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Risk of Dyslipidemia After Weight Gain in Advanced HIV Disease: A Prospective Cohort Study

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Abstract

Antiretroviral therapy (ART) has transformed HIV infection into a manageable chronic condition, but metabolic complications such as weight gain and dyslipidemia have become important clinical concerns. While weight gain after ART initiation may reflect a "return-to-health" phenomenon, its metabolic consequences may differ according to immune status at ART initiation. We evaluated the risk of incident dyslipidemia according to changes in body mass index (BMI), stratified by CD4+ T-cell count at ART initiation, among 392 participants in the Korean HIV/AIDS Cohort Study, a nationwide, prospective, multicenter cohort from 2006 to 2022. Participants were categorized by advanced HIV disease status (AHD, CD4+ <200 cells/μL; non-AHD, ≥200 cells/μL) and BMI change after ART initiation (increase vs. no increase), yielding four groups. Compared with non-AHD participants with BMI increase (n=160), those with AHD and BMI increase (n=125) had a significantly higher risk of dyslipidemia (aHR, 2.01; 95% CI 1.15–3.53), whereas no significant association was observed in the other groups. These findings suggest that BMI gain after ART initiation confers a substantially higher metabolic risk among individuals with advanced HIV disease, highlighting the importance of early HIV diagnosis, timely ART initiation, and close metabolic monitoring of late presenters.

Keywords

HIV; Advanced HIV disease; CD4 count; Body mass index; Dyslipidemia; Antiretroviral therapy

Introduction

People living with human immunodeficiency virus (HIV) may experience HIV wasting syndrome during the course of the disease. This condition, characterized by unintentional weight loss exceeding 10% of baseline body weight, is associated with immune dysfunction, an increased risk of opportunistic infections, and reduced survival. Prior to the introduction of antiretroviral therapy (ART), this syndrome was a major cause of mortality among individuals with HIV [1, 2].

The advent of ART has markedly improved life expectancy among people living with HIV, bringing it closer to that of the general population and transforming HIV infection into a manageable chronic condition [3–5]. Furthermore, early initiation of ART, even in asymptomatic individuals with CD4+ T-cell counts ≥500 cells/μL, has been shown to reduce morbidity and mortality compared with deferred initiation [6].

While immune recovery and weight gain under ART have enabled long-term survival, this shift has also introduced new clinical challenges. Beyond the initial 'return-to-health' phenomenon, excessive weight gain has been increasingly reported among individuals receiving ART [7–10], contributing to a rising incidence of metabolic complications such as diabetes mellitus, non-alcoholic fatty liver disease, dyslipidemia, and hypertension [11, 12].

The impact of ART on metabolic outcomes may vary depending on immune status at treatment initiation, particularly baseline CD4+ T-cell count. Individuals with advanced HIV disease (AHD) tend to exhibit elevated triglyceride levels and reduced high-density lipoprotein (HDL) cholesterol

levels [13], both of which are associated with an increased risk of dyslipidemia [14]. Progression to AHD is characterized by profound immunosuppression and weight loss, factors that may collectively exacerbate lipid dysregulation and increase cardiovascular risk.

Although several studies in Korea have examined ART-related weight gain and dyslipidemia, prospective cohort studies evaluating the impact of weight change on dyslipidemia risk according to immune status at ART initiation remain unclear.

A comprehensive evaluation of the interplay between baseline CD4+ T-cell counts, subsequent changes in body weight, and the development of dyslipidemia is essential for optimizing metabolic health and reducing cardiovascular risk in people living with HIV. Therefore, this study aimed to investigate the risk of incident dyslipidemia according to CD4+ T-cell count at ART initiation and subsequent changes in body mass index (BMI), using data from a large prospective cohort of people living with HIV in Korea.

Methods

1. Data Source

The Korean HIV/AIDS Cohort Study is a nationwide, prospective multicenter cohort supported by the Korea Disease Control and Prevention Agency (KDCA). Established in 2006, the cohort currently includes 15 tertiary hospitals across Korea and prospectively follows adults (≥18 years) with confirmed HIV infection who provide written informed consent. Participants undergo follow-up assessments every 6 months, including standardized case report forms and laboratory evaluations. Data are centrally managed through the KDCA data management system. For the present study, we used data from standardised case report form (CRF) version 3.1.2 collected between December 1, 2006, and December 31, 2022. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (approval No. 4-2025-0037). All participants provided written informed consent at enrollment in the Korean HIV/AIDS Cohort Study, and the requirement for additional informed consent for this secondary analysis was waived by the Institutional Review Board. All methods were performed in accordance with relevant guidelines and regulations, including the Declaration of Helsinki.

2. Study Population

A total of 1,608 individuals enrolled in the Korean HIV/AIDS Cohort were initially screened. Participants were excluded if they had no documented history of ART, had ≥20% missing data for key variables (including body weight and CD4+ T-cell count), were diagnosed with dyslipidemia prior to ART initiation, were enrolled more than 6 months after ART initiation, or had less than 3 years of follow-up (Figure 1). BMI change was assessed over the first 3 years after ART initiation (up to seven visits).

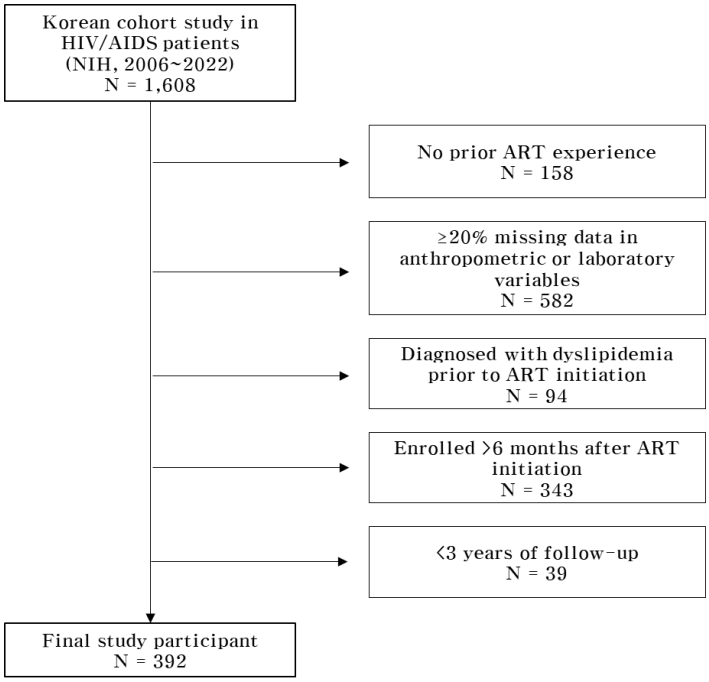
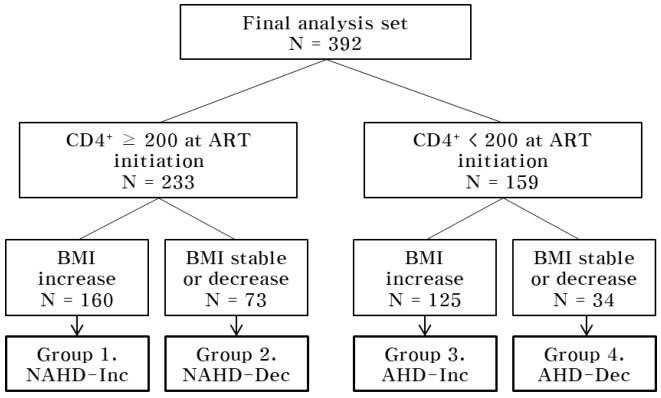


Figure 1. Flowchart of study participant selection.

3. Study Design

Participants were stratified into advanced HIV disease (AHD) and non-AHD groups based on their CD4+ T-cell count at ART initiation. Within each category, participants were further subdivided according to changes in body mass index (BMI) during follow-up—categorized as increase versus no increase (unchanged or decreased)—resulting in four groups (Figure 2).



Abbreviations: NAHD-Inc, non-AHD at ART initiation and BMI increase; NAHD-Dec, non-AHD and BMI stable or decrease; AHD-Inc, AHD and BMI increase; AHD-Dec, AHD and BMI stable or decrease.

Figure 2. Analytical model of study groups.

BMI change was determined by comparing BMI at ART initiation with that at the 3-year follow-up (seventh visit). Participants whose BMI at the 3-year visit was higher than at ART initiation were classified as the BMI increase group, and those whose BMI was unchanged or lower were classified as the stable/decrease group. These four groups served as the primary exposure variables, and the primary outcome was the incidence of dyslipidemia during follow-up. This design allowed assessment of the combined effects of baseline immune status and subsequent BMI changes on dyslipidemia risk.

4. Variable Definition

Dyslipidemia was defined according to the Korean Guidelines for the Management of Dyslipidemia, 5th edition [15]. BMI at ART initiation was categorized as underweight (<18.5 kg/m²), normal or overweight (18.5–24.9 kg/m²), and obese (≥25 kg/m²) according to the WHO Asia-Pacific criteria [16].

5. Statistical Analysis

Among participants with less than 20% missing data (missing proportion, 16.7%), missing BMI and CD4+ T-cell count values were imputed once using participant-specific regression models that predicted missing values from each individual's observed longitudinal pattern of change.

Categorical variables were summarized as frequencies and percentages, while continuous variables were presented as medians with interquartile ranges (IQRs).

Group comparisons were performed using independent t-tests or Mann–Whitney U tests for continuous variables, and Pearson's χ^2 test or Fisher's exact test for categorical variables, as appropriate.

The association between study groups and the risk of incident dyslipidemia was evaluated using multivariable Cox proportional hazards models, with results reported as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was assessed using Schoenfeld residual tests.

To evaluate differences in longitudinal BMI changes across groups, linear mixed-effects models (LMMs) were applied. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a two-sided p-value <0.05 was considered statistically significant.

Results

1. Baseline Characteristics of the Study Population

Among the 1,608 individuals initially enrolled in the Korean HIV/AIDS Cohort between December 1, 2006, and December 31, 2022, a total of 392 participants met the eligibility criteria and were included in the final analysis. The demographic and clinical characteristics at ART initiation are summarized in Table 1.

At ART initiation, the median age was 36 years (interquartile range [IQR], 27.5–44.0), with the largest proportion of participants aged 30–39 years (n=125, 31.9%). The cohort was predominantly male (n=373, 95.2%). In terms of nationality, the vast majority were Korean (n=386, 98.5%), while a small proportion consisted of naturalized Asian individuals (n=6, 1.5%).

The median CD4+ T-cell count at baseline was 285 cells/μL (IQR, 174.0–427.5); 159 participants (40.6%) had advanced HIV disease (CD4+ <200 cells/μL) and 233 (59.4%) had CD4+ ≥200 cells/μL. The median BMI at ART initiation was 21.6 kg/m² (IQR, 19.8–23.3). Thirty participants (7.7%) were underweight (BMI <18.5 kg/m²), 305 (77.8%) had a BMI of 18.5–24.9 kg/m², and 57 (14.5%) were obese (≥25 kg/m²). The median time from HIV diagnosis to ART initiation was 122.5 days (IQR, 33–1,015).

2. Comparison Between Participants with and without Dyslipidemia

During follow-up, 145 participants (37.0%) developed dyslipidemia, while 247 (63.0%) did not. Baseline characteristics of the two groups are presented in Supplementary Table S1.

Participants who developed dyslipidemia were significantly older than those who did not (median

age: 39 years [IQR, 34–45] vs. 32 years [IQR, 26–42]; p<0.0001). No significant differences were observed in sex (male: 95.2% vs. 95.1%; p=0.989) or nationality (Korean: 97.9% vs. 98.8%; p=0.255).

Baseline BMI was higher in participants who developed dyslipidemia (p=0.0003), and the distribution of BMI categories also differed between groups (p=0.047), with a higher proportion of obese individuals (BMI ≥25 kg/m²) in the dyslipidemia group (19.3%) than in the non-dyslipidemia group (11.7%).

The median time from HIV diagnosis to ART initiation was longer in participants who developed dyslipidemia (272 days [IQR, 39–1,372]) than in those who did not (88 days [IQR, 30–684]; p=0.007). Family history of dyslipidemia did not differ between groups (p=0.709), whereas diabetes mellitus was more prevalent in the dyslipidemia group (p<0.0001).

3. Baseline Characteristics According to AHD Status at ART Initiation

When stratified by immune status at ART initiation, participants in the AHD group were older (p<0.001) and had lower CD4+ T-cell counts (p<0.0001) than those in the non-AHD group. Baseline BMI was also lower in the AHD group (p<0.0001).

The time from HIV diagnosis to ART initiation was longer in the non-AHD group (p<0.0001). The distribution of drinking status differed between groups (p<0.001), with more previous drinkers in the AHD group (23.3% vs. 8.6%) (Supplementary Table S2).

4. Incidence of Dyslipidemia Across Study Groups

The crude incidence rates of dyslipidemia per 1,000 person-years were 60.39 in the NAHD-Inc group, 63.94 in the NAHD-Dec group, 61.70 in the AHD-Inc group, and 35.23 in the AHD-Dec group (Supplementary Table S3). The AHD-Dec group showed a relatively lower incidence compared to the other groups.

5. Risk of Dyslipidemia Based on Cox Proportional Hazards Models

Using the NAHD-Inc group as the reference, the AHD-Inc group had a significantly higher risk of dyslipidemia in the crude model (hazard ratio [HR], 2.04; 95% confidence interval [CI], 1.22–3.42; p=0.007). The NAHD-Dec group (HR, 1.15; 95% CI, 0.73–1.82; p=0.541) and the AHD-Dec group (HR, 0.75; 95% CI, 0.50–1.12; p=0.157) were not statistically significant.

In Model 1 (adjusted for age and sex), none of the groups showed statistically significant associations. In the fully adjusted model (Model 2), which included age, sex, diabetes mellitus, hypertension, family history of dyslipidemia, and ART regimen, the AHD-Inc group remained significantly associated with dyslipidemia risk (HR, 2.01; 95% CI, 1.15–3.53; p=0.023), whereas the other groups did not (Table 2).

6. Longitudinal Changes in BMI Across Study Groups

The longitudinal patterns of BMI change varied significantly across the four study groups over the follow-up period. Compared to the NAHD-Inc group, the AHD-Inc group demonstrated a markedly steeper upward trajectory in BMI, representing the most substantial overall increase among all cohorts (Figure 3).

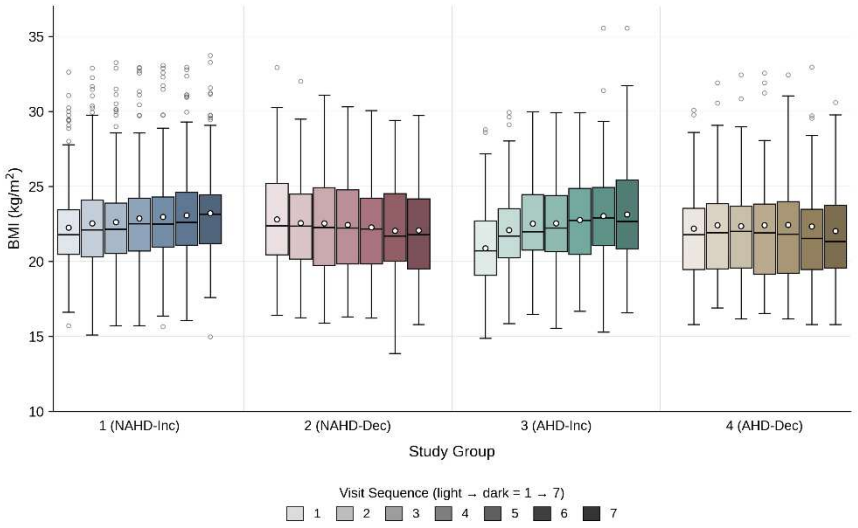


Figure 3. Distribution of BMI by visit sequence across study groups.

Visual analysis of mean BMI changes across the seven follow-up visits further corroborated that the AHD-Inc group experienced the most pronounced weight gain (Figure 4).

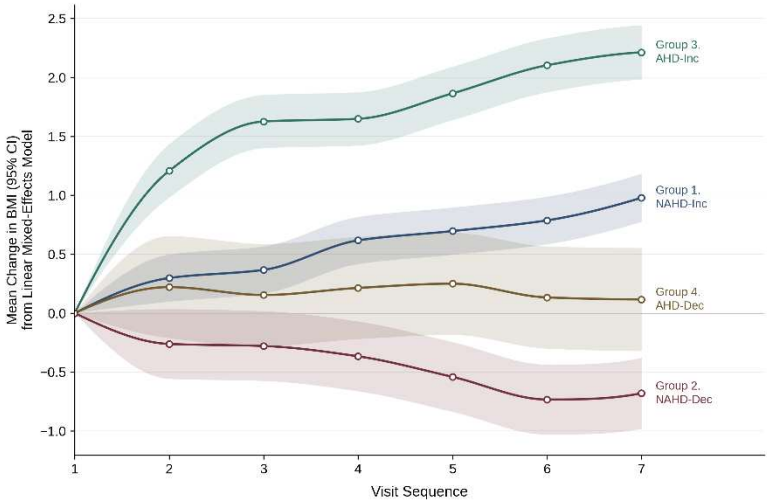


Figure 4. Changes in BMI (from baseline) by visit sequence across study group.

Notably, BMI in the AHD-Inc group exhibited a rapid escalation during the first 12 months post-ART initiation (up to the third visit), followed by a more gradual, stabilized increase thereafter.

To further quantify these differences, linear mixed-effects models were employed, incorporating interaction terms between the study group and visit number (Supplementary Table S4).

The analysis revealed that both the NAHD-Dec and AHD-Inc groups exhibited BMI trajectories that were significantly distinct from the reference group (NAHD-Inc). In particular, the AHD-Inc group showed consistently greater BMI increments at every time point compared to the reference ($p<0.001$), underscoring the intensive "return-to-health" weight gain characteristic of individuals starting ART at an advanced disease stage.

Discussion

In this study, we evaluated the risk of incident dyslipidemia according to BMI trajectories, stratified by CD4+ T-cell count at ART initiation. Our primary finding demonstrates that individuals with advanced HIV disease (AHD; CD4+ <200 cells/μL) who experience BMI increase following ART initiation face approximately a twofold higher risk of developing dyslipidemia compared to their non-AHD counterparts who also exhibit weight gain. Furthermore, the magnitude of BMI increase was consistently more pronounced in the AHD-Inc group throughout the follow-up period. These results suggest that weight gain following ART initiation, particularly in the context of severe baseline immunosuppression, may amplify metabolic risk beyond a simple 'return-to-health' phenomenon.

Since the advent of ART, the clinical focus has shifted from mortality prevention to the management of HIV as a chronic condition, given the substantial improvements in life expectancy. Post-ART weight gain, often termed recovery-associated weight gain, is frequently observed alongside immune restoration [3, 5]. However, accumulating evidence indicates that such weight gain can exceed physiological recovery, leading to adverse metabolic outcomes including dyslipidemia [7, 8, 10]. Our study adds to this evidence by clarifying that the metabolic impact of this weight gain is significantly modulated by the individual's baseline immune status.

Previous studies have shown that people living with HIV have a higher risk of dyslipidemia than the general population, often independent of obesity [17, 18]. In our cohort, only 14.5% of participants had a BMI ≥25 kg/m² at ART initiation, yet 37.0% developed dyslipidemia during follow-up. This discrepancy underscores that HIV- or ART-related factors may contribute to lipid abnormalities independently of traditional adiposity measures.

Several mechanisms may explain these observations. Chronic immune activation and persistent systemic inflammation associated with HIV can significantly alter lipid metabolism by dysregulating fatty acid turnover and hepatic lipid synthesis [19]. Additionally, specific ART regimens—particularly those involving protease inhibitors—have been implicated in elevating triglycerides and low-density lipoprotein cholesterol while reducing high-density lipoprotein cholesterol [20, 21]. Lifestyle factors, including nutritional habits and physical activity, also serve as independent contributors to the metabolic landscape of this population [22, 23].

In Korea, although associations between ART-related weight gain and dyslipidemia have been reported [24, 25], prior studies have largely examined weight change in isolation from baseline immune status. By integrating AHD status and longitudinal BMI trajectories into a unified analytical framework, our study demonstrates that weight gain in the presence of advanced immunosuppression confers a substantially higher metabolic burden. This finding emphasizes the clinical necessity of considering both baseline immunologic markers and weight dynamics when assessing long-term cardiovascular risk.

This study has several notable strengths. First, we used data from a nationwide prospective multicenter cohort with standardized, regularly scheduled assessments. Second, we considered baseline immune status and post-ART weight change. Third, longitudinal BMI trajectories were modeled with linear mixed-effects models, allowing characterization of the timing and magnitude of weight gain across groups.

Nevertheless, this study has several limitations. First, the lack of detailed data on lifestyle factors and genetic predisposition may have led to residual confounding. Second, although BMI is a practical clinical tool, it is only a proxy for body composition and does not distinguish lean mass from fat mass or fat distribution. Third, ART regimens were categorized only as INSTI-based or non-INSTI-based, which precluded evaluation of drug-specific effects on weight and lipid metabolism, such as those of protease inhibitors or individual INSTIs. Changes in regimen during follow-up were also not considered. Fourth, immunologic status was assessed only at ART initiation, and subsequent CD4+ T-cell recovery or viral suppression was not incorporated into the analysis. Fifth, missing BMI and

CD4+ T-cell count values were imputed once using participant-specific regression models rather than multiple imputation; because a single imputation does not account for imputation uncertainty, standard errors may have been underestimated, and imputed values may not fully reflect true individual variability. sixth, the study population was predominantly male (95.2%) and Korean (98.5%), which may limit the generalizability of our findings to women and other ethnic groups. Future research using direct measures of body composition, detailed ART regimen data, and longer follow-up in more diverse populations is warranted to validate these findings.

Conclusions

Among people living with HIV in Korea, those who initiated ART with advanced HIV disease and subsequently gained weight had a higher risk of incident dyslipidemia than non-AHD individuals who gained weight. This group also showed the largest increase in BMI, particularly during the first year of treatment. These findings suggest that post-ART weight gain in late presenters warrants attention. Early HIV diagnosis and timely ART initiation may benefit long-term metabolic health as well as immune recovery, and regular monitoring of weight and lipid profiles may be particularly important for individuals who start ART with advanced HIV disease.

Data Availability Statement

The data underlying this study were obtained from the Korean HIV/AIDS Cohort Study, a national cohort supported by the Korea Disease Control and Prevention Agency (KDCA), under institutional review board approval (No. 4-2025-0037). Due to institutional data governance policies, these data are not publicly available. Access is restricted to investigators affiliated with the Korean HIV/AIDS Cohort Study consortium and is granted upon approval by the KDCA. Requests for data access may be directed to the Korean HIV/AIDS Cohort Study Steering Committee at oeuk0423@korea.kr.

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Competing interests

The authors declare no competing interests.

Figure legends

Figure 1. Flowchart of study participant selection. Of 1,608 individuals initially enrolled in the Korean HIV/AIDS Cohort Study between December 1, 2006, and December 31, 2022, participants were sequentially excluded for the following reasons: no documented history of antiretroviral therapy (ART) (n=158); ≥20% missing data in anthropometric or laboratory variables (n=582); diagnosis of dyslipidemia prior to ART initiation (n=94); enrollment more than 6 months after ART initiation (n=343); and less than 3 years of follow-up (n=39). A total of 392 participants met the eligibility criteria and were included in the final analysis.

Figure 2. Analytical model of study groups. Participants were first stratified by CD4+ T-cell count at ART initiation into advanced HIV disease (AHD; CD4+ <200 cells/μL) and non-AHD (CD4+ ≥200 cells/μL) groups, and then further subdivided according to change in body mass index (BMI) between ART initiation and the 3-year follow-up visit (increase vs. stable or decrease), yielding four mutually exclusive groups. NAHD-Inc, non-AHD at ART initiation and BMI increase; NAHD-Dec, non-AHD and BMI stable or decrease; AHD-Inc, AHD and BMI increase; AHD-Dec, AHD and BMI stable or decrease.

Figure 3. Distribution of BMI by visit sequence across study groups. Box plots show the distribution of BMI (kg/m²) at each of the seven follow-up visits (visit 1, ART initiation, through visit 7, 3-year follow-up) for each of the four study groups. Boxes represent the interquartile range, horizontal lines within boxes indicate the median, circles indicate the mean, whiskers extend to the most extreme values within 1.5 times the interquartile range, and open circles beyond the whiskers represent outliers. NAHD-Inc, non-AHD at ART initiation and BMI increase; NAHD-Dec, non-AHD and BMI stable or decrease; AHD-Inc, AHD and BMI increase; AHD-Dec, AHD and BMI stable or decrease.

Figure 4. Changes in BMI (from baseline) by visit sequence across study groups. Lines represent the mean change in BMI (kg/m²) from baseline (visit 1) at each of the seven follow-up visits, estimated from a linear mixed-effects model; shaded bands indicate 95% confidence intervals. NAHD-Inc, non-AHD at ART initiation and BMI increase; NAHD-Dec, non-AHD and BMI stable or decrease; AHD-Inc, AHD and BMI increase; AHD-Dec, AHD and BMI stable or decrease.

Tables

Table 1. The anthropometric and clinical characteristics of participants at baseline

Variables	n = 392
Age, years (median, IQR)	36 (27.5-44.0)
18-29	120 (30.6)
30-39	125 (31.9)
40-49	89 (22.7)
50-59	41 (10.5)
≥60	17 (4.3)
Person-years, PY (median, IQR)	5.8 (2.8-9.6)
Male sex	373 (95.2)
Korean	386 (98.5)
CD4+ cell counts, cells/μL (median, IQR)	285 (174.0-427.5)
<200	159 (40.6)
≥200	233 (59.4)
BMI, kg/m^2 (median, IQR)	21.6 (19.8-23.3)
< 18.5	30 (7.7)
18.5-24.9	305 (77.8)
≥25	57 (14.5)
Days from diagnosis to ART	122.5 (33-1015)
Smoking	
Current	214 (54.6)
Previous	61 (15.6)
Never	111 (28.3)
Drinking	
Current	212 (54.1)
Previous	57 (14.5)
Never	102 (26.0)
Family history of dyslipidemia	3 (0.8)
Diabetes mellitus	20 (5.1)
Hypertension	51 (13.0)

ART regimen	
INSTI	341 (87.0)
non-INSTI	51 (13.0)

All values are presented as median (IQR) or n (%).
Unknown values: smoking, n = 6 (1.5%); drinking, n = 21 (5.4%); family history of dyslipidemia, n = 11 (2.8%).

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of dyslipidemia by study group

Study Group	Crude Model (HR, 95% CI)	Model 1† (HR, 95% CI)	Model 2‡ (HR, 95% CI)
Group 1 (NAHD-Inc)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Group 2 (NAHD-Dec)	1.15 (0.73-1.82)	1.01 (0.63-1.61)	1.02 (0.63-1.65)
Group 3 (AHD-Inc)	2.04 (1.22-3.42)*	1.63 (0.95-2.81)	2.01 (1.15-3.53)*
Group 4 (AHD-Dec)	0.75 (0.50-1.12)	0.66 (0.44-1.01)	0.71 (0.47-1.10)
Sex	-	0.67 (0.31-1.46)	0.69 (0.31-1.53)
Age	-	1.02 (1.01-1.03)*	1.01 (1.00-1.02)
Diabetes mellitus	-	-	2.49 (1.43-4.35)*
Hypertension	-	-	1.73 (1.12-2.68)*
Family history of dyslipidemia	-	-	3.10 (0.92-10.17)
ART regimen	-	-	1.39 (0.72-2.67)

*p-value < 0.05

†Model 1: Adjusted for age and sex

‡Model 2: Adjusted for Model 1 and diabetes mellitus, hypertension, family history of dyslipidemia, and ART regimen

Supplementary Files

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