger, haptoglobin has crucial immunomodulatory effects, such as controlling the activity of macrophages and changing how cytokines respond. During infection and inflammation, its levels rise a lot, which makes it a useful biomarker for systemic inflammatory state and tissue damage.

In addition to their traditional biochemical tasks, these macromolecules are also very important for regulating the immune system, repairing tissue, and protecting the body as a whole. Their dynamic alterations during infection underscore their diagnostic and prognostic significance, especially in cases of HIV, HBV, and HCV co-infections, where sustained immune activation and chronic inflammation facilitate disease advancement [2].

T cells and activated macrophages are the main producers of the powerful pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α). It plays a role in immune cell control, apoptotic cell death induction, and liver acute phase protein synthesis stimulation. Increased hepatic inflammation and the development of liver fibrosis are linked to elevated TNF-α levels, which have been reported in HBV and HCV infections. Chronic overexpression of TNF-α promotes a pro-inflammatory milieu, which damages the liver and may have an impact on the development of hepatocellular carcinoma [3].

The liver produces fibrinogen, a soluble plasma glycoprotein that serves as both an acute phase reactant and a coagulation factor. Cytokines like TNF-α and IL-6 increase its production in response to hepatic inflammation. In viral hepatitis, elevated fibrinogen levels have been linked to the severity of liver illness and are suggestive of systemic inflammation. Furthermore, by mediating the activation of hepatic stellate cells and promoting the deposition of extracellular matrix, fibrinogen may aid in the development of hepatic fibrogenesis [4].

Haptoglobin is an acute phase glycoprotein produced by the liver that is very important for the body's defence systems. Its main job in the body is to bind free haemoglobin that is produced during intravascular haemolysis. This stops oxidative stress, iron loss, and possible kidney damage caused by haemoglobin. Haptoglobin protects tissues from oxidative damage by creating stable haptoglobin–hemoglobin complexes that macrophages quickly remove through the CD163 receptor. It also helps recycle iron and keep the body's metabolism in balance.

Haptoglobin is an acute phase protein that usually rises when there is inflammation, infection, or tissue damage. This is because pro-inflammatory cytokines including interleukin-6 (IL-6) and TNF-α stimulate hepatocytes. In pathological conditions marked by chronic haemolysis or compromised hepatic synthetic function, including severe liver disease, cirrhosis, or fulminant hepatitis, serum haptoglobin levels may paradoxically decline. This dual response pattern renders haptoglobin a valuable, albeit context-dependent, biomarker.

In the context of HBV and HCV infections, haptoglobin possesses considerable diagnostic and prognostic significance. High levels may mean that the liver is still inflamed and the immune system is still active, while low levels may mean that the liver is getting worse or that fibrosis is getting worse. Changes in haptoglobin levels over time can be used to tell how active a disease is, how well treatment is working, and how likely it is to proceed to cirrhosis or hepatocellular carcinoma. Additionally, haptoglobin engages with both the immune system and oxidative stress pathways, serving as a marker of inflammation and a modulator of host–virus interactions. So, keeping an eye on haptoglobin levels in people with HBV/HCV infection, especially those who also have HIV, could give us important information about how the disease works and how well treatments work [5].

Assessing TNF-α, fibrinogen, and haptoglobin levels in patients with HBV and HCV infections provide vital information about the hepatic and systemic inflammatory reactions brought on by these persistent infections. Disease staging, risk assessment, and the tracking of treatment interventions may all benefit from an understanding of the trends and consequences of these biomarkers. In order to provide a better understanding of these markers' significance in viral pathogenesis and the progression of liver disease, this study investigates their expression and clinical relevance in patients with chronic hepatitis B and C [6].

Due to common modes of transmission, co-infection with HIV and viral hepatitis (HBV or HCV) is frequent and can complicate the course of the disease and the effectiveness of treatment. Acute phase reactants like fibrinogen and haptoglobin, as well as inflammatory cytokines like tumor necrosis factor (TNF), are crucial biomarkers for tracking systemic inflammation and immune activation in viral infections [7]. The main goal of this study is to look at the effects of treatment and compare the levels of important inflammatory and acute phase biomarkers—tumor necrosis factor-alpha (TNF-α), fibrinogen, and haptoglobin—among people who have both HBV and HCV and are also infected with HIV. These biomarkers were chosen due to their recognised functions in systemic inflammation, immunological modulation, and hepatic damage, all of which are integral to the pathophysiology of chronic viral infections. TNF-α is an important pro-inflammatory cytokine that activates the immune system and damages liver cells. Fibrinogen is both a

coagulation factor and a sign of inflammation. Haptoglobin shows how well the liver is making new cells, how well it protects against oxidative stress, and how well it responds to an acute phase. Their evaluations collectively yield a more thorough understanding of host–virus interactions and illness advancement.

The prevalence and impact of HBV/HCV and HIV co-illnesses in sub-Saharan Africa are little characterised, despite the region being disproportionately affected by both infections. This knowledge gap exists because there aren't enough modern diagnostic facilities, people aren't reporting cases accurately, and the modes of transmission—especially sexual contact, blood exposure, and vertical transmission—are all mixed up. It is consequently essential to comprehend biomarker dynamics in this high-prevalence context for both epidemiological mapping and clinical therapy.

The assessment of TNF-α, fibrinogen, and haptoglobin levels in individuals co-infected with HBV or HCV and HIV is clinically significant, as early identification and prompt beginning of therapy enhance prognosis. These assessments not only show how active the illness is and how well treatment is working, but they may also assist find people who are more likely to quickly proceed to cirrhosis, liver failure, or hepatocellular carcinoma. By incorporating biomarker profiling into standard care, healthcare professionals can create better monitoring procedures, improve treatment plans, and ultimately get better results for patients in places where these co-infections are most common and resources are limited [8].

This kind of research is especially important in areas where hepatitis B and C viruses are very common because it helps create effective public health policies and get people to understand how important it is for them to know their hepatitis status. Comprehending the dynamics of HBV and HCV infections, especially regarding HIV co-infection, facilitates the identification of susceptible populations that could otherwise stay undiagnosed until the disease progresses significantly. Raising awareness in the community and running focused screening initiatives can help stop the cycle of late presentation, delayed treatment, and bad clinical outcomes.

The results of this study can furnish essential evidence to assist health managers and policymakers in formulating and executing context-specific interventions. By detecting patterns of biomarker changes and their connection with illness development, health planners can better characterise at-risk populations, quantify the burden of co-infection, and anticipate future healthcare needs. Moreover, this information can help make sure that limited resources are used wisely by making sure that high-priority groups have access to the right diagnostic services, antiviral therapy, and ongoing monitoring.

The results of this study can also help create integrated programs that bring together diagnostic, therapeutic, and preventive services into one system. This means increasing hepatitis screening in HIV clinics, getting more people vaccinated against HBV, making it easier for those with HCV to get direct-acting antivirals, and making it easier for people to stick to their antiretroviral therapy. Ultimately, these evidence-based methods help create long-term public health plans that aim to lower the number of cases of viral hepatitis, lessen the complications of the condition, and make life better for people who have it.

2. Materials and Methods

2.1 Study Area

The study was carried out in Imo State University, Owerri, Imo state, Nigeria. Owerri is the capital of Imo State in Nigeria, set in the heart of Igboland. It is also the state's largest city.

2.2 Study Population/Sample Size

The study was conducted in Owerri Imo State of Nigeria, The climate of the study area has two main regimes; dry (November- February) and rainy or wet (March-October) seasons. Rainfall in the study area is between 1800 - 2700 mm and average temperature of 28±2oC. The study area has inhabitants who are predominantly farmers, traders, civil servants, cyclist riders and students. The study was a hospital based type conducted within the period of February, 2023 to July, 2024. The study population included 500 HIV patients on Highly Active Antiretroviral Therapy (HAART) who attended Specialist Hospital Umuguma Owerri during the period of the study.

2.3 Ethical Approval

The study was approved by the Ethical and Research Committees of the Specialist Hospital Owerri used in the study. Informed consent was also obtained from all participating patients. For subjects under 18 years, parental consent was sought and obtained.

2.4 Collection of Blood Samples

Blood samples were collected aseptically by venopuncture, using a 5ml sterile disposable syringe and needle from all the subjects and was then dispensed into a labeled plain dry specimen container. The samples were centrifuged at 3,000pm for 5 minutes after clotting to separate and to obtain the serum. The sera were extracted using a Pasteur pipette and put into appropriate specimen container, and stored at -20^{o}C prior to use.

3. Laboratory Procedures

All reagents were commercially purchased and the manufacturer's standard operational procedure (SOP) was strictly followed.

3.1 Determination of TNF, Fibrinogen and Haptogloblin using ELISA Method

Serum concentrations of TNF, Fibrinogen and Haptogloblin were determined with the ELISA Method

3.2 Statistical Analysis

All data generated in this study was subjected to statistical analysis using SPSS version 23. Mean and standard deviation, student t-test and correlation were determined. The level of significant will be taken at $p<0.05$.

4. Results

According to table 1, it is shown that the mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis B subjects co-infected with HIV and Control.

Table 1. The mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis B subjects co-infected with HIV and Control

Parameters	HBV/HIV	Control	t-value	p-value
TNF (pg/ml)	206.15±21.43	190.15±21.99	3.769	0.044
Fibrinogen (g/L)	8.2 ± 0.69	9.33 ± 4.26	3.391	0.037
Haptoglobin (g/L)	3.05±1.0	1.08±0.09	3.054	0.040

According to Table 2, it is shown that the mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis B subjects co-infected with HIV and HBV coinfected HIV.

Table 2. The mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis B subjects co-infected with HIV and HBV coinfected HIV

Parameters	HBV/HIV	HBV/HIV on T	Control	p-value
TNF (pg/ml)	206.15±21.43	191.10±19.45	3.421	0.040
Fibrinogen (g/L)	8.2 ± 0.69	3.37 ± 4.15	3.830	0.030
Haptoglobin (g/L)	3.05±1.0	2.05±0.03	2.561	0.040

According to Table 3, it was shown that the mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis C subjects co-infected with HIV and control.

Table 3. The mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis C subjects co-infected with HIV and control

Parameters	HBV/HIV	Control	t-value	p-value
TNF (pg/ml)	209.84±20.65	190.15±21.99	4.122	0.034
Fibrinogen (g/L)	8.2 ± 0.69	9.33 ± 4.26	4.052	0.037
Haptoglobin (g/L)	3.05±1.0	1.08±0.09	5.412	0.040

According to Table 4, it was display with the mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis C subjects co-infected with HIV and HCV/HIV on therapy.

Table 4. The mean standard deviation of the levels of TNF, Fibrinogen and Haptogloblin in hepatitis C subjects co-infected with HIV and HCV/HIV on therapy

Parameters	HBV/HIV	HBV/HIV on T	t-value	p-value
TNF (pg/ml)	209.84±20.65	193.86±14.91	5.011	0.030
Fibrinogen (g/L)	8.2 ± 0.69	3.37 ± 4.15	4.53	0.030
Haptoglobin (g/L)	3.05±1.0	2.05±0.03	3.01	0.040

5. Discussion

The findings suggest that HIV co-infection with HBV or HCV leads to increased systemic inflammation, as reflected by elevated TNF and haptoglobin levels. The paradoxical reduction in fibrinogen among co-infected individuals may reflect hepatic synthetic dysfunction or consumption due to ongoing inflammation [9]. Antiretroviral therapy (ART) considerably diminished the overall inflammatory burden in co-infected patients, illustrating its efficacy in inhibiting viral replication and mitigating immune system hyperactivation. Nevertheless, despite this significant enhancement, biomarker levels—such as pro-inflammatory cytokines and acute phase reactants—did not completely revert to the baseline values seen in uninfected individuals. This partial normalisation indicates that ART, although essential for disease treatment, fails to fully rectify the chronic immunological dysregulation caused by prolonged viral infections. Ongoing immune activation, even with appropriate treatment, may lead to continued liver damage, faster fibrosis, and a higher chance of getting other diseases that aren't AIDS, like heart disease and metabolic disorders. These results underscore the necessity for supplementary therapy approaches specifically designed to directly address persistent

inflammation and immunological activation, alongside rigorous compliance with ART, to attain more holistic clinical outcomes [10].

In contrast to healthy controls, this study examined the levels of fibrinogen, haptoglobin, and tumor necrosis factor-alpha (TNF-α) in patients with chronic hepatitis B and C co-infection with HIV, both with and without antiretroviral therapy (ART). The results shed crucial light on the immunoinflammatory terrain of viral co-infections as well as how ART modifies hepatic stress and systemic inflammation [11].

TNF-α levels were considerably higher in patients co-infected with HIV than in uninfected controls in both hepatitis B (HBV) and hepatitis C (HCV) cohorts. Compared to controls (190.15 ± 21.99 pg/ml, $p = 0.044$), TNF-α was considerably greater in HBV/HIV patients (206.15 ± 21.43 pg/ml), and the same pattern was seen in HCV/HIV patients (209.84 ± 20.65 pg/ml vs. 190.15 ± 21.99 pg/ml, $p = 0.034$). The sustained pro-inflammatory state in HIV co-infected patients is highlighted by these higher TNF-α levels, which are probably caused by immunological activation brought on by both viral replication and immune dysregulation. TNF-α is a key player in liver fibrosis and inflammation, and its upregulation in co-infected people indicates a higher risk of hepatic damage and a quicker course of the disease [12].

It's interesting to note that co-infected participants had lower fibrinogen levels than controls, albeit still within high ranges. The mean fibrinogen concentration was 8.2 ± 0.69 g/L in the HBV/HIV and HCV/HIV groups, while it was 9.33 ± 4.26 g/L in healthy persons. Despite its apparent contradiction, this probably illustrates the intricate dynamics of fibrinogen synthesis in liver failure and chronic inflammation. Fibrinogen is an acute phase reactant, but because of reduced hepatic synthesis, its levels might decrease in the context of chronic liver illness, indicating growing hepatic impairment in individuals who are co-infected [13].

On the other hand, all HIV co-infected groups had significantly higher haptoglobin levels than controls (HBV/HIV: 3.05 ± 1.0 g/L vs. 1.08 ± 0.09 g/L, $p = 0.040$; HCV/HIV: 3.05 ± 1.0 g/L vs. 1.08 ± 0.09 g/L, $p = 0.040$). Elevated haptoglobin levels, an acute phase protein, are indicative of persistent systemic inflammation and potentially subclinical hemolysis or oxidative stress, both of which are prevalent in HIV infection [14].

It was clear how antiretroviral therapy (ART) affected these indicators. TNF-α, fibrinogen, and haptoglobin levels were consistently lower in HBV/HIV and HCV/HIV patients receiving ART than in those not receiving treatment. For example, TNF-α decreased in HBV/HIV patients receiving therapy from 206.15 ± 21.43 pg/ml to 191.10 ± 19.45 pg/ml ($p = 0.040$) and in HCV/HIV patients receiving therapy from 209.84 ± 20.65 pg/ml to 193.86 ± 14.91 pg/ml ($p = 0.030$). Even more sharply, fibrinogen levels decreased, indicating that ART may be able to effectively reduce the systemic inflammatory response. Although less noticeable, the statistically significant decrease in haptoglobin levels nevertheless demonstrates the anti-inflammatory effect of ART.

When combined, these results imply that HIV co-infection considerably worsens inflammation and interferes with acute phase protein production in patients with HBV and HCV. Relatively lower fibrinogen and elevated TNF-α and haptoglobin levels suggest continued immunological activation and potential hepatic impairment. These indicators are significantly mitigated by ART, underscoring its critical function in lowering inflammation and possibly delaying the onset of liver disease in co-infected people [15].

For those who have both HBV/HCV and HIV, keeping an eye on inflammatory and acute phase indicators including tumour necrosis factor-alpha (TNF-α), fibrinogen, and haptoglobin can give you useful information about how the disease is becoming worse and how well treatments are working. Increased levels of these biomarkers frequently indicate persistent systemic inflammation, immunological dysregulation, and hepatic damage, which are critical factors influencing morbidity in this demographic. Regular evaluation of these markers can assist doctors in customising individualised treatment plans, assessing responses to antiretroviral therapy (ART), and identifying early indicators of liver decompensation or treatment failure. Moreover, in these high-risk populations, the prompt commencement of antiretroviral therapy (ART) and sustained adherence are crucial in diminishing immunological activation, curtailing viral replication, and maintaining liver function. Controlling systemic inflammation well lowers the incidence of opportunistic infections and slows the advancement of fibrosis and the development of hepatocellular carcinoma in people with chronic HBV/HCV infection. Therefore, integrating biomarker monitoring into standard clinical practice may improve patient outcomes, refine therapy strategies, and facilitate a more proactive approach to long-term management in HIV-viral hepatitis co-infection [16].

6. Conclusion

HIV co-infection in hepatitis B and C patients is associated with significant alterations in TNF, fibrinogen, and haptoglobin levels, suggesting heightened inflammatory responses. While therapy reduces these markers, their persistently abnormal levels highlight the need for ongoing monitoring and possibly adjunctive anti-inflammatory strategies. These biomarkers may serve as valuable tools in the management and prognosis of co-infected individuals.

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