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Impact of First-Line Highly Active Antiretroviral Therapy on Metabolic Syndrome: Predictors and Comparative Analysis

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Abstract

Even though highly active antiretroviral therapy (HAART) is successful in decreasing HIV-related illness and death, concerns about metabolic syndrome (MetS) are increasing. However, there is limited evidence on the predictors of MetS among adults undergoing first-line HAART regimens in Malaysia. This study aimed to compare the MetS components between first-line HAART regimens containing integrase strand transfer inhibitor (INSTI) and non-INSTI regimens at baseline and 12-month follow-up. Additionally, it aimed to identify predictors of MetS among HIV patients on first-line HAART. This prospective cohort study included adults diagnosed with HIV from January 2023 till April 2023 and receiving first-line HAART for a minimum of 6 months, undergoing follow-up at Hospital Sungai Buloh, Malaysia. Data from 210 patients, mostly males (91.9%) and Malays (47.1%), were analyzed. Significant mean differences in MetS components were observed between patients receiving INSTI and non-INSTI regimens. Multivariate binary logistic regression analysis identified depressive disorders, non-INSTI HAART regimens, and age as significant predictors of MetS among HIV patients. The incidence of MetS was considerable among the study population, highlighting the significance of routinely monitoring patients' clinical and laboratory data and promoting health education to effectively manage and avoid HIV patients' metabolic illnesses.

Keywords: Predictors, Metabolic syndrome, First-line HAART, HIV, Malaysia

Introduction

MetS is characterized by a set of risk factors associated with cardiovascular and metabolic conditions, including insulin resistance, dyslipidemia, central obesity, and hypertension. These factors significantly elevate the likelihood of developing cardiovascular diseases (CVDs) and type 2 diabetes mellitus (DM) (1). Several criteria are available for defining MetS, with the guidelines outlined by the United States National Cholesterol Education Program: Adult Treatment Panel III (US NCEP-ATP III) being widely adopted for diagnostic purposes (2). Utilizing these guidelines aids clinicians in promptly identifying individuals with MetS, enabling proactive interventions to mitigate their predisposition to CVDs and DM. The Malaysian Consensus Guidelines for antiretroviral therapy (ART) (3) stated that

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initial HAART regimens for treatment-naive patients typically comprise either a non-nucleoside reverse transcriptase inhibitor (NNRTI) like efavirenz (EFV) or an INSTI like dolutegravir (DTG) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) like tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). The recommended first-line regimen for adults and adolescents beginning ART includes either TDF/FTC/EFV or TDF/FTC/DTG in cases of NNRTI intolerance. The adoption of HAART has significantly improved the prognosis for HIV patients, resulting in decreased mortality and morbidity rates (4).

The use of HAART has been demonstrated to extend therapeutic effectiveness, postpone the establishment of viral drug resistance, raise the cluster of differentiation 4 (CD4) counts, and considerably lower viral load (5). Nevertheless, HAART regimens have been linked to the emergence of metabolic abnormalities such as MetS and lipodystrophy (6). This shift in the pattern of morbidity associated with HIV/AIDS has moved from predominantly focusing on immunodeficiency and opportunistic infections to placing greater emphasis on metabolic complications (7). Calza et al. (8) stated that treated individuals had a substantially greater prevalence of MetS (20.9% vs. 7.1%; p = 0.014) than naïve patients, according to NCEP-ATP III criteria. Although the incidence of MetS among people living with HIV (PLWH) could be influenced by multiple factors, the choice of initial first-line HAART regimens may significantly contribute (9).

Due to the lack of evidence regarding metabolic abnormalities and factors predicting MetS among HIV-positive individualsreceiving first-line HAART in Malaysia, as well as the infeasibility of generalizing information from developed to underdeveloped nations without taking into account the variations in patient demographics, HIV subtypes, and lifestyle variables (10), this study aimed to fill this void. Specifically, it aimed to compare the MetS components between first-line HAART regimens containing INSTI and non-INSTI regimens, and to identify predictors of MetS among PLWH receiving first-line HAART. Our goal in emphasizing these data objectives was to increase alertness among healthcare providers about the magnitude of MetS among HIV patients on HAART in order to improve the disease management and to achieve optimal viral load control with the least metabolic complications among Malaysians.

Materials and Methods

Study Design and Study Population

This study was an observational prospective cohort employing purposive sampling conducted at Hospital Sungai Buloh's infectious disease (ID) clinic, Selangor, a prominent governmental hospital offering secondary and tertiary services and recognized as Malaysia's largest ID hospital. The study recruited adult participants aged 18 years and above diagnosed with HIV from January 2023 till April 2023, who had been on a first-line HAART regimen with or without INSTI for at least 6 months. Individuals who fulfilled the requirements for enrollment were sorted into two categories; one consisting of 104 patients on first-line HAART with INSTI, and the other comprising 106 patients receiving a standard-care regimen without INSTI. Exclusion criteria for the study included patients with incomplete medical records, pregnant women, individuals with pre-existing DM, dyslipidemia, and hypertension prior to starting HAART, as well as those who had switched between INSTI and non-INSTI regimens for less than 6 months. The data collection process occurred from June 2023 to March 2024. Initially, data previously recorded when the patient was initiated on HAART were collected, followed by a 12-month follow-up period.

Sample Size Calculation

The 210-sample size was established using the principle of 10 events per variable

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(EPV) (11), with 7 independent variables considered. These variables included factors such as age, gender, first-line HAART regimens, chronic kidney disease (CKD), liver impairment, depressive disorders and drug addiction. Additionally, assumptions were made regarding a 40% MetS prevalence rate in HIV patients receiving first-line HAART regimen based on the study site, along with a 20% allowance for missing data, ensuring a robust and statistically sound analysis.

Data Collection

Application to Hospital Sungai Buloh's Information Technology (IT) department was sent to get the access to the electronic hospital information system (eHIS). Upon obtaining permission for data access, a list of patients monitored by the ID clinic at Hospital Sungai Buloh was compiled based on specified inclusion and exclusion criteria. Subsequently, a pre-determined data collection form (DCF) was created and subjected to a pilottest to ensure its relevance and user-friendliness before actual data collection commenced. The patients' profiles were screened using their medical record number (MRN) via the eHIS live system to get the required sample size. Data were collected on socio-demographic and clinical traits, clinical and laboratory markers, as well as the prescribed first-line HAART regimen. Blood pressure (BP) measurements adhered to the standard operating procedures practiced by the hospital, while biochemical measurements, including fasting blood glucose (FBG), and lipid profile were gathered by qualified labtechnicians in accordance with the regular operating procedures of the laboratory. CKD, liver impairment, depressive disorders and drug addiction measurements were collected from the patients' past medical history.

Data Analysis

The data were input and analyzed using version 24.0 of the Statistical Package for Social Sciences (SPSS).Descriptive statistics, including frequency and percentage (%), were applied to sociodemographic and epidemiological data. Parametric tests were utilized since, with the exception of age, all numerical data were normally distributed. To compare the MetS components between INSTI and non-INSTI HAART regimens, independent t-tests were employed. Using the Chi-square test, the association between first-line HAART use and hypertension was investigated. The study employed both univariate and multivariate binary logistic regression to determine the clinical and nonclinical predictors of MetS in the participants, with statistical significance determined at a p-value less than 0.05.

Definition of Metabolic Syndrome

The modified NCEP ATP III was used in this study to diagnose MetS, requiring the presence of at least three specific parameters for diagnosis. These criteria comprised abdominal obesity (specifically, for individuals of Asian origin, WC ≥ 90 cm for men and ≥ 80 cm for women); triglycerides (TG) level ≥ 1.7 mmol/L; low high-density lipoprotein cholesterol (HDL-c) ≤ 1.03 mmol/L in men and ≤ 1.29 mmol/L in women; BP ≥ 130/85 mmHg; and FBG level ≥ 5.6 mmol/L. According to NCEP criteria, abdominal obesity is regarded as one element of the syndrome, but it is not compulsory for its diagnosis (12).

Results and Discussion

Patients' characteristics

Among the 210 participants analyzed, 193 (91.9%) were males and 99 (47.1%) were of Malay ethnicity. The median and interquartile range (IQR) of age was 36 (14) years (Table 1). This study found that there were more Malays and Chinese compared to Indians and other races. This trend could be linked to high-risk behaviors and a lack of awareness regarding HIV transmission methods among Malays. A previous study (13) assessing HIV awareness among Malaysian high school students, found that Malays had the lowest overall understanding of HIV/AIDS (52.5%), compared to Chinese students (64.9%) and Indian students (65.9%). This observation may also

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reflect the racial demographics of Malaysia, especially in West Malaysia, where ethnic Malays constitute the majority, followed by Chinese and Indian populations.

Comparing the MetS components between INSTI and non-INSTI HAART regimens

A significant mean difference in hypertriglyceridemia was observed at 12-month follow-up between patients on non-INSTI regimen 1.65 (0.075) mmol/L and those on INSTI regimen 1.62 (0.091) mmol/L, P <0.05 as shown in (Table 2). This study found that patients on non-INSTI regimen had a significant hypertriglyceridemia compared to those on INSTI regimen. A comparative investigation by Quercia et al. (14) revealed similar results, indicating that DTG had a typically neutral effect on lipid levels in contrast to EFV. Patients on DTG had somewhat higher levels of TC, LDL-C, and TG in both comparisons. The combined DTG study showed only slight increases in TG and LDL-C, with mean values at 48 weeks still falling short of the NCEP criteria's target ranges. The differential impact of EFV on lipid profiles may account for these outcomes, as EFV is closely linked to dyslipidemia in HIV patients. Specifically, EFV has been shown to reduce lipid storage and downregulate sterol regulatory element-binding proteins (SREBPs), which are essential for lipid synthesis regulation. This disruption results in elevated plasma cholesterol levels, increased fatty acid synthesis, and decreased TG storage (15).

As shown in Table 3, there was a significant mean difference in HDL

Table 1: Demographic characteristics of study subjects

Characteristic	Frequency (%)	Median (IQR)
Age (years)	(N= 210)	36 (14)
Gender Male	193 (91.9%)	
Female	17 (8.1%)	
Race Malay	99 (47.1%)	
Chinese	68 (32.4%)	
Indian	19 (9%)	
Others	24 (11.4%)	

Table 2: Comparison of hypertriglyceridemia between INSTI and non-INSTI HAART regimens

Variable	First-line HAART		Mean difference (95% CI)	P value [a]
	INSTI regimen (n = 104) Mean (SD)	Non-INSTI regimen (n = 106) Mean (SD)		
TG at baseline (mmol/L)	1.34 (0.26)	1.37 (0.25)	-0.033 (-0.103, 0.036)	0.349
TG at 12-month follow-up (mmol/L)	1.62 (0.091)	1.65 (0.075)	-0.03 (-0.053, -0.007)	0.009

[a]Independent t-test

Table 3: Comparison of HDL hypocholesterolemia between INSTI and non-INSTI HAART regimens

Variable	First-line HAART		Mean difference (95% CI)	P value [a]
	INSTI regimen (n = 104) Mean (SD)	Non-INSTI regimen (n = 106) Mean (SD)		
HDL-C at baseline (mmol/L)	1.86 (0.07)	1.849 (0.06)	0.012 (-0.006, 0.031)	0.206
HDL-C at 12-month follow-up (mmol/L)	1.22 (0.29)	1.01 (0.27)	0.206 (0.128, 0.284)	<0.001

[a]Independent t-test

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hypocholesterolemia at 12-month follow-up between patients on non-INSTI regimen 1.01 (0.27) mmol/L and those on INSTI regimen 1.22 (0.29) mmol/L, P <0.001. This study found that patients on non-INSTI regimen had a significant HDL hypocholesterolemia compared to those on INSTI regimen. Taramasso et al. (16) has indicated that shifting from EFV to DTG improved lipid profiles and probably lowered the risk of CVDs. However, a recent study (17) found an association between DTG usage and decreased HDL-C values, which could potentially elevate the risk of CVDs. In contrast to our own findings, a prospective cohort study (18) of people with HIV who were at least 18 years old and had received EFV-based medication for at least 6 months before switching to DTG-based therapy in Thailand, revealed reductions from baseline in HDL-C at week 24 post-switching therapy. The discrepancies in HDL-C outcomes across studies could be attributed to variations in population characteristics and follow-up durations. For instance, some studies involved participants with higher baseline risks for CVD or MetS, while our study featured patients with different metabolic baselines or more favorable profiles at the start. Additionally, the timing of the follow-up played a crucial role, as lipid changes may fluctuate initially and then stabilize over time. For instance, Khemla et al. (18) observed changes at 24 weeks, whereas our study had a longer follow-up of 12 months, allowing more time for lipid profile normalization or different trends to emerge.

A statistically significant mean difference in prediabetes was observed at 12-month follow-up between patients on INSTI regimen, with value of 5.54 (0.291) mmol/L, and those on non-INSTI regimen with value of 5.29 (0.221) mmol/L, P <0.001 (Table 4). This study also found that patients on INSTI regimen had a significant prediabetes compared to those on non-INSTI regimen. Similarly, a recent systematic review and meta-analysis (19) aimed at exploring the correlation between INSTI usage and overall outcomes revealed that within the first 6 months of commencing ART, the initiation of INSTI-based therapy was associated with a 31% increased likelihood of developing glucose intolerance or DM (HR, 1.31; 95% CI, 1.15–1.48; P < 0.001). This finding could be explained by the mechanism of action of INSTIs, which inhibit the integrase enzyme by binding to magnesium, preventing viral replication. Since magnesium is crucial for glucose metabolism and insulin action, its depletion can impair enzyme function and insulin receptor activity, leading to increased insulin resistance (20).

As shown in Table 5, there was no significant difference in hypertension tendency among the patients receiving different types of first-line HAART regimen at 12-month follow-up, P-value >0.05. contrary to our findings, Musekwa et al. (21) found that individuals on DTG-containing regimens were twice as prone to hypertension compared to those on NNRTIs, notably EFV (aOR: 2.44, 95% CI 1.22-4.86; p = 0.01), according to a study that examined the association between

Table 4: Comparison of prediabetes between INSTI and non-INSTI HAART regimens

Variable	First-line HAART		Mean difference (95% CI)	P value [a]
	INSTI regimen (n = 104) Mean (SD)	Non-INSTI regimen (n = 106) Mean (SD)		
FBG at baseline (mmol/L)	4.98 (0.365)	4.94 (0.215)	0.041 (-0.04, 0.123)	0.313
FBG at 12-month follow-up (mmol/L)	5.54 (0.291)	5.29 (0.221)	0.254 (0.184, 0.325)	<0.001

[a]Independent t-test

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ART regimen and hypertension in PLWH in Zambia. Brennan et al. (22) examined the risk of developing hypertension among patients in South Africa who transitioned from EFV to DTG as part of first-line ART. Their findings indicated that, within one year of switching, there was a 14.2% increase in hypertension risk for those on DTG compared to those who continued with EFV. The differences in findings could be attributed to variations in population characteristics and ART duration. While some studies included both normotensive and hypertensive patients on ART for over two years, allowing pre-existing hypertension or long-term ART effects to manifest, our study excluded individuals with pre-existing hypertension and had a shorter follow-up period of 12 months. This shorter duration might not have allowed for the detectionof significant changes in blood pressure. Furthermore, metabolic effects of DTG, such as weight gain and insulin resistance, may require a longer time to impact hypertension.

Predictors of MetS among the study subjects

As shown in Table 6, binary logistic regression was performed to assess how different predictors affected the probability of developing MetS in adults receiving a first-line HAART regimen. The model comprised 7 independent variables; age, gender, first-line HAART regimen, CKD, liver impairment, depressive disorders and drug addiction. 4 out of 7 of the independent variables (age, non-INSTI HAART regimen, depressive disorders and addiction) provided a distinct and statistically meaningful input to the model when univariate binary logistic regression was employed to measure each variable's impact without controlling other independent variables. However, when multivariate binary logistic regression was applied to assess the impact of additional independent variables by holding all other variables to get the effect of the variable of interest, 3 out of 7 of the independent variables (age, non-INSTI HAART regimen and depressive disorders) contributed a distinct and statistically significant element to the model.

Patients with depressive disorders were over 4.3 times more likely to report MetS at 12-month follow-up compared to non-depressed patients (AOR 4.33, 95% CI 1.329-14.16). This could be supported by a meta-analysis (23) that investigated the association between depression and MetS, showing that individuals with depression were at a greater risk for MetS compared to those without, indicated by odds ratios of 1.48 (95% CI: 1.33–1.64) versus 1.38 (95% CI: 1.17–1.64) for the respective groups. While the exact mechanisms connecting MetS to depression remain unclear, several hypotheses have been suggested. On the one hand, it has been determined that a sedentary lifestyle and poor nutrition are significant causes of MetS, factors that might be more prevalent among individuals experiencing depression compared to non-depressed people. The diminished physical activity associated with depression placed individuals at risk of weight gain, MetS, and, ultimately, the development of DM and CVDs (23). Conversely, recent research revealed a connection between persistent, low-grade inflammation and both MetS and depression. The pro-inflammatory cytokine levels in the blood were higher in this case. Insulin resistance is directly induced by cytokines that

Table 5: Association between first-line HAART and hypertension tendency among studied subjects

Variable	Hypertension at 12-month follow-up		X2 statistic (df)	P value
	Yes n (%)	No n (%)		
First-line HAART				
INSTI regimen	93 (89.4%)	11 (10.6%)	0.95 (1)	0.328[a]
Non-INSTI regimen	90 (84.9%)	16 (15.1%)		

[a]Chi-Square test

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Table 6: Univariate and multivariate binary logistic regression predicting likelihood of MetS

variable	B	P-value	COR	95% C.I. for OR		B	P-value	AOR	95% C.I. for OR	
				Lower	Upper				Lower	Upper
Age	0.05	0.005	1.049	1.014	1.085	0.079	0.001	1.079	1.03	1.129
Gender[a]	0.35	0.595	1.419	0.39	5.159	0.658	0.348	1.931	0.489	7.625
Male										
First-line HAART[b]	0.75	0.028	2.115	1.085	4.123	0.813	0.038	2.255	1.048	4.852
Non-INSTI regimen										
CKD patients[c]	0.39	0.277	1.483	0.729	3.018	0.299	0.527	1.348	0.535	3.4
Liver impairment patients[d]	0.1	0.785	1.104	0.542	2.251	0.081	0.855	1.084	0.455	2.582
Depressive disorders patients[e]	1.38	<0.001	3.969	2.015	7.819	1.467	0.015	4.337	1.329	14.16
Drug addicted patients[f]	1.29	<0.001	3.64	1.865	7.106	0.422	0.469	1.524	0.487	4.773

[a]as compared to female
[b]as compared to INSTI regimen
[c]as compared to non-CKD patients
[d]as compared to non- liver impairment patients
[e]as compared to non-depressive disorders patients
[f]as compared to non-drug addicted patients

are raised in obese situations, which may contribute to the evolution of MetS. Research has indicated that these cytokines may cause depression-like behavior under chronic stress settings by interfering with neurotransmitter production and signal transduction (24). Lin et al. (25) demonstrated that the use of antidepressants was associated with an increased risk of hypertension (OR= 1.40), higher TG levels (OR= 1.43), and the presence of all components of MetS (OR= 1.74).

Patients on non-INSTI regimen were over 2.2 times more likely to report MetS at 12-month follow-up compared to patients on INSTI regimen, (AOR 2.25, 95% CI 1.048-4.852). In a cross-sectional study (26) aimed at identifying independent predictors of MetS in HIV-positive patients, it was found that the use of HAART was independently associated with MetS (OR 1.46; P= 0.02). In contrast to our study findings, the ADVANCE trial (27) which intended to ascertain the prevalence of MetS in HIV patients found a higher incidence of treatment-emergent MetS with TDF/FTC/DTG (10%) compared to TDF/FTC/EFV (7%). This variance could be explained by the variability in defining MetS, as illustrated by different criteria. The ADVANCE trial, for instance, employed the International Diabetes Federation (IDF) criteria, which necessitate central obesity as a diagnostic prerequisite. Notably, recent trials have pointed towards a stronger association between weight gain and INSTI regimens (28). In contrast, our study adopted the modified NCEP ATP III criteria, where central

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obesity was just one of several potential components. Moreover, the availability of data on waist circumference were inconsistent and were excluded from the final analysis.

This study also found that age was the third predictor of reporting MetS at 12-month follow-up, where with every one-year increase in age, the odds of MetS increased by 1.079, (AOR 1.079, 95% CI 1.03-1.129). This finding was consistent with several studies (9, 29, 30) where age (AOR=1.09, 95% CI (1.05-1.12) was identified as a non-modifiable independent risk factor of MetS. With aging, a variety of predisposing conditions become more prevalent, such as high consumption of high-calorie and low-fiber food, diminished physical activity, obesity, insulin resistance, inflammation, changes in the functioning of the hypothalamus-pituitary-adrenal axis, stress, increased visceral adipose tissue, and hypertension. Collectively, these factors contributed to high prevalence of MetS in the elderly populations (31, 32).

One of the strengths of this study was its attempt to emphasize the impact of first-line HAART on MetS components and to identify certain MetS risk factors among individuals with HIV receiving first-line HAART in Malaysia. However, integrating early diagnosis for its components into good clinical practices is crucial. This proactive approach may help slow down its impact on the development of CVDs. On the other hand, our study encountered a limitation as the availability of data on waist circumference and height were inconsistent and were excluded from the final analysis, which posed a challenge in using waist circumference as a component for diagnosing MetS according to the modified NCEP ATP III criteria. Consequently, this limitation resulted in an underdiagnosis of MetS, particularly among patients on INSTI regimen.

Conclusion

Our study established that INSTI-based HAART regimen may demonstrate a more favorable lipid safety profile compared to alternative ART, particularly conventional treatment protocols involving EFV. However, they have been associated with an elevated occurrence of prediabetes and risk of type 2 DM when compared to other ART regimens. The study also revealed that depressive disorders, non-INSTI HAART regimens and age were robust predictors for reporting MetS among HIV patients.

This innovative research with such a strong study design emphasized the importance of health education promotion and regular monitoring of patients' clinical and laboratory parameters for managing and preventing metabolic disorders in HIV patients. Routine metabolic monitoring and early intervention should be integrated into HIV care to mitigate long-term cardiovascular and metabolic complications. Moreover, our findings highlighted the urgent need for further future studies to develop guidelines and recommendations for healthcare providers, ensuring the integration of MetS management into routine HIV care.

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Conflict of interest

The authors declared no conflict of interest.

Ethical Approval

The study protocol and DCF were screened and accepted by the Medical Research and Ethics Committee (MREC), and ethical clearance was secured prior to commencing data collection and access to patients' medical records. The National Medical Research Register (NMRR) ID obtained for this study after online registration

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was NMRR ID-22-02650-ISQ. Additionally, authorization was obtained from the Director of Hospital Sungai Buloh to access the medical records.

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