

# Incidence of Metabolic Syndrome among Adults on First-Line Highly Active Antiretroviral Therapy Regimens in Malaysia

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**Abstract Introduction:** Despite the established effectiveness of highly active antiretroviral therapy (HAART) in reducing HIV-related morbidity and mortality, concerns are rising regarding the emergence of metabolic syndrome (MetS). However, there is inadequate evidence regarding the incidence of MetS among adults starting first-line HAART regimens in Malaysia. **Objectives:** This study was conducted to determine overall incidence of MetS in HIV patients on first-line HAART regimens and to assess the association between first-line HAART and incidence of MetS at 6-month and 9-month follow-ups among studied subjects. **Methodology:** This was a prospective cohort study involving adult patients ( $\geq 18$  years old) diagnosed with HIV from January 2023 till May 2023 and on first-line HAART regimen with or without integrase strand transfer inhibitor (INSTI) for at least 6 months undergoing follow-up at infectious disease (ID) clinic at a tertiary Malaysian hospital. The study subjects were screened and recruited using purposive sampling after being selectively allocated into 2 groups according to inclusion and exclusion criteria. The patients' profiles were screened via the electronic

hospital information system (eHIS) using a pre-prepared data collection form. **Results:** A total of 210 patients were included in this study with median and interquartile range (IQR) of age was 36 (14) years. The majority of the participants were males ( $n=193$ , 91.9%) and Malays ( $n=99$ , 47.1%). The study results showed that overall incidence of MetS was seen the most in about one fourth of studied subjects ( $n=48$ , 22.9%) at 9-month follow-up, whereas only 5 (2.4%) patients had MetS at 6-month follow-up. This study also found a significant association between first-line HAART and incidence of MetS at 9-month follow-up, where there was a significant increase in MetS among patients on non-INSTI regimen (29.2%) compared to those on INSTI regimen (16.3%). **Conclusion:** This study found that initiation of first-line HAART regimens, particularly regimens without INSTI, in individuals with HIV has been associated with an increased incidence of MetS. Thus, promoting health education and consistently monitoring patients' clinical and laboratory parameters during each visit, while implementing appropriate measures, are deemed ideal.

**Keywords** Incidence, Metabolic Syndrome, First-Line HAART Regimens, HIV, Malaysia

## 1. Introduction

HIV is identified as a retrovirus that selectively targets the cluster of differentiation 4 (CD4) T-lymphocytes, a distinctive subset of white blood cells vital for the immune system. This viral attack leads to the depletion of these cells, resulting in severe immunodeficiency in the infected individual. As the CD4 count decreases to a critical level, the host's immune defenses become inadequate to protect against opportunistic infections and malignancies [1].

Highly active antiretroviral therapy comprising a blend of three or more potent antiretroviral (ARVs) drugs from a minimum of two distinct classes, has significantly diminished mortality and morbidity rates in individuals living with HIV. It has notably enhanced the quality of life, achieved sustained and effective suppression of plasma HIV RNA, restored and preserved immunologic function, and prevented drug resistance and HIV transmission. This is accomplished by effectively suppressing HIV replication in individuals living with the virus [2]. The Malaysian Consensus Guidelines on antiretroviral therapy (ART) [3] highlighted that the initial HAART regimens for treatment-naïve patients typically include two nucleoside reverse transcriptase inhibitors (NRTIs) like tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as efavirenz (EFV) or an INSTI such as dolutegravir (DTG). The recommended first-line regimen for adults and adolescents initiated on ART is either TDF/FTC/EFV or TDF/FTC/DTG in cases of NNRTI intolerance.

The connection between HAART usage and the development of metabolic abnormalities and lipodystrophy is significant [4], [5]. This transformation in the pattern of HIV/AIDS morbidity has shifted from predominantly immunodeficiency and opportunistic infections to a more prominent role of metabolic complications [6].

The metabolic syndrome involves a combination of metabolic irregularities, including insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension. When untreated, MetS is significantly associated with an increased risk of developing diabetes mellitus (DM) and cardiovascular diseases (CVDs) [7]. Various criteria exist for defining MetS, with the guidelines established by the United States National Cholesterol Education Program: Adult Treatment Panel III (US NCEP-ATP III) being among the most widely utilized for its diagnosis [8].

Because of the absence of data on metabolic complications and the incidence of MetS among HIV-infected individuals undergoing HAART in Malaysia, and

the impracticality of extrapolating findings from developed nations to developing societies due to variations in patient demographics, HIV subtypes, and lifestyle factors [9], there is a need for tailored research in the Malaysian context. This study aimed to address this gap, specifically, it aimed to determine the overall incidence of MetS in HIV patients on first-line HAART regimens and to assess the association between first-line HAART and incidence of MetS at 6-month and 9-month follow-ups among studied subjects. Through these data objectives, our goal was to raise awareness among healthcare providers regarding the magnitude of MetS among HIV patients undergoing HAART in order to enhance disease management and attain optimal viral load control while minimizing metabolic complications within the Malaysian population.

## 2. Materials and Methods

### 2.1. Study Design and Study Population

This was a prospective cohort observational study utilising purposive sampling conducted at ID clinic at Hospital Sungai Buloh, Selangor, a large government hospital that provides secondary and tertiary services and the largest ID hospital in Malaysia. The study involved adult patients ( $\geq 18$  years old) diagnosed with HIV from January 2023 till May 2023 and on first-line HAART regimen with or without INSTI for at least 6 months. Study subjects who met the inclusion criteria were selectively allocated into 2 groups, 104 patients were on first-line HAART with INSTI, while 106 patients were receiving standard care regimen without INSTI. Patients with incomplete medical profile, pregnant women, patients with pre-existing DM, dyslipidaemia and hypertension before commencing HAART and switching period between INSTI and non-INSTI regimens that is less than 6 months were excluded. The data collection process was undertaken between June 2023 to January 2024. This study comprised both retrospective and prospective elements: initially, data previously recorded when the patient was initiated on HAART were collected, followed by a 6-month and 9-month follow-up period.

### 2.2. Sample Size Calculation

Sample size was estimated using Cochran's formula [10] with the following assumptions; 30% prevalence (P) of MetS in HIV patients on first-line HAART regimen based on a previous study [11], 5% margin of error (d), 95% confidence interval and statistic for level of confidence (Z) of 1.96.

$$n1 = (Z^2 \times P \times (1-P)) / d^2 \quad (1)$$

The new, adjusted sample size of 210 was calculated by using the following equation:

$$n2 = (n1) / (1 + ((n1 - 1) / N)) \quad (2)$$

Where,  $n_2$  is required sample size adjusted for a smaller population,  $n_1$  is Cochran's sample size for a large population, and  $N$  is estimated number of adult patients diagnosed with HIV from January 2023 till May 2023 and on first-line HAART for at least 6 months at the study site which was determined to be 380 patients, considering a 20% allowance for non-response.

### 2.3. Data Collection

An application was submitted to the Information Technology (IT) department of Hospital Sungai Buloh to request access to the eHIS. Upon obtaining authorization for data access, a comprehensive list of patients under the care of the ID clinic at Hospital Sungai Buloh was compiled. This compilation adhered to specific inclusion and exclusion criteria. Afterwards, a pre-determined data collection form (DCF) was created and underwent testing during a pilot study. This pilot study involved 21 patients and aimed to ensure the relevance and feasibility of the DCF before the actual data collection process commenced. The patients' profiles were screened using their medical record number (MRN), and data were extracted solely by the principal investigator via the eHIS to obtain the required sample size. Therefore, data collection remained consistent throughout the study.

The DCF included various sections covering socio-demographic and clinical characteristics, clinical and laboratory parameters, as well as details about the prescribed first-line HAART regimen. Blood pressure (BP) was measured following the standard operating procedures practiced by the hospital. Similarly, biochemical measurements, including fasting blood glucose (FBG) and lipid profile were collected in adherence to laboratory standard operating procedures by a trained laboratory technologist. However, measurements for variables such as waist circumference (WC) and height were not conducted by the hospital, impacting the calculation of the percentage incidence of MetS since WC is one of the components used for MetS diagnosis.

A pre-determined data collection form was used to ensure consistency and the data were verified by 2 other co-researchers at the study site prior to data analysis to maintain validity and reliability. Numerous steps were implemented to mitigate bias in the study. Firstly, clear eligibility criteria were established for participant selection, and baseline characteristics among patient groups were ensured to be similar. This not only rendered the study population relevant but also minimised selection bias. Exclusion criteria were set for patients with pre-existing conditions such as DM, dyslipidaemia, and hypertension before starting HAART, as well as for those experiencing a switching period between INSTI and non-INSTI regimens that lasts less than six months. This was crucial to prevent potentially misleading data. Additionally, efforts were also made to minimise loss to follow-up, which was instrumental in ensuring that the collected data remained

representative of the initial study population and helped to mitigate attrition bias.

### 2.4. Data Analysis

The data were input into Statistical Package for Social Sciences (SPSS) version 24.0 for analysis. Descriptive statistics, involving frequency and percentage (%), were conducted for socio-demographic, epidemiological, clinical, and laboratory variables. Paired t-test was used to compare clinical parameters at baseline and 9-month follow-up. Association between first-line HAART usage and the incidence of MetS was examined through the Chi-square test, with statistical significance declared at a  $p$ -value  $< 0.05$ .

### 2.5. Outcome Definition

The modified NCEP ATP III defined MetS as meeting three or more of the following criteria: abdominal obesity (specifically, for individuals of Asian origin, WC  $\geq 90$  cm for men and  $\geq 80$  cm for women); triglycerides (TG) level  $\geq 1.7$  mmol/L; low high-density lipoprotein cholesterol (HDL-c)  $\leq 1.03$  mmol/L in men and  $\leq 1.29$  mmol/L in women; BP  $\geq 130/85$  mmHg; and FBG level  $\geq 5.6$  mmol/L. For NCEP criteria, abdominal obesity is considered a component of the syndrome but is not a mandatory prerequisite for its diagnosis [12].

### 2.6. Ethical Considerations

#### 2.6.1. Confidentiality and Security of Data

The privacy of subjects' personal information was treated with full confidentiality where only the principal investigator was able to access the study data. However, to ensure the research study was conducted in accordance to proper protocol and all of the data was recorded thoroughly, other personnel such as qualified monitors, auditors, governmental or regulatory authorities might also have the access to subjects' personal information.

To further protect subject's confidentiality and to ensure it was preserved, the copy of study data was only limited to two copies in which one copy which was kept by the principal investigator and another copy was kept in the library for archival purpose. After a maximum of 2 years, these study data will be completely disposed.

#### 2.6.2. Ethical Approval

All aspects of this study protocol and data collection form were reviewed and approved by Medical Research and Ethics Committee (MREC). The National Medical Research Register (NMRR) ID obtained for this study after online registration is NMRR ID-22-02650-ISQ. Ethical approval by MREC was also obtained before commencing on data collection and access to patient's medical record. Besides that, approval from the Director of Hospital Sungai Buloh was obtained to gain the access to medical records.

### 3. Results

A total of 250 patients were screened over the study period. Patients were selectively allocated into 2 groups; 112 patients were on INSTI regimen and 138 patients were on non-INSTI regimen. A total of 40 cases were excluded from both groups due to incomplete data, leaving a final number of subjects of 210. Among these, 104 patients were under the INSTI regimen, while 106 patients were following a non-INSTI regimen. The median (IQR) of age was 36 (14) years with nearly two-thirds of the patients

aged between 18 and 39 years. The majority of the subjects were males (n= 193, 91.9%) and Malays (n= 99, 47.1%). The majority of the subjects were identified as homosexual men, specifically men who have sex with men (MSM) (n=126, 60%), while the smallest group consisted of intravenous drug users (n=21, 10%). Regarding clinical parameters, there were highly significant mean differences observed in MetS components, including TG, HDL-C, systolic BP, diastolic BP, and FBG, both at baseline and at the 9-month follow-up, with a p-value <0.001 (Table 1).

**Table 1.** Patients' demographics and clinical characteristics

Characteristic	Frequency (%) (N= 210)	Median (IQR)	Mean (SD)	Mean Diff. (95% CI)	P-value <sup>a</sup>
<b>Age (years)</b>		36 (14)			
18-29 years	53 (25.2%)				
30-39 years	82 (39%)				
40-49 years	57 (27.1%)				
≥ 50 years	18 (8.6%)				
<b>Gender</b>					
Male	193 (91.9%)				
Female	17 (8.1%)				
<b>Race</b>					
Malay	99 (47.1%)				
Chinese	68 (32.4%)				
Indian	19 (9%)				
Others	24 (11.4%)				
<b>HIV mode of transmission</b>					
Homosexual (MSM)	126 (60%)				
Heterosexual	63 (30%)				
Intravenous drug use	21 (10%)				
<b>TG (mmol/L)</b>					
At baseline			1.35 (0.257)	-0.282	<0.001
At 9-month follow up			1.64 (0.08)	(-0.31, -0.24)	
<b>HDL-C (mmol/L)</b>					
At baseline			1.85 (0.07)	0.738	<0.001
At 9-month follow up			1.11 (0.3)	(0.69, 0.77)	
<b>Systolic BP (mmHg)</b>					
At baseline			127.19 (1.92)	0.738	<0.001
At 9-month follow up			134.31 (5.45)	(0.69, 0.77)	
<b>Diastolic BP (mmHg)</b>					
At baseline			80.66 (2.71)	-1.70	<0.001
At 9-month follow up			82.37 (4.08)	(-2.32, -1.09)	
<b>FBG (mmol/L)</b>					
At baseline			4.96 (0.29)	-0.45	<0.001
At 9-month follow up			5.41 (0.28)	(-0.50, -0.40)	

<sup>a</sup>Paired t-test

\*P value < 0.05 is statistically significant

Major depressive disorder (MDD) was the most frequent comorbidity, identified in the majority of patients (n=82, 39%) followed by chronic liver disease (n=58, 27.6%) and chronic kidney disease (CKD) (n=53, 25.2%) as shown in Table 2.

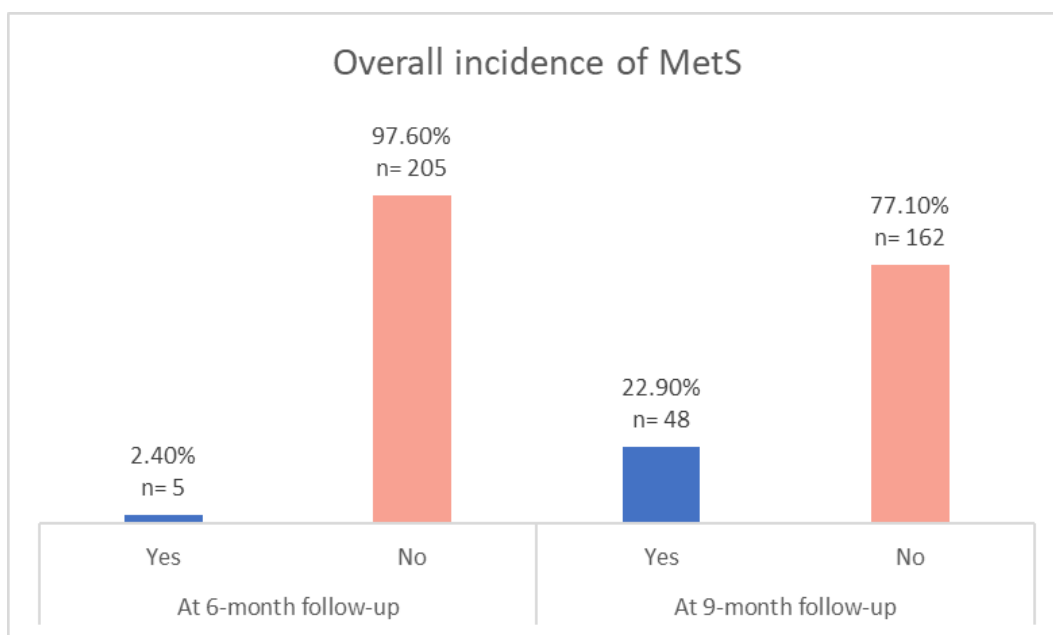
Overall incidence of MetS was seen the most in about one fourth of studied subjects (n=48, 22.9%) at 9-month follow-up, whereas only 5 (2.4%) patients had MetS at 6-month follow-up as shown in Figure 1. The most common combination of MetS components was HDL hypocholesterolaemia, hypertriglyceridaemia and hypertension (n=24, 11.4%), followed by HDL hypocholesterolaemia, hypertension and glucose intolerance (n=15, 7.1%), and HDL hypocholesterolaemia, hypertriglyceridaemia, hypertension and glucose intolerance (n=5, 2.4%), while HDL hypocholesterolaemia, hypertriglyceridaemia and glucose intolerance (n=4, 1.9%) were the least frequent combination as shown in Figure 2.

There was a significant increase in MetS at 9-month follow-up among patients on non-INSTI regimen 31

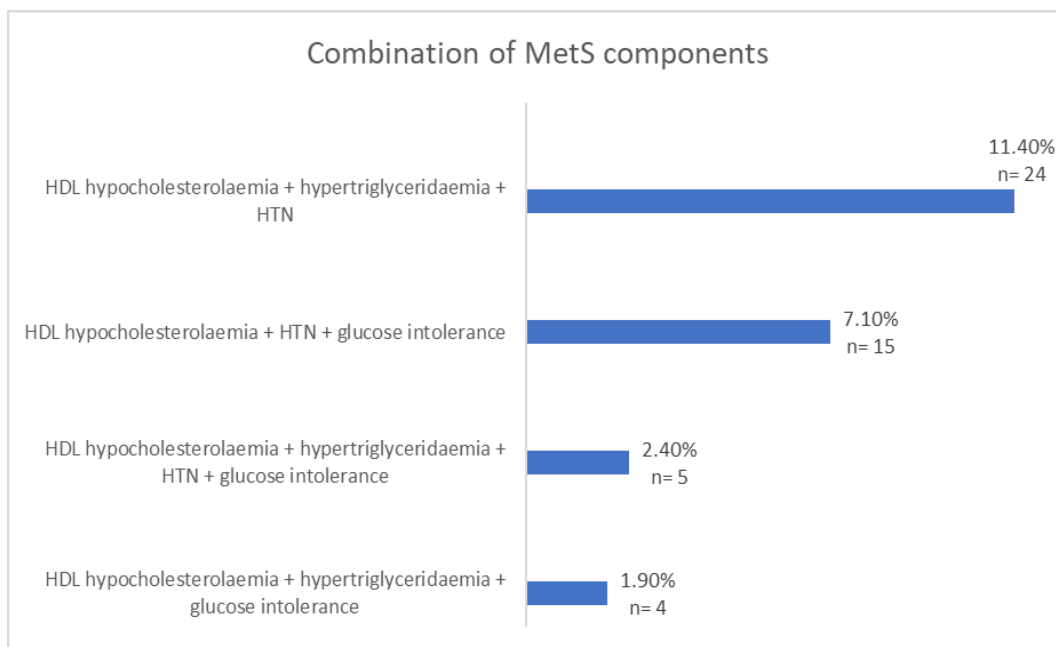
(29.2%) compared to those on INSTI regimen 17 (16.3%), (P value <0.05) as shown in Table 3.

**Table 2.** Patients' concurrent comorbidities

Comorbidity	Frequency (%) (N= 210)
<b>MDD</b>	82 (39%)
<b>Chronic liver disease</b>	58 (27.6 %)
<b>CKD</b>	53 (25.2%)
<b>Anaemia</b>	51 (24.3%)
<b>Asthma</b>	38 (18.1%)
<b>COPD</b>	25 (11.9%)
<b>Coronary artery disease (CAD)</b>	25 (11.9%)
<b>Acute kidney injury (AKI)</b>	18 (8.6%)
<b>Others</b>	49 (23.3%)



**Figure 1.** Overall incidence of MetS at 6-month and 9-month follow-ups



**Figure 2.** Combination of MetS components among studied subjects at 9-month follow-up

**Table 3.** Association between first-line HAART and incidence of MetS among studied subjects

Variable	MetS at 6-month follow-up		X <sup>2</sup> statistic (df)	P value	MetS at 9-month follow-up		X <sup>2</sup> statistic (df)	P value
	Yes n (%)	No n (%)			Yes n (%)	No n (%)		
<b>First-line HAART</b>								
INSTI regimen	2 (1.9%)	102 (98.1%)	NA	1 <sup>b</sup>	17 (16.3%)	87 (83.7%)	4.954	0.026 <sup>a</sup>
Non-INSTI regimen	3 (2.8%)	103 (97.2%)			31 (29.2%)	75 (70.8%)		

<sup>a</sup>Chi-Square test

<sup>b</sup>Fisher's Exact test

## 4. Discussion

This study found that the median (IQR) age of the studied patients was 36 (14) years with almost two-thirds of the patients fell within the 18-39 age range. Sharma et al. [13] documented comparable results, revealing a median age of 36 (29-44) years with an interquartile range. The Malaysian global AIDS monitoring report [14] confirmed these findings, indicating that over three-quarters of new HIV infections in 2022 occurred among individuals aged 20 to 39 years. Specifically, 45% of the cases were in the 20-29 age group, while 32% fell within the 30-39 age range. Specific subsets of young individuals faced an increased risk of HIV due to engaging in behaviors that, if not undertaken with precautions, heighten the probability of virus transmission. These high-risk groups include young men involved in same-sex relationships, individuals engaged in sex work, and those participating in drug injection. Additionally, adolescents were particularly susceptible to acquiring HIV, influenced by factors such as involvement in multiple short-term sexual relationships

without consistent condom use and lack of comprehensive knowledge and understanding about HIV/AIDS [15].

This study also revealed that higher proportion of HIV patients on first-line HAART in male compared to female. Abiola et al. [16] also reported a comparable finding, indicating that among the 242 HIV patients on the HAART regimen, 215 (88.8%) were males, while 27 (11.2%) were females. This pattern may be influenced by the prevalent stigma and discriminatory attitudes towards females, more pronounced in socially and religiously conservative societies like Malaysia. Such biases could contribute to the higher proportion of people living with HIV (PLWH) and those on first-line HAART among males compared to females [17]. Chong et al. [18] similarly documented a shift in the primary driver of the HIV epidemic in Malaysia, transitioning from people who inject drugs to HIV transmission through sexual contact, particularly among men who have sex with men. This aligns with our study's findings, where a majority of the HIV patients were identified as MSM.

Meanwhile, there were more Malays and Chinese

compared to Indians and other races. This finding was similar to data by Velvanathan et al. [19] who reported that out of 120 HIV patients on the HAART regimen at the infectious disease clinic of Hospital Sungai Buloh, Malaysia, Malays constituted the largest proportion (n=77, 64.2%), followed by Chinese (n=35, 29.2%), and Indians (n=8, 6.7%). This observation may be attributed to the racial distribution within the Malaysian population, particularly in West Malaysia, where the majority are ethnic Malays, followed by Chinese, and then Indians.

Additionally, this study revealed higher levels of TG, systolic BP, diastolic BP, and FBG at the 9-month follow-up compared to baseline levels. Conversely, the levels of HDL-C at the 9-month follow-up were lower than those observed at baseline. These findings are consistent with a cross-sectional survey [9] aimed at evaluating the prevalence of metabolic abnormalities among HIV-infected patients on HAART for at least 6 months, which indicated that a majority of the subjects (60%) had elevated TG levels, while a smaller proportion exhibited high FBG levels (38.2%) and low HDL-C levels (28.7%).

This study also found that MDD was the most common comorbidity which accounted for 39% of the studied subjects. Similar findings were reported by a systematic review and meta-analysis, where major depression was the most common mental disorder among PLWH with estimates indicating a two to threefold higher occurrence compared to the general population [20]. Asrat et al. [21] revealed a high frequency of MDD among PLWH, attributable to their susceptibility to diverse influencing factors. These factors were classified into three main categories: 1) psychosocial elements such as HIV-related stigma, disability, and poverty; 2) biological factors, encompassing structural and functional changes in the brain resulting from HIV infection, including alterations in the hypothalamic-pituitary-thyroid pathway, and chronic immune activation; and 3) additional comorbid conditions, including pre-existing illnesses beyond HIV/AIDS, which may amplify the likelihood of experiencing depression.

This study showed that overall incidence of MetS was seen the most in about one fourth of studied subjects (22.9%) at 9-month follow-up. A prior study revealed a MetS prevalence of 21.1% among 313 HIV patients undergoing HAART in South West Ethiopia. Notably, the study identified that a HAART duration exceeding 12 months independently correlated with a significantly increased likelihood of MetS [22]. Although MetS was associated with both HIV infection and use of HAART, individuals with HIV receiving HAART had a significantly higher burden of MetS and cardiovascular disease risk factors compared to treatment-naïve patients. Additionally, on multivariate analysis, long duration of combined antiretroviral therapy (cART) was among other factors significantly associated with a higher risk of MetS [23].

This study also showed that HDL hypocholesterolaemia, hypertriglyceridaemia and hypertension were the most common combination of MetS components (11.4%),

followed by HDL hypocholesterolaemia, hypertension and glucose intolerance (7.1%), and HDL hypocholesterolaemia, hypertriglyceridaemia, hypertension and glucose intolerance (2.4%), while HDL hypocholesterolaemia, hypertriglyceridaemia and glucose intolerance (n= 4, 1.9%) were the least frequent combination. Similar findings were reported by Ang et al. [24] in Singapore, where the overall prevalence of MetS was 23.6% and of the 526 with MetS, the most common combination was HDL hypocholesterolaemia, hypertriglyceridaemia and hypertension (51.0%). This could be attributed to the patients' risk factors of MetS and the criteria used to define MetS among studied subjects.

This study also found a significant association between first-line HAART and incidence of MetS at 9-month follow-up, where there was a significant increase in MetS among patients on non-INSTI regimen (TDF/FTC/EFV) (29.2%) compared to those on INSTI regimen (TDF/FTC/DTG) (16.3%). In contrast to our study's findings, the ADVANCE trial [25] which was conducted to assess the incidence of MetS among HIV patients, with half of them on the TDF/FTC + DTG arm and the other half on the TDF/FTC + EFV arm, revealed a higher incidence of treatment-emergent MetS with INSTI regimen (10%) compared to non-INSTI regimen (7%). This variance may be explained by differences in defining MetS, as exemplified by various criteria. The ADVANCE trial utilized The International Diabetes Foundation (IDF) criteria, which necessitate central obesity as a diagnostic prerequisite. Notably, recent trials have indicated a notable association between INSTI regimens and weight gain. In contrast, our study employed the modified NCEP ATP III criteria for MetS definition, where central obesity was just one of several possible components. Additionally, the measurement of patients' waist circumference was not conducted at the study site.

One notable strength of this study was its focus on highlighting the incidence of MetS and its association with first-line HAART among HIV-infected patients in Malaysia. However, it is imperative to integrate early diagnosis of MetS components into good clinical practices to mitigate its impact on CVDs development.

Nevertheless, our study faced certain limitations. The lack of measurement of patients' waist circumference or height at the study site posed challenges in using waist circumference as a diagnostic component for MetS according to the modified NCEP ATP III criteria. Consequently, this limitation led to an underdiagnosis of MetS, particularly among patients on INSTI regimens. Additionally, the study was conducted at a single center and had a relatively small sample size, which might have been inadequate for robust comparative analysis and may not fully represent HIV-positive individuals receiving care at other healthcare institutions. However, it's noteworthy that Hospital Sungai Buloh, being the largest Infectious Disease hospital in Malaysia and the primary referral center for HIV care in the country, serves the largest population

of PLWH in Malaysia. Therefore, our study offers valuable insights into the incidence of MetS among PLWH in Malaysia.

## 5. Conclusions

Our study found that approximately one-fourth of the subjects exhibited incidence of MetS at the 9-month follow-up, with HDL hypocholesterolaemia, hypertriglyceridaemia, and hypertension were the most common combination of MetS components. Additionally, our findings indicated a significant increase in MetS among patients on non-INSTI regimens compared to those on INSTI regimens. Therefore, promoting health education and consistently monitoring patients' clinical and laboratory parameters during each visit, while implementing appropriate measures, are deemed ideal.

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None to declare.

## Conflict of Interest

The authors declare that there is no financial, personal, authorship, or any other type of conflict of interest associated with this research that may have an effect on the findings of the research.

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