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ORIGINAL RESEARCH

Changes in liver function test levels in HIV patients undergoing highly active antiretroviral therapy (HAART). Longitudinal study in Lima, Peru

Cambios en los valores de las pruebas de función hepática en pacientes con VIH en terapia antirretroviral de gran actividad (TARGA). Estudio longitudinal en Lima, Perú

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Abstract

Introduction: Estimating and monitoring changes in liver function tests is necessary to prevent the occurrence of chronic liver disease in HIV patients undergoing highly active antiretroviral therapy (HAART).
Objective: To determine the variation liver profile test levels in HIV patients undergoing HAART.
Materials and methods: Retrospective longitudinal study conducted in 100 HIV patients treated at the Hospital Nacional Hipólito Unanue, Lima, Peru, between 2015 and 2017. Patients in all stages of clinical infection under HAART and with liver function panel results for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total protein (TP) were included. Three follow-up liver function tests (every 3 months) were performed while undergoing HAART and participants were categorized as having normal or elevated levels for all liver markers. Differences between the samples analyzed were determined using the paired-samples T test, with a 95% confidence interval and a significance level of $p<0.05$.
Results: Participants' mean age was 33±9.56 years and 67% were male. Mean serum AST, ALT and ALP values decreased between the first and the third measurement ($p=0.021$, $p=0.076$ and $p=0.002$, respectively). No significant differences in GGT and TP levels were observed between the three measurements, nor between patients with normal and elevated AST, ALT, ALP and TP values, but significant differences were observed for GGT ($p=0.010$).
Conclusions: Variations in liver marker levels were observed in all participants, with a decreasing trend in AST, ALT and ALP between the early and late stages of HAART, implying that this therapy could play a role in liver tissue damage.

Resumen

Introducción. Para prevenir el desarrollo de enfermedad hepática crónica en pacientes con VIH, durante la terapia antirretroviral de gran actividad (TARGA) se deben estimar y monitorear cambios en el perfil hepático.
Objetivo. Determinar la variación de las concentraciones del perfil hepático en pacientes con VIH durante la TARGA.
Materiales y métodos. Estudio retrospectivo longitudinal realizado en 100 pacientes con VIH atendidos en el Hospital Nacional Hipólito Unanue, Lima, Perú, entre 2015 y 2017. Se incluyeron pacientes en todos los estadios de infección clínica que estuvieran recibiendo TARGA y en los que se contara con resultados del perfil hepático para alanina aminotransferasa (ALT), aspartato aminotransferasa (AST), fosfatasa alcalina (FA), gammaglutamiltranspeptidasa (GGT) y proteínas totales (PT). Se realizaron tres análisis de control de la función hepática durante la TARGA (1 cada 3 meses) y los participantes se agruparon en niveles normales y elevados para todos los marcadores hepáticos. Las diferencias entre las muestras analizadas fueron determinadas mediante la prueba t-Student para muestras relacionadas, con un intervalo de confianza de 95% y un nivel de significancia de $p<0.05$.
Resultados. La edad promedio fue de 33±9.56 años y el 67% fueron varones. Los valores séricos promedio de AST, ALT y FA disminuyeron entre la primera y la tercera medición ($p=0.021$, $p=0.076$ y $p=0.002$, respectivamente). No se observaron diferencias significativas en los niveles de GGT y PT entre las tres mediciones, ni entre los pacientes con valores normales y elevados para AST, ALT, FA y PT, pero sí para GGT ($p=0.010$).
Conclusiones. Se observaron variaciones en los niveles de los marcadores hepáticos de todos los participantes, con una tendencia a la reducción en AST, ALT y FA entre las etapas iniciales y finales de la terapia, lo que implica que la TARGA podría ejercer un rol en el daño tisular hepático.

Introduction

Throughout history, a variety of diseases have affected the integrity and development of communities by causing high rates of morbidity and mortality. Even though environmental conditions have improved, there are emerging and re-emerging diseases that generate a high economic impact due to the disease burden they cause.

Some of the diseases that have had the greatest impact on public health around the world are leprosy (caused by *Mycobacterium leprae*), Black Death (caused by *Yersinia pestis*), acquired immunodeficiency syndrome (AIDS, caused by the human immunodeficiency virus (HIV)) and, more recently, coronavirus disease 2019 (COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)).[1,2]

HIV is a retrovirus with two subtypes: HIV-1, which is the most common and is found worldwide, and HIV-2, which is mostly found in West Africa.[3] It is considered a global pandemic due to its high incidence rates and major threat to global public health since, as reported by Pandey & Galvani,[1] almost 36 million people were living with this virus in 2019, and it had also caused around 39 million deaths by that time.

Given that it causes generalized immunosuppression, HIV infection can favor co-infection with other microorganisms such as *Mycobacterium tuberculosis, Candida* sp, *Aspergillus* sp, among others; have a greater impact on population groups with comorbidities or debilitating diseases such as cancer, diabetes, cardiovascular diseases, and others; and cause resistance to antiretrovirals.[4] These complications are linked to a number of factors including drug adherence, poor social and health care, migration, limitations in HIV/AIDS prevention and control programs, access to highly active antiretroviral treatment (HAART), etc.[4-7]

According to UNAIDS Data 2018,[8] in Central Europe and North America, among 2.1 million [1.9-2.4 million] people living with HIV at the end of 2016, 85% [65->95%] were aware of their HIV status, and approximately 1.6 million [1.4-1.7 million] of them had access to antiretroviral therapy and 65% achieved viral suppression. In the case of Eastern Europe and Central Asia, UNAIDS reported that of 1.4 million [1.3-1.6 million] people living with HIV at the end of 2017, 73% [59-83%] were aware that they had HIV, and about 520 000 million [458 000-541 000 million] of them had access to antiretroviral therapy and 26% achieved viral suppression. In addition, according to the same report, in Asia and the Pacific, also at the end of 2017, of the 5.2 million [4.1-6.7 million] people living with HIV, 74% [52->95%] were aware of their condition, and nearly 2.7 million [2.4-2.9 million] of them had access to antiretroviral therapy and 45% achieved viral suppression.

Regarding Central and East Africa, UNAIDS[8] reported that, at the end of 2017, of the 6.1 million [4.4-8.1 million] people living with HIV, 48% [31-66%] were aware of their disease, and about 2.4 million [2.1-2.5 million] had access to antiretroviral therapy, with 29% achieving viral suppression. Concerning South and West Africa, it was reported that, also at the end of 2017, of the 19.6 million [17.5-22.0 million] people living with HIV, 81% [64-95%] were aware of their HIV status, and about 12.9 million [11.4-13.4 million] of them had access to antiretroviral therapy and 52% achieved viral suppression.

Finally, the UNAIDS[8] report indicated that in Latin America, at the end of 2017, of the 1.8 million [1.5-2.3 million] people with HIV, 77% [54->95%] were aware that they had the disease and that about 1.1 million [992 000-1 200 000] of them had access to antiretroviral therapy and 52% achieved viral suppression. Regarding the Caribbean, of the 310 000 [260 000-420 000] people with HIV, 73% [53-95%] were aware that they had this

virus, and approximately 181 000 [159 000-188 000] of them had access to antiretroviral therapy and 40% achieved viral suppression.

The impact of HIV has led to the introduction of a chronic care model for its treatment, which addresses broader health needs, particularly those related to non-communicable diseases and mental or substance use disorders.[9]

Several studies have found that liver disease in HIV-positive patients may be caused by the virus itself,[10-12] antiretroviral therapy,[13] or the presence of comorbidities.[14] Changes in liver function in patients with HIV undergoing HAART are monitored by means of the liver profile panels and constant clinical surveillance.[15]

In Peru, despite the fact that in 2018 the Ministry of Health estimated that 72 000 people were living with HIV[16] and that the National Program of Highly Active Antiretroviral Therapy (HAART Program) for the management of this infection began on May 13, 2004,[17] reports on liver marker levels and their fluctuations in HIV-positive patients treated with this therapy are scarce. Consequently, the objective of this study was to determine the variation in liver profile test values in patients with HIV undergoing HAART.

Materials and methods

Study design and population, and sample

Retrospective longitudinal study. The study population consisted of HIV patients admitted between January 2015 and December 2017 to the HIV Prevention and Control Program of the Hospital Nacional Hipólito Unaune (HNHU) in Lima, Peru (N=364). The HNHU is a secondary healthcare center that belongs to the Ministry of Health (MINSA) and serves an average of 40 000 patients per year, the majority of whom have infectious diseases such as tuberculosis and AIDS.[18]

Only patients over the age of 18 who had complete liver function tests in their HIV follow-up, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total proteins (PT); were at any stage of clinical infection; and were receiving HAART were considered for inclusion. Individuals who had interrupted or abandoned therapy, had incomplete liver function test results and/or were diagnosed with other concomitant conditions (diabetes, cancer, cardiovascular diseases, etc.) or infections (tuberculosis, aspergillosis, candidiasis, etc.) were excluded. Considering the foregoing, the final sample consisted of 100 patients.

Blood tests and data collection

Blood samples were obtained by venipuncture according to participants' care schedules and following the procedures for collecting blood samples for diagnosis by venipuncture.[19] Liver function tests were carried out at the HNHU's Biochemistry department utilizing an automated ARCHITECT C800 equipment (Abbot diagnostics, Illinois, US), the same manufacturer's reagents, and the colorimetry.[20] Blood testing procedures involved daily quality controls conducted in accordance with current international standards.[21] Samples were processed in accordance with the procedures outlined in the HNHU Standard Operating Procedures Manual.

Three follow-up liver function tests were performed during HAART (one every three months), and participants were categorized as having normal or elevated levels (above

the upper limit) for all liver markers (AST, ALT, FA, GGT, and PT). The liver profile data of the patients were obtained from the hospital's Integrated Health Data Management System (SIGOS by its acronym in Spanish) and, following verification, were coded according to the control analysis number for each of the liver function markers.

Statistical analysis

Descriptive analysis of the data was performed using means and standard deviations for quantitative variables, and frequencies and percentages for categorical variables. Data normality was assessed with the Kolmogorov–Smirnov test after estimating absolute values in each study year. Differences between the samples analyzed were estimated with the t-Student test for related samples with a confidence interval (CI) of 95% and a significance level of $p<0.05$. All statistical analyzes were performed in SPSS v22.0 (IBM, Armonk, USA) for Google Chrome.

Ethical considerations

The study, which was approved by the HNHU Ethics Committee in accordance with Minutes No. HNHU-2020-1-024 of February 28, 2020, took into account the ethical principles for medical research involving human subjects established by the Declaration of Helsinki.[22]

Results

The mean age of participants was 33±9.56 years (95%CI: 31.1-34.9), with a range of 19 to 60 years. The most common age groups were 18-30 years (n=45) and 31-40 years (n=39). Moreover, 67% were male.

The mean concentration ranges were as follows: AST: 6.5-388.4 U/L; ALT: 4.8-320.7 U/L; ALP: 63.3-5239.8 U/L; GGT: 8.2-2062.4 U/L; and PT: 2.9-20.8 gr/dL. (Figure 1).

GGT, AST, ALP, PT, and ALT were normal in all measurements in more than 44%, 51%, 52%, 57%, and 70% of patients, respectively (Figure 2).

There were no significant differences between patients with normal and elevated values ($p>0.05$) for AST, ALT, ALP, and PT markers. In the case of GGT, 56% of participants had elevated levels in the first measurement, while 50% and 46% had elevated levels in the second and third measurements, respectively, with a significant difference between the first and third measurements ($p=0.010$).

On the other hand, changes in mean AST levels were found in all measurements, with a downward trend between the first and third, and a statistically significant difference ($p=0.021$). Concerning ALT, there was also a reduction in concentration levels between the first and third measurements, although the difference was not statistically significant ($p=0.076$). Figure 3 depicts the changes in the mean concentrations of these two transaminases. It should be noted that, while there was a decline in the third measurement, it was not significant, and so no significant changes between the two markers were identified ($p=0.304$).

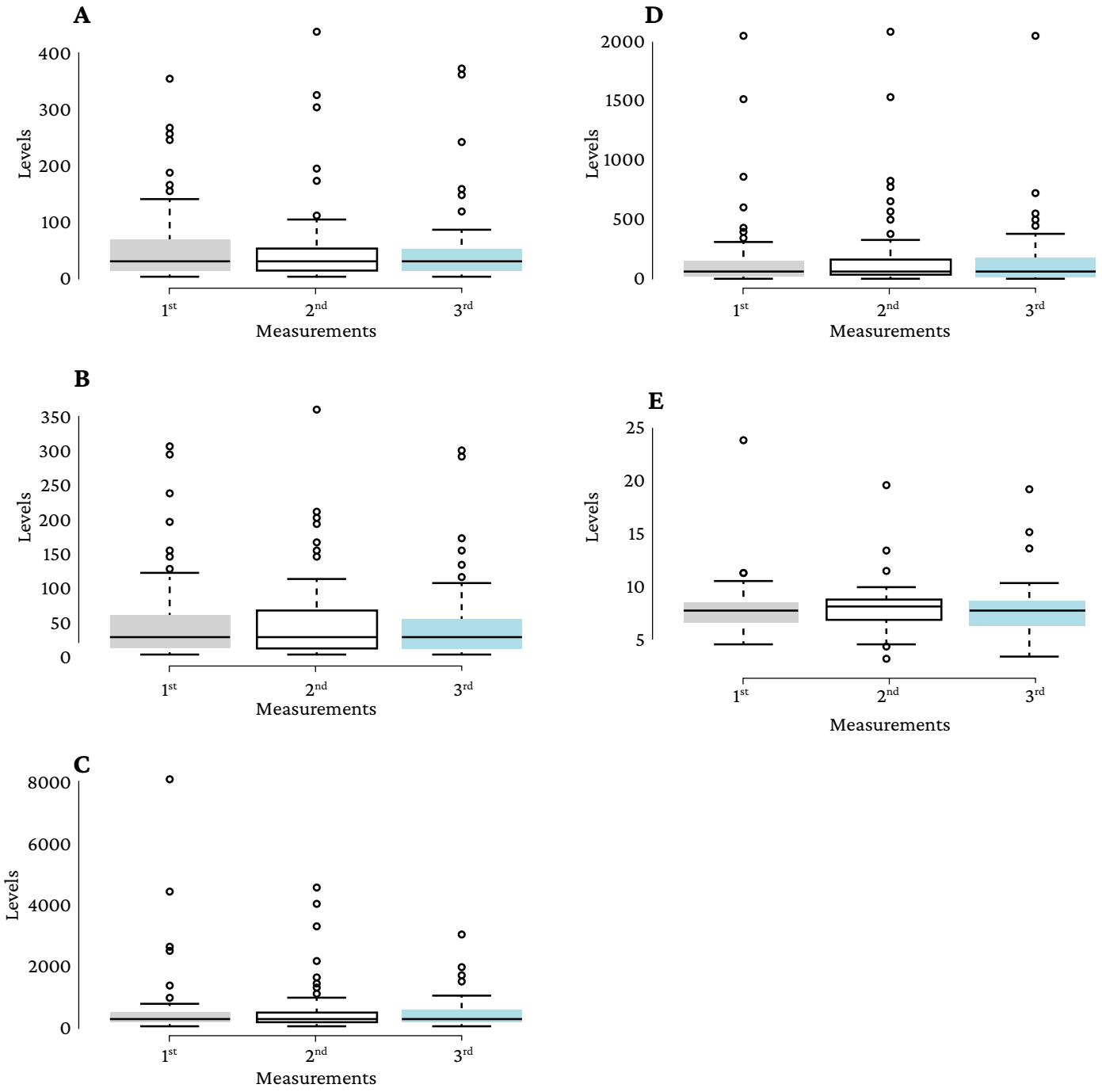

Figure 1. Distribution of liver function marker concentrations in the three blood tests of the participants. A) aspartate aminotransferase (U/L); B) alanine aminotransferase (U/L); C) alkaline phosphatase (U/L); D) gamma-glutamyl transferase (U/L); E) total proteins (gr/dl).
Source: Own elaboration.

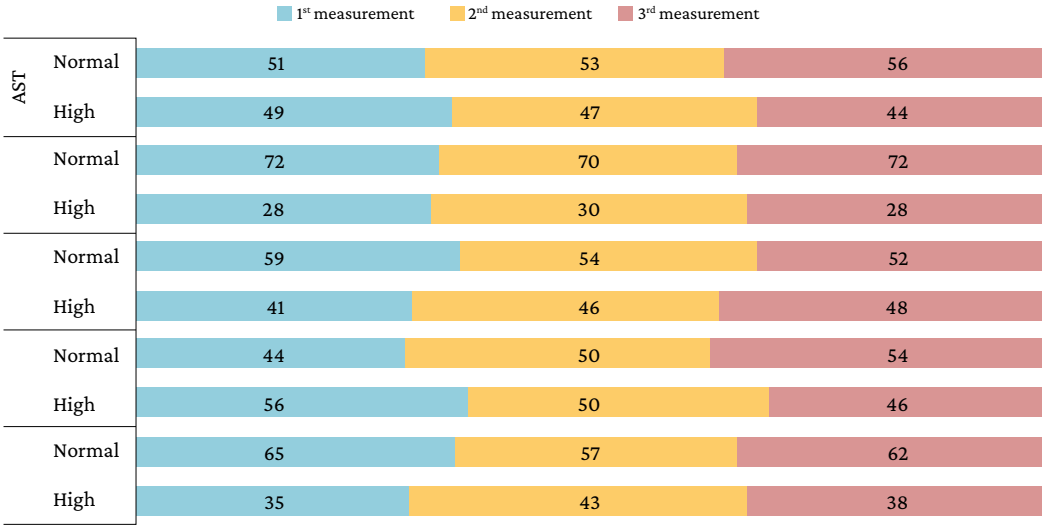

Figure 2. Distribution of normal and elevated liver marker test results in the three blood tests in the study population (n=100).
Source: Own elaboration.

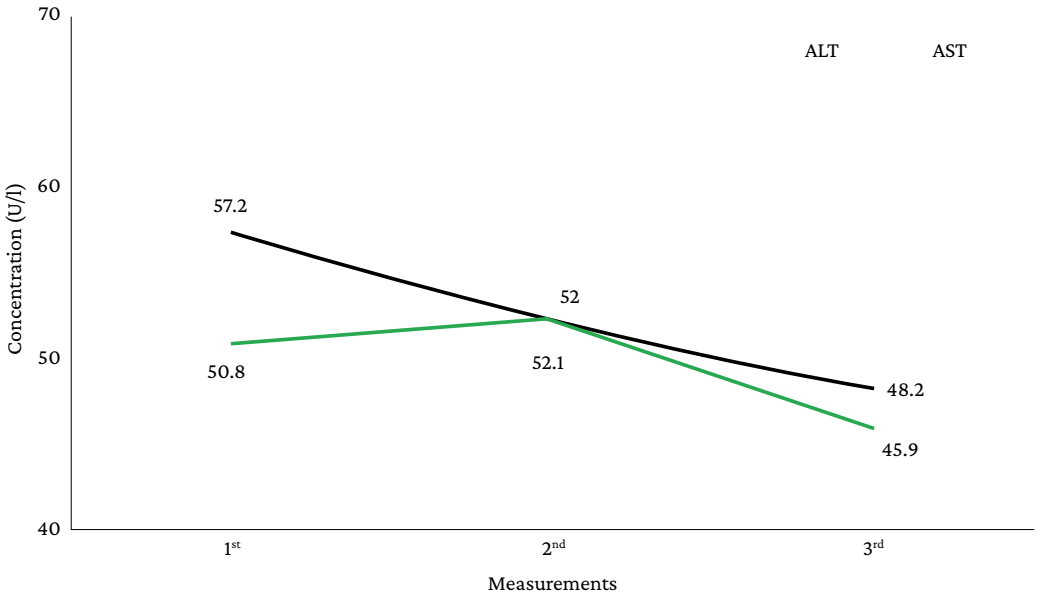

Figure 3. Variations in mean aspartate aminotransferase and alanine aminotransferase concentrations.
Source: Own elaboration.

On the other hand, the mean levels of ALP dropped between the first and third measurements, with the difference being statistically significant (p=0.002), whereas GGT and PT did not show significant differences between the three measurements despite the fluctuations observed (p>0.05) (Table 1).

Table 1. Liver marker concentrations in HIV-positive patients with active HAART according to serological control.

Biological magnitude	Measurements			*p-value*
	1st X̄±SD	2nd X̄±SD	3rd X̄±SD	
Aspartate aminotransferase (U/L)	57.2±61.9	52±63.2	48.2±58	0.021
Alanine aminotransferase (U/L)	50.8±55.3	52.1±53.9	45.8±48.8	0.076
Alkaline phosphatase (U/L)	525.8±951.3	511.4±709	455.4±495	0.002
Gamma-glutamyl transferase (U/L)	138.2±273.2	158.7±284.2	139.6±231	0.088
Total protein (g/dL)	7.4±2.2	7.6±1.9	7.4±2.15	0.074

X̄: mean; SD: standard deviation.
Source: Own elaboration.

When assessing the proportion of patients with increased or decreased liver marker levels, AST and ALT were found to be 50% lower in all three measurements, with no significant differences between measurements or between both markers (p>0.05). The remaining markers had similar concentrations (Table 2) and remained invariable at ≤10% in all concentrations.

Table 2. Variations of liver markers in the study population.

Biological magnitude	Measurements *	Variation			*p-value*
		Went down	Normal	Went up	
Aspartate aminotransferase	D (2nd-1st)	50	5	45	0.083
	D(3rd-2nd)	50	0	50	
Alanine aminotransferase	D (2nd-1st)	48	4	48	0.062
	D(3rd-2nd)	46	1	53	
Alkaline phosphatase	D (2nd-1st)	44	6	50	0.107
	D(3rd-2nd)	47	0	53	
Gamma-glutamyl transferase	D (2nd-1st)	58	7	35	0.091
	D(3rd-2nd)	62	0	38	
Total proteins	D (2nd-1st)	52	10	38	0.082
	D(3rd-2nd)	44	4	52	

D: difference.
* Estimation of the difference between the second and first measurements, and between the third and first measurements.
Source: Own elaboration.

Discussion

The present study found that during HAART, the analyzed HIV patients did not have differences in their PT and GGT levels in the three measurements made, contrary to what happened with the liver markers ALT, AST, and ALP, whose levels tended to decrease between the first and third measurements.

According to previous studies, liver function abnormalities in blood tests are evident in 20% to 93% of HIV-positive or AIDS patients.[12,23] In fact, Palella *et al.*,[24] in a cohort study of HIV outpatients who received HAART between January 1996 and December 2004, found that liver disease was the only reported cause of death for which absolute rates increased over time, though not significantly, from 0.09/100 person-years in 1996 to 0.16/100 person-years in 2004 (p=0.10). Thus, there is a clear need for adequate follow-up of liver markers in patients with HIV, since complications could arise, and the immunocompromised status of these individuals could worsen without proper monitoring.

Furthermore, it has been established that risk factors for liver damage may be increased in these patients because they undergo extensive treatments (resulting in decreased drug adherence), are more vulnerable to co-infections, and face the disease with the possibility of first-line treatment resistance.[25-27]

The presence of cardiovascular, renal or hepatic diseases significantly increases morbidity and mortality in patients with HIV.[28,29] Pathania *et al.*,[12] in a study of 247 HIV patients treated at an antiretroviral therapy center in Pune, India, found that there was a significant increase in ALT levels between the group of participants with normal liver function tests (n=119) and the group with abnormal liver function tests (n=128) (36.454±29.460 vs. 46.273±44.203; p=0.0401), but this increase was not significant for AST (40.311±34.294 vs. 48.711±52.265; p=0.134).

In turn, the study by Iddi *et al.*,[30] conducted in July 2017 on blood samples from 230 HIV patients from different regions of Lake Victoria, Tanzania, demonstrated that 26.09% and 23.9% of participants had elevated AST and ALT levels, respectively, with AST levels significantly higher among patients with high HIV viral load (p=0.002), while ALT was significantly higher among those co-infected with hepatitis C virus (HCV) (p=0.017) and hepatitis B virus (p<0.001). These results are consistent with those of the present study.

Other studies have described that variations in ALT levels may behave as predictors of liver disease in HIV patients whether or not they are receiving HAART.[31-33] These variations can be extrapolated to the Peruvian population due to the presence of numerous risk factors in the country, such as high alcohol consumption and the high prevalence of hepatitis and fatty liver, demonstrating the importance of considering ALT as a useful marker for the identification of hepatotoxicity and liver fibrosis in HIV-positive patients.[34,35]

It is clear that patients treated with HAART have elevations in liver marker levels due to tissue damage. However, these increases are greater in patients with risk factors such as HCV[10,36] and alcoholism,[13,37] and even in patients with any recent infection. In this regard, in a study carried out in 59 Mexican patients diagnosed with HIV and without previous treatment, Mata-Marin *et al.*[38] found that there was a moderately strong positive correlation between serum AST levels (37.73±29.94 U/L) and HIV viral load (r=0.439, p<0.001), and a weak correlation between serum ALT levels (43.34±42.41 U/L) and HIV viral load (r=0.276, p=0.034).

Changes in enzyme values therefore depend on the population evaluated and the risk factors present. In the African population, for example, O'Hara *et al.*[39] found that infection was associated with a lower proportion of liver disease and transiently elevated liver enzyme concentrations, whereas, in the Mexican population, Mata-Marin *et al.*[38] found that liver enzyme levels increase depending on the viral load. Thus, to establish the risk factors for the development of liver damage in the Peruvian population with HIV, longitudinal studies are necessary in cohorts of HIV-positive patients receiving HAART.

Unlike other studies,[10-14,30,36-38] the results reported here demonstrated a reduction in ALT levels between the first and third measurements (50.8±55.3 U/L vs. 45.8±48.8 U/L). This also differs from the findings by Mgogwe *et al.*,[40] who, in a study in Tanga, Tanzania, with 107 HIV-positive patients aged 18 to 65 years on first-line antiretroviral therapy, reported an increase in ALT levels over 6 months (40.27 vs. 47.42 U/L). The reduction observed in the present study could be attributed to a variety of factors, including the HAART scheme and its duration in participants based on their liver marker levels (normal and elevated); the use of other drugs with hepatotoxicity potential; viral coinfections; and the state of the immune system.[11,14,28]

The limitations of this study include that variations in serum levels of liver markers were not differentiated based on antiviral treatment regimens, that enzyme changes

were not assessed in conjunction with other drug treatments that HIV-positive patients may have been taking during the study period, and that no correlations were established between the patients' immune system status and the serum values of liver markers, which would have allowed significant differences to be found. Given these limitations, additional research is required to supplement the findings presented here.

Conclusions

Variations in liver marker levels were observed in all participants, with a downward trend in AST, ALAT, and ALP levels between the initial and final stages of treatment, implying that HAART may play a role in liver tissue damage. Therefore, biochemical monitoring of HIV patients during this therapy is necessary to avoid complications associated with adverse reactions.

Conflicts of interest

None stated by the authors.

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