

Low Body Mass Index as a Risk Factor for Antiretroviral Drug-Related Liver Injury Among HIV Patients

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ABSTRAK

Latar belakang: antiretroviral drug-related liver injury (ARLI) adalah salah satu jenis hepatotoksitas terkait obat yang disebabkan karena obat antiretroviral (ARV). Kejadian ARLI sering mengganggu kepatuhan berobat dan menyebabkan putus berobat pada pasien HIV. Beberapa penelitian telah dilakukan untuk mempelajari faktor predisposisi kejadian ARLI, di antaranya adalah penelitian tentang indeks massa tubuh (IMT) dan cluster of differentiation 4 (CD4). Hubungan nilai IMT dan CD4 dengan kejadian ARLI masih menjadi kontroversi karena keluaran yang berbeda dari beberapa penelitian sebelumnya. Penelitian ini dilakukan untuk mengetahui hubungan IMT dan CD4 awal yang rendah sebagai faktor risiko kejadian ARLI pada pasien HIV. **Metode:** penelitian ini merupakan studi potong lintang pada 75 orang dengan HIV-AIDS (ODHA) yang mendapat terapi ARV dalam bentuk kombinasi dosis tetap (tenofovir, lamivudine, efavirenz) di Poliklinik Teratai Rumah Sakit Hasan Sadikin. Pemeriksaan Serum Glutamic Pyruvic Transaminase (SGPT) dilakukan sebelum ODHA memulai pengobatan ARV dan diulang pada bulan ke-6 pengobatan ARV. **Hasil:** tidak terdapat perbedaan bermakna proporsi hitung CD4 awal yang rendah antara kelompok ARLI dan kelompok non-ARLI ($p=0,155$). Analisis bivariat menunjukkan bahwa terdapat perbedaan bermakna proporsi nilai IMT awal yang rendah antara kelompok ARLI dan kelompok non-ARLI ($p=0,001$). Analisis multivariat dengan regresi logistik mendapatkan bahwa $IMT < 18,5 \text{ kg/m}^2$ meningkatkan risiko 5,53 kali untuk terjadinya ARLI, sedangkan $CD4 < 200 \text{ sel}/\mu\text{l}$ tidak meningkatkan risiko untuk terjadinya ARLI. **Kesimpulan:** nilai IMT awal yang rendah akan meningkatkan risiko terjadinya ARLI sedangkan hitung CD4 awal yang rendah tidak meningkatkan risiko terjadinya ARLI. Oleh karena itu, kami menyarankan bahwa pemeriksaan SGPT sebaiknya dilakukan secara rutin pada ODHA sebagai deteksi dini terjadinya ARLI, khususnya pada pasien dengan IMT rendah.

Kata kunci: antiretroviral drug-related liver injury (ARLI), indeks massa tubuh (IMT), cluster of differentiation 4 (CD4).

ABSTRACT

Background: antiretroviral drug-related liver injury (ARLI) is a drug-induced hepatotoxicity due to antiretroviral medication (ARV). It commonly disrupts compliance to treatment and causes treatment discontinuation in HIV-infected patients. Several studies have been conducted on predisposing factors for ARLI including studies on body mass index (BMI) and cluster of differentiation 4 (CD4). The association of BMI and CD4 with ARLI remains controversial as previous studies have demonstrated different outcomes. Our study was conducted to identify the association of low baseline BMI and CD4 cell count as risk factors for ARLI in HIV-infected patients. **Methods:** this is a cross-sectional study. Subjects were 75 patients with HIV-AIDS who received ARV therapy using

fixed-dose combination (tenofovir, lamivudine, efavirenz) at the Teratai HIV outpatient clinic of Hasan Sadikin Hospital in Bandung city. Alanine aminotransferase (ALT) test was performed prior to starting ARV treatment and the test was repeated on the sixth month of therapy. Results: there was no significant difference on the proportion of low baseline CD4 count between ARLI and non-ARLI group ($p=0.155$). Bivariate analysis demonstrated that regarding the proportion of low baseline BMI, there was a significant difference between ARLI and non-ARLI group ($p= 0.001$). Multivariate analysis using logistic regression showed that BMI of $<18.5 \text{ kg/m}^2$ increased the risk for developing ARLI by 5.53 fold; while CD4 cell count of $<200 \text{ cells}/\mu\text{L}$ did not the risk. Conclusion: our study indicates that low baseline BMI may increase the risk for developing ARLI; while low baseline CD4 cell count does not; therefore, we suggest that ALT test should be performed on a routine basis among HIV-AIDS patients for early detection of ARLI, particularly in patients with low BMI.

Keywords: antiretroviral drug-related liver injury (ARLI), body mass index (BMI), cluster of differentiation 4 (CD4).

INTRODUCTION

Antiretroviral drug-related liver injury (ARLI) is drug-induced liver injury caused by antiretroviral medication (ARV), particularly efavirenz and nevirapine.¹ It is defined by elevated serum levels of liver enzymes and typically alanine aminotransferase (ALT) level is greater than aspartate aminotransferase (AST). Antiretroviral drug-related liver injury (ARLI) is a common cause of morbidity, mortality and treatment discontinuation in HIV-infected patients.^{1,2}

Some risk factors for ARLI have been reported, which are female, viral hepatitis co-infection, alcoholism, concurrent use of ARV with cotrimoxazole, low or high cluster of differentiation (CD4) count, antituberculosis drugs, low albumin serum, body mass index (BMI) and HIV-1 RNA load $<20,000$ copies/ml.^{1,3-6} There are different outcomes in some studies about BMI and CD4 count as risk factors for ARLI.³⁻⁶

Sanne et al⁷ found that low BMI ($<18.5 \text{ kg/m}^2$) is a risk factor for ARLI. In contrast, Chalermchai et al⁸ demonstrated that high BMI ($\geq 23 \text{ kg/m}^2$) is a risk factor for ARLI. Tseng et al³ found that high baseline CD4 count ($\geq 200 \text{ cell}/\mu\text{L}$) is a risk factor for ARLI; while Hamzah et al⁴ found that low baseline CD4 cell count ($<200 \text{ cell}/\mu\text{L}$) is a risk factor for ARLI.

Low BMI causes altered drug absorption, distribution and excretion. Such conditions subsequently predispose HIV patients to hepatotoxicity.⁹ Cluster differentiation acts

as a coordinator in various immune function. The loss of this function causes progressive disturbance in immune response.¹⁰ It results in increased risk of having opportunistic infection on liver, which induces hepatotoxicity.⁴

All kinds of ARV medication can cause ARLI, especially nevirapine and protease inhibitors.¹ Most of HIV patients in Bandung have been receiving ARV medication using the fixed-dose combination (tenofovir, lamivudine, efavirenz) and they have lost more than 10 % of their weight as well as having low baseline CD4 cell count. There has been no data regarding the association of low baseline BMI and CD4 cell count with ARLI in HIV patients in Bandung city, West Java. The aim of our study was to identify the association of low baseline BMI and CD4 cell count with their roles as risk factors for ARLI.

METHODS

The present study was a clinical epidemiological study using cross-sectional design. The study was conducted starting from September to November 2017. It included subjects of >18 year-old HIV patients who received ARV treatment using fixed dose combination (tenofovir, lamivudine, efavirenz) at the Teratai HIV Outpatient Clinic in Hasan Sadikin Hospital. Subjects with ALT ≥ 1.25 x the upper limit of normal (ULN) ALT levels before receiving ARV treatment, patients with pregnancy, concurrent use of antifungal treatment (fluconazole), TB-HIV co-infection or

using antituberculosis medicine were excluded. The exclusion was performed to minimize any bias that might cause elevated ALT level. Ethical approval was obtained from the Ethics Committee of Faculty of Medicine, Padjadjaran University/Hasan Sadikin Hospital, Bandung on September 11, 2017 with a reference number of LB.04.01/A05/EC/271/IX/2017.

In the present study, randomized consecutive sampling was utilized with minimum sample size of 68 subjects. History taking, physical examination and laboratory tests examination were carried out at the Teratai Outpatient Clinic. BMI, CD4 cell count and ALT baseline data were documented before HIV patients started their ARV regimens. The second ALT test was taken within six months after the subjects had started their ARV treatment. The sixth month was selected as the cut-off time to re-asses ALT level considering that Chalasani et al¹¹ had demonstrated that the event of drug-induced liver injury usually occurs within the first six months after a patient starting any new medication. Subjects with an increase of ALT level $<1.25x$ the ULN were categorized into the non-ARLI group; while subjects with increased ALT level $\geq 1.25x$ the ULN were categorized into the ARLI group.

Human Immunodeficiency Virus (HIV) infection was confirmed by reactive anti-HIV test. By dividing body weight (kg) with the square of height (m^2), we got the BMI. Low BMI was defined as BMI <18.5 kg/m^2 .^{4,7} Low CD4

cell count was defined as CD4 count of <200 cells/ μl .⁴ Antiretroviral drug-related liver injury (ARLI) was defined when there was an increased ALT level $\geq 1.25x$ the upper limit normal (ULN) on the sixth month of ARV therapy.¹ The ULN for ALT in our study was 40 IU/ml.

Data were analyzed using bivariate analysis with chi square test or Fisher's exact test when the criteria for chi square were not fulfilled. It was then continued by multivariate analysis using logistic regression. The evaluated parameters were expressed in confidence interval (CI), probability (p value) and odd ratio (OR). All statistical tests were evaluated using SPSS software program version 25.0.

RESULTS

Seventy-five subjects were selected including 34 subjects in ARLI group and 41 subjects in non-ARLI group. Baseline characteristics such as age, sex, baseline CD4 cell count, baseline BMI, viral hepatitis B coinfection and cotrimoxazole usage can be seen in **Table 1**. The average age of our subjects was 32 years old. There were 61 (81.3%) male and 14 (18.7%) female subjects. The CD4 cell count ranged between 6 and 554 cells/ μL (with a median of 210 cells/ μL). There were 33 (44%) subjects with low baseline CD4 cell count (<200 cells/ μl) and there were 42 (56%) subjects with baseline CD4 cell count ≥ 200 cells/ μl . The average BMI of our subjects before starting their ARV

Table 1. Baseline characteristics with ARLI

Characteristics	Total (n = 75)	ARLI (n=34)	Non-ARLI (n=41)	p value
Age (years old), Mean (SD)	32 (9)	33 (7)	30 (10)	0.148 ^a
Sex, n (%)				
- Male	61 (81.3)	29 (85.3)	32 (78.0)	0.423 ^b
- Female	14 (18.7)	5 (14.7)	9 (22.0)	
Viral hepatitis B coinfection, n (%)	6 (8.0)	4 (11.8)	2 (4.9)	0.401 ^c
Cotrimoxazole prophylaxis, n (%)	32 (42.7)	16 (47.1)	16 (39.0)	0.484 ^b
CD4 (cells/ μl), n (%)				
- CD4 <200	33 (44.0)	18 (52.9)	15 (36.6)	0.155 ^b
- CD4 ≥ 200	42 (56.0)	16 (47.1)	26 (63.4)	
BMI (kg/m ²), n (%)				
- BMI <18.5	31 (41.3)	21 (61.8)	10 (24.4)	0.001 ^{b*}
- BMI ≥ 18.5	44 (58.7)	13 (38.2)	31 (75.6)	

Abbreviations: SD=standard deviation, n=amount, %=percentage, at test, bChi Square, cFisher Exact

therapy was 19.5 kg/m². There were 31 (41.3%) subjects with low baseline BMI (<18.5 kg/m²) and 44 (58.7%) subjects with BMI ≥ 18.5 kg/m². There were 6 (8%) subjects with viral hepatitis B coinfection and 32 (42.7%) subjects were using cotrimoxazole coincidentally with ARV. There were no significant differences in age, sex, viral hepatitis B coinfection and cotrimoxazole prophylaxis treatment between ARLI group and non-ARLI group (p>0.05).

There were 34 subjects with ARLI including 27 (79.4%) subjects experiencing ARLI grade 1, 4 (11.8%) subjects with ARLI grade 2, 2 (5.9%) subjects experiencing ARLI grade 3 and 1 subject (2.9%) with ARLI grade 4.

Bivariate analysis on baseline CD4 cell count between ARLI and non-ARLI group was performed using chi-square test. There were 18 (52.9%) subjects with low baseline CD4 cell count (CD4 <200 cells/μl) and 16 (47.1%) subjects with CD4 cell count ≥ 200 cells/μl in ARLI group. There were 41 subjects non-ARLI group including 15 (36.6%) subjects with low baseline CD4 count (<200 cells/μl) and 26 (63.4%) subjects with CD4 cell count of ≥ 200 cells/μl. There was no significant statistical difference between both groups (p=0.155).

Bivariate analysis on baseline BMI between ARLI and non-ARLI was also performed using chi-square test. There were 21 (61.8%) subjects with baseline BMI <18.5 kg/m² and 13 (38.2%) subjects with baseline BMI ≥18.5 kg/m² in ARLI group. There were 41 subjects in non-ARLI group and there were 10 (24.4%) subjects with baseline BMI <18.5 kg/m² and 31 (75.6%) subjects with baseline BMI ≥18.5 kg/m². Statistically, there was a significant difference (p=0.001) between both groups.

Body mass index <18.5 kg/m² increased the risk for ARLI 5.53 folds; however, the CD4 cell count of <200 cells/μl did not increase the

risk for ARLI. All subjects received fixed-dose combination ARV treatment, which consisted of tenofovir, lamivudine and efavirenz.

DISCUSSION

The results showed that there was no significant difference in low baseline CD4 cell count proportion between ARLI and non-ARLI group (p=0.155). Multivariate analysis using logistic regression showed that low baseline CD4 cell count (<200 cells/μl) did not increase the risk for ARLI (p=0.754). Chaponda et al¹² and Nunez¹³ found that HIV patients with baseline CD4 > 250 cell/μl suffer ARLI more often. This may be caused by hypersensitivity reaction. Hypersensitivity reaction in ARLI is often caused by nevirapine (NVP).^{1,12,13} Nevirapine induces hepatotoxicity more frequently than efavirenz (EFV). Nevirapine-based hepatotoxicity comes in two different onsets. The first one can be found within six weeks after the initiation of NVP. The other one may occur within 2 to 3 months after the initiation of NVP.^{12,14}

Although the mechanisms of hepatotoxicity are not clear, recent evidence has pointed to a specific mitochondrial action of EFV accompanied by the induction of an endoplasmic reticulum stress or unfolded protein response in human hepatocytes. Endoplasmic reticulum stress, which is triggered by EFV, can be exacerbated in any settings that may further compromise liver function including viral hepatitis and drug or alcohol abuse.¹⁵

Cluster differentiation produces cytokines such as IL-5, granzyme and eotaxin, which play big roles in eosinophil growth and differentiation. High levels of CD4 cells will produce more eosinophils. Eosinophil has a significant role in allergic reaction and hypersensitivity.¹²

Our study showed that there was a significant difference regarding the proportion of low BMI

Table 2. The association of baseline CD4 cell count and BMI with ARLI

	Coefficient B	SE	p-value	Odd Ratio (95% CI)
BMI < 18.5 kg/m ²	1.710	0.602	0.005*	5.530 (1.699 – 17.999)
CD4 < 200 cells/μl	-0.188	0.599	0.754	0.829 (0.259 – 2.681)
Constant	-0.828	0.354	0.020	

Multivariate analysis logistic regression, *significant if p<0.05; dependent variable: ARLI

between ARLI and non-ARLI group ($p=0.001$). Multivariate analysis using logistic regression showed that there was a correlation between low baseline BMI and ARLI ($p=0.005$). Low BMI ($<18.5 \text{ kg/m}^2$) increases the risk for ARLI as many as 5.53 folds. The result was consistent with a study by Sanne et al⁷, which found 65% ARLI proportion in subjects with baseline BMI $<18.5 \text{ kg/m}^2$. Hamza et al⁴ in Nigeria also found that baseline BMI $<18.5 \text{ kg/m}^2$ had a significant correlation with ARLI.

Malnutrition (BMI $<18.5 \text{ kg/m}^2$) results in changes in drug metabolisms starting from absorption, distribution to excretion. The disruption of gut wall function in patients with malnutrition causes drug malabsorption.⁹ Gut wall plays an essential role in drug absorption. Enterocytes in gut wall contain many types of enzymes such as cytochrome P450 3A4 (CYP3A4), peptide transporter 1 (PEPT1) and P-glycoprotein (P-gp). Cytochrome P450 3A4 (CYP3A4) is a dominant enzyme in drug absorption and metabolism.¹⁶ In malnutrition, the amount and function of those enzymes attenuate resulting in drug malabsorption.⁹

Reduced lipid tissue and hypoalbuminemia in malnutrition cause disruption in drug distribution. Malnutrition may result in reduced amount and function of cytochrome in the liver. Cytochrome plays a role in the first phase of drug metabolism. Reduced cytochrome enzyme may cause increased drug level and delayed formation of drug metabolites, which may lead to hepatotoxicity.⁹

One limitation of our study was our cross-sectional design; therefore, we could not study ARLI incidence with a time frame of more than six month after the subjects has initiated their ARV treatment. Moreover, other factors such as ARV regimen, other hepatic diseases (other than viral hepatitis B), alcohol consumption, serum albumin and other medication (other than antituberculosis and fluconazole) were also not in our study. There was also cost limitation in our study that prevented us to assess the association between viral hepatitis C co-infection and HIV.

CONCLUSION

Our study concludes that low baseline BMI is a risk factor for ARLI. There are no

significant differences in age, sex, viral hepatitis B co-infection and cotrimoxazole prophylaxis between ARLI group and non-ARLI group. There is a significant difference of low BMI proportion between ARLI and non-ARLI group. Low BMI ($<18.5 \text{ kg/m}^2$) increases the risk for ARLI 5.53 folds; while CD4 cell count $<200 \text{ cells}/\mu\text{l}$ does not increase the risk for ARLI.

We suggest a routine ALT test every six months after ARV treatment is initiated for HIV patients with malnutrition (BMI $<18.5 \text{ kg/m}^2$) for early detection of ARLI.

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