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Early drug-induced hepatotoxicity in newly diagnosed HIV-positive patients on ARV therapy: A retrospective follow-up study of liver function profiles

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ABSTRACT

Antiretroviral therapy (ART) is a primary therapeutic modality for managing individuals with Human Immunodeficiency Virus (HIV) infection, and its efficacy has been established. However, the safety profiles of ART need to be continually monitored, including early elevated liver function test (LFT) after antiretroviral (ARV) initiation. This study aimed to assess the incidence of abnormal LFT among HIV-positive patients receiving initial ARV and to identify factors associated with abnormal LFT. A retrospective cohort study without a control group summarised medical records from Dr Sardjito General Hospital, Yogyakarta between January 2014 and December 2021. The study subjects were adult HIV patients taking their first ARV and underwent follow-up visits for at least two weeks. Study outcomes were LFT levels, abnormal LFT, and factors associated with abnormal LFT during follow-up visits at 2 wk, 6 mo, and 12 mo. Univariate and multivariate analyses will be performed with a significance level of $p<0.05$. A total of 137 subjects with 203 visits were retrieved from medical records. The subjects' mean age was 33.4 years, predominantly male, younger, unmarried, in the early stage of HIV infection, and without comorbidities. The findings showed a significant increase in alanine transaminase (ALT) at all three follow-up visits: 2 wk ($p=0.02$), 6 mo ($p=0.003$), 12 mo ($p=0.001$) and an increase in aspartate aminotransferase (AST) after 6 mo ($p=0.007$) and 12 mo ($p=0.04$). Abnormal LFT levels (AST and/or ALT) were observed in 23.4% of patients after a normal baseline, with ALT increase being more common. Furthermore, homosexuality was identified as a significant independent factor associated with abnormal LFT (AOR=3.1; 95% CI 1.27-7.51; $p=0.01$). The findings indicate exceptionally elevated LFT levels and the occurrence of abnormal LFTs among HIV-positive patients initiating ARVs. The increase in abnormal LFTs was significantly associated with patients identifying as homosexual, where hepatitis co-infection may be a contributing factor. The limited study design and measured variables warrant further investigation.

ABSTRAK

Terapi antiretroviral (ART) merupakan modalitas terapeutik utama dalam manajemen infeksi Human Immunodeficiency Virus (HIV), dengan efikasi yang telah terbukti. Namun, profil keamanan dari ART perlu terus dipantau, termasuk peningkatan awal pada tes fungsi hati setelah inisiasi antiretroviral (ARV). Penelitian ini bertujuan untuk menilai tes fungsi hati yang abnormal pada pasien HIV positif yang menerima ARV awal dan mengidentifikasi faktor-faktor yang terkait dengan tes fungsi hati abnormal. Studi kohort retrospektif tanpa kelompok kontrol ini akan merangkum catatan medis dari Rumah Sakit Umum Dr. Sardjito, Yogyakarta antara Januari 2014 dan Desember 2021. Subjek penelitian adalah pasien HIV dewasa yang menjalani pengobatan ARV pertama, dan menjalani kunjungan tindak lanjut selama minimal 2 minggu. Hasil studi adalah kadar fungsi hati dan jumlah yang abnormal, serta faktor-faktor yang terkait dengan keabnormal fungsi hati selama kunjungan follow-up pada minggu ke 2, bulan ke 6, dan bulan ke 12. Analisis univariat dan multivariat menggunakan tingkat signifikansi $p<0,05$. Sebanyak 137 subjek dengan 203 kunjungan diperoleh dari catatan medis. Rerata usia subjek adalah 33,4 tahun, dengan mayoritas laki-laki, usia muda, belum menikah, dalam tahap awal infeksi HIV, dan tanpa

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komorbiditas. Temuan menunjukkan peningkatan yang signifikan dalam alanine transaminase (ALT) pada ketiga kunjungan follow-up, yaitu pada 2 minggu (p=0,02), 6 bulan (p=0,003), dan 12 bulan (p=0,001), dan peningkatan aspartate aminotransferase (AST) setelah 6 bulan (p=0,007) dan 12 bulan (p=0,04). Proporsi subjek dengan kadar fungsi hati yang menjadi abnormal (AST dan/atau ALT) setelah penggunaan ARV sebesar 23,4%, dengan peningkatan ALT dominan. Homoseksualitas diidentifikasi sebagai faktor independen yang signifikan terkait dengan kadar fungsi hati abnormal (AOR=3,1; 95% CI 1,27-7,51; p=0,01). Temuan ini mengindikasikan peningkatan yang signifikan pada kadar fungsi hati pada pasien HIV positif yang memulai pengobatan ARV. Peningkatan kadar fungsi hati yang abnormal lebih cenderung ditemukan pada subjek homoseksual, dimana ko-infeksi hepatitis kemungkinan menjadi faktor yang mempengaruhi. Desain studi yang terbatas dan kurangnya variabel yang dapat diukur mendorong untuk dilakukan penelitian lebih lanjut.

INTRODUCTION

Antiretroviral therapy (ART) is the primary treatment for individuals with Immunodeficiency Virus (HIV) infection. The development of ART has progressed since Zidovudine in 1987, with now over 40 single drugs and 22 fixed-drug combinations from seven different classes currently available.[1] The introduction of Highly Active Antiretroviral Therapy (HAART) in 1996 was a significant breakthrough in HIV management. It enabled treating HIV patients with three or more combinations of ARTs from different classes. This program has controlled the virus progressiveness and decreased mortality and morbidity associated with HIV infection. A randomised controlled trial (RCT) that supported HAART implementation demonstrated an almost 60% efficacy in reducing HIV-related deaths.[2] The HAART regimen is continuously evolving to maintain the effectiveness and safety of ARTs in managing HIV infection worldwide.

The advancement of antiretroviral (ARV) and the combinations in HAART are frequently associated with new safety profiles. A review reported various short-term and long-term adverse events of ARV treatment, including drug-induced hepatitis, hypersensitivity reactions, acidosis, anemia, lipoatrophy, dyslipidemia, lipo-hypertrophy, diabetes, and cardiovascular disease.[3] Drug-induced liver injury (DILI) or hepatotoxicity is one of ARV's most significant adverse events. In patients with HIV undergoing ARV therapy, DILI can occur due to direct toxicity of ARVs, hypersensitivity reactions in the liver, co-infection with hepatitis viruses that trigger immune reconstitution, mitochondrial toxicity, and other unknown mechanisms.[4] Hepatic injury can be traditionally identified through increased liver enzymes and bilirubin, indicating hepatocellular damage.[3] It is crucial to detect early signs of liver injury to modify ARV regimens and provide hepato-protective agents to prevent severe liver complications.

A review reported that the frequency of liver toxicity among patients receiving ARVs ranges from 2 to 18%.[4] However, a cohort study in Ethiopia found a higher incidence rate of more than 22% of subjects with elevated aspartate aminotransferase (AST) and/or alanine transaminase (ALT) levels, although all cases were classified as mild to moderate hepatotoxicity after 18 months.[5] Studies that had analysed the prevalence of hepatotoxicity in ARV-treated patients have shown comparable results, with hepatotoxicity rates of 15% for ALT and 20% for AST.[6] Several risk factors were significantly related to an elevated liver function profile, such as HIV viral load levels and hypertension.[6] The type of

ARV used may also affect the incidence of hepatotoxicity, with nevirapine being linked to a greater risk of liver toxicity during long-term use.[7] On the other hand, one study found that protease inhibitors have a hepatoprotective effect.[6]

The possibility of liver damage after initiating ARVs is usually identified from increased AST/ALT levels.[4-6] However, there is limited data identifying the very early effects of ARV on liver function. The study will evaluate AST/ALT levels in newly initiated HIV-positive patients on ARVs to detect early increases. Additionally, it will identify factors associated with LFT abnormalities, particularly related to patient demographics and clinical characteristics. The findings are expected to add to the growing evidence of the significant risk of hepatotoxicity associated with ARVs, specifically at the initiation of treatment.

MATERIALS AND METHODS

Design

This is a cohort study without controls using retrospective data from medical records at Dr. Sardjito General Hospital in Yogyakarta, Indonesia, covering the period from January 1, 2014, to December 31, 2021. The study included HIV-positive patients over 18 undergoing their first ARV therapy and had follow-up data available for at least two weeks after starting the treatment. Incomplete data were excluded from the study. Eligible subjects were evaluated for baseline demographic and clinical characteristics, as well as clinical profiles at the follow-up periods of 2 wk, 6 mo, and 12 mo after the initiation of ARV therapy. A consecutive sampling technique was used to fulfil the sample size requirement of the cohort study.

Procedure

The study assessed independent variables, including demographic criteria such as age, sex, marital status, employment status, educational background, and sexual orientation, as well as clinical measures such as the type of ARV used, HIV stages, comorbidities, and TB status. The dependent variables (outcomes) assessed were AST and ALT levels at 2 wk, 6 mo, and 12 mo at follow-up periods. The study aimed to achieve several effect sizes, including the mean difference of increased AST/ALT levels, the proportion of abnormal AST/ALT, and factors associated with abnormal AST/ALT. Abnormal LFT was determined using the Indonesian Association of Internal Medicine Specialists (PAPDI) criteria, ranging from 5-42 μ/L for AST to 7-56 μ/L for ALT. Data were collected retrospectively from medical records, which might limit the ability to control measurement bias.

Statistical analysis

The data obtained from the medical records were analysed descriptively and statistically. Descriptive analysis was presented in tables and narrations, providing an overview of the demographic and clinical criteria, AST/ALT levels and their frequency of abnormality across the follow-up periods of 2 wk, 6 mo, and 12 mo. Numerical data were shown as mean and standard deviation (SD) or median and interquartile range (IQR), if the data did not meet the normal distribution assumption. Categorical data were presented as frequency and proportion. The paired t-test, or Wilcoxon sign test as an alternative non-parametric test, was used to assess the mean AST/ALT levels between baseline and follow-up periods. The factors associated with abnormal AST/ALT were analysed using the Chi-square test and represented as the Odds ratio (OR). Binary logistic regression determined the independent factor for identified some potential variables. The significance level for all analyses used $p<0.05$ or 95% confidence interval (95% CI). The software used for analysis was SPSS version 26 (IBM Corps.).

Ethical statement

The ethical approval was granted by the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr Sardjito General Hospital, Yogyakarta. The reference number is KE/0634/04/2023.

RESULTS

A total of 137 subjects were included in this retrospective analysis, with 203 follow-up visits recorded. Among all visits, 69 patients completed a 2-wk follow-up, 68 completed a 6-mo follow-up, and 66 completed a 12-mo follow-up. The mean age of the participants was 33.4 ± 9.8 years, with the majority in were young adult age group of 18-30 years (43.8%). More than three-quarters of the subjects were male. The most prevalent demographic characteristics included being unmarried (56.2%), employed (76.6%), and senior high school graduates (54.7%). TABLE 1 provides a summary of the predominant clinical criteria of the participants, such as the use of the tenofovir, lamivudine, and efavirenz (TLE) ARF regimen (86.1%), HIV stage I-II (56.2%), absence of comorbidities (84.7%), and no TB co-infection (67.2%). Detailed information on the subjects is referred to in TABLE 1.

TABLE 1. Characteristics of study subjects

Characteristics	Value (n= 137)
Age (mean ± SD years)	33.4 ± 9.8
Group age [years, n (%)]	
• 17 - 30	60 (43.8)
• 31 - 45	55 (40.1)
• > 45	2 (16.1)
Gender [n (%)]	
• Male	107 (78.1)
• Female	30 (21.9)
Marital status [n (%)]	
• Not married	77 (56.2)
• Married	49 (35.8)
• Divorced	11 (8.0)
Employment status [n (%)]	
• Unemployed	32 (23.4)
• Employed	105 (76.6)
Education background [n (%)]	
• Primary school	16 (11.7)
• Junior high school	7 (5.1)
• Senior high school	75 (54.7)
• Undergraduate	33 (24.1)
• Postgraduate	6 (4.4)
Homosexual [n (%)]	
• Yes	68 (49.6)
• No	69 (50.4)

TABLE 1. Characteristics of study subjects (cont.)

ARV therapy [n (%)]	
• TLE	119 (86.1)
• TLN	1 (0.7)
• DE	1 (0.7)
• DN	12 (8.8)
• Atripla	4 (2.9)
HIV stage [n (%)]	
• Stage I	40 (29.2)
• Stage II	37 (27.0)
• Stage III	51 (37.2)
• Stage IV	9 (6.6)
Comorbidities [n (%)]	
• Yes	45 (32.8)
• No	92 (67.2)
TB status [n (%)]	
• Yes	21 (15.3)
• No	116 (84.7)

SD: standard deviation; ARV: antiretroviral; TLE: tenofovir + lamivudine + efavirenz; TLN: tenofovir + lamivudine + nevirapine; DE: duviral + efavirenz; DN, duviral + neviral; HIV, Human immunodeficiency virus; TB: tuberculosis

TABLE 2. Liver function test profiles of subjects at 2-wk, 6-mo, and 12-mo follow-up periods

Outcomes	AST (unit/L)		p*	ALT (unit/L)		p*
	baseline	follow-up		baseline	follow-up	
LFT value (median±IQR)						
• 2-wk follow-up	20.0 ± 12.5	25.0 ± 10.5	0.07	20.0 ± 22.0	31.0 ± 25.5	0.02
• 6-mo follow-up	21.5 ± 10.0	27.5 ± 12.5	0.007	22.5 ± 22.0	33.0 ± 28.2	0.03
• 12-mo follow-up	22.0 ± 12.5	28.0 ± 19.0	0.04	26.0 ± 25.5	42.5 ± 38.5	0.001

*Wilcoxon signed rank test; LFT: liver function test; IQR: interquartile range; AST: aspartate transaminase; ALT: alanine transaminase

TABLE 3. Incidence of abnormal LFT at follow-up after normal initial LFT (n=137)

Variable	AST	ALT	AST and/or ALT
Incidence of abnormal LFT [n (%)]	16 (11.7)	29 (21.2)	32 (23.4)

LFT: liver function test; IQR: interquartile range; AST: aspartate transaminase; ALT: alanine transaminase

TABLE 3 presents the proportion of subjects who experienced abnormal LFT levels at any follow-up visit after having normal baseline levels. Of the total subjects, 32 (23.4%) showed abnormal LFT levels at least once, with 29 (21.2%) with increased ALT levels and only 16 (11.7%) having abnormal AST. In summary, abnormal LFT can be observed in 1 out of 5 HIV-positive patients receiving initial ARV therapy.

TABLE 4. Factors affecting the incidence of abnormal LFT after initiating ARV therapy (n=137)

Variables	Abnormal LFT [n (%)]	OR (95%CI)	p*	AOR (95%CI)	p*
Age group (≤ 30 yo)	18 (56.3)	1.9 (0.86 – 4.29)	0.10	1.5 (0.63 – 3.40)	0.37
Male gender	27 (84.4)	1.7 (0.58 – 4.84)	0.32		
Sex orientation (same sex)	23 (71.9)	3.4 (1.43 – 8.07)	0.004	3.1 (1.27 – 7.51)	0.01
ARV used (nevirapine-based)	1 (3.1)	0.3 (0.03 – 2.00)	0.29	-	
Late HIV stage	13 (40.6)	0.8 (0.37 – 1.88)	0.68	-	
With comorbidities	12 (37.5)	1.3 (0.57 – 2.99)	0.52	-	
TB co-infections	4 (12.5)	0.7 (0.23 – 2.38)	0.61		

*Chi-square test; LFT: liver function test; ARV: antiretroviral; HIV: human immunodeficiency virus; TB: tuberculosis; OR: odds ratio; AOR: adjusted odds ratio

Among abnormal LFT levels, individuals who reported same-sex orientation or homosexual practices were found to have a significant association with LFT abnormalities. Homosexuals had three times higher risk of LFT abnormalities (OR=3.4, 95% CI 1.43-8.07; p=0.004), and remained significant after multivariate analyses (AOR=3.1, 95% CI 1.27-7.51; p=0.01) as shown in Table 4. This finding indicates that homosexuality becomes the only factor independently associated with abnormal LFT. On the other hand, , age, gender, type of ARV, HIV stage, comorbidities, and TB co-infection did not significantly correlate with abnormal LFT events in patients receiving ARVs.

DISCUSSION

This study demonstrates the significant increase in LFT levels in the early use of ARV among naïve HIV-positive patients. Elevating AST is not observed in the early weeks, but a gradual increase is kept in the subsequent follow-up periods. A more notable increase is shown in the ALT, which has consistently risen since the earlier visit. Despite the significant changes, the median AST/ALT levels are generally within the normal range. Typically, hepatotoxicity occurs through direct and indirect mechanisms. Direct hepatotoxicity occurs due to the drug profile or metabolite, which can directly damage liver cells in the early weeks of use.[8] Liver cell damage in direct hepatotoxicity is associated with increased ALT and alkaline phosphatase (ALP) without hyperbilirubinemia.[9] In this study, ALT levels appear more dominant in increasing, possibly related to direct hepatotoxicity. However, a further examination is required because ALP and bilirubin levels are not calculated.

The increased levels of ALT are evident in abnormal LFT events during follow-up after a normal baseline. This study revealed that almost one-fourth of the subjects experienced abnormal AST/ALT at one or more follow-up periods. The ratio of participants with abnormal ALT was twice as large as those with abnormal AST, consistent with a higher increase in the median ALT level. The incidence of increased ALT at the beginning of ARV use was also observed in a study by Alghamdi et al., where 27.9% of subjects who consumed ARV showed an elevation in ALT after 3-12 months.[10] In contrast, a large multicenter study in Tanzania reported lower results, with only 13% of subjects showing abnormal LFT after one week of ARV use.[11] A longitudinal

study conducted in Peru showed different results, where using ARV for three months resulted in a decline in both AST and ALT levels.[12] Intrinsic and extrinsic factors may also influence these variations in hepatotoxicity profiles in the studies' subjects.

This study indicated that a sexual orientation-related variable was associated with abnormal LFT events. Homosexuals were found to have a threefold increased incidence of abnormal LFT events compared to heterosexuals, and multivariate analysis confirmed this factor's independence. The association between homosexual behaviour and increased LFT levels was often associated with a higher incidence of hepatitis B or C co-infection in men who have sex with men (MSM).[13,14] Hepatitis viruses directly cause damage to liver cells, increasing LFT levels. This factor may be the basis for the strong association between homosexuals, who have a high incidence of hepatitis and HIV co-infection, and the increase in LFT after ARV use. Similar modes of transmission between hepatitis and HIV, such as through sexually transmitted or blood-borne routes, contribute to the increased likelihood of co-infection between these two diseases. Therefore, hepatitis B or C virus infection tends to directly affect the increase in LFT rather than the homosexual population itself. Hepatitis B and C infections, as well as alcohol consumption, were also known to be essential factors in LFT levels among HIV patients.[13] Other studies also identified antibiotics such as antituberculosis and cotrimoxazole contributing to liver damage.[14] Unfortunately, our study was limited by the availability of secondary data and did not examine many of these factors. In addition to these factors, the type of ARV used also increases the risk of liver injury. Certain ARVs, such as Nevirapine, Efavirenz, and Ritonavir, were often associated with hepatotoxicity.[7, 15, 16] However, our study could not establish a link between ARV use and abnormal LFT events due to limited data on using only one type of ARV. The long-term use of ARVs in combination can increase the risk of liver cell damage, and monitoring drug safety remains crucial.

CONCLUSION

This study overviews the increase in LFT levels during the early use of ARVs and the factors influencing this increase. Elevated LFT levels, particularly ALT, consistently occurred from the first follow-up up to the initial 12-mo of ARV use. Considering the long-term nature of ARV therapy, this finding emphasises the need for early drug safety monitoring to prevent more severe liver damage. The incidence of abnormal LFTs was strongly associated with homosexuals. Therefore, heightened attention should be given to HIV-positive individuals in this population by identifying other factors such as hepatitis co-infection, alcohol consumption, or other factors that directly worsen liver health. Guidelines for drug safety monitoring, both by healthcare professionals and patients, need to be improved to ensure the ARVs administered have no or minimal adverse events. Closer monitoring for LFT should also be conducted on the homosexual population. In brief, the findings of this study can provide valuable support to the clinical decision-making process in ARV therapy, such as the continuation of current treatment, switching to alternative regimens, or considering the addition of hepatoprotective agents to the treatment plan for individuals living with HIV.

Despite conducting analyses on all samples meeting inclusion and exclusion criteria and performing regression analysis to eliminate confounding factors, the study has several major limitations. Firstly, it employs a cohort design without a comparison group and uses secondary data. Using single proportions in a cohort design makes optimally calculating causality difficult. Therefore, the conclusions drawn about risk factors

lack solid clinical implications. Using retrospective data (medical records) may introduce measurement or selection bias, rendering the results less accurate. Despite its limitation, this study provides valuable insights into improving HIV patient services, particularly concerning drug safety.

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