Short-term Increase in Risk of Overweight and Concomitant Systolic Blood Pressure Elevation in Treatment Naïve Persons Starting INSTI-based Antiretroviral Therapy

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Summary

In treatment-naïve PWH who started ART, INSTI-based regimens were associated with an increased risk of overweight/obesity and systolic blood pressure elevation. Persons who reached the overweight/obesity status showed a significant change in LDL cholesterol, other metabolic markers were not affected.
ABSTRACT

Background: Integrase strand transfer inhibitors (INSTI) have been associated with weight gain, but their effect on short-term overweight/obesity incidence, blood pressure (BP) and metabolic markers change has not been described in treatment-naïve people with HIV (PWH).

Methods: Medical records of treatment-naïve persons starting ART at the HIV Clinic of University Hospital of Elche (Spain), between January 2007 and July 2019 were retrospectively reviewed. Standard procedures included measurements of weight, BP and metabolic assessment. Data at baseline, 48, 72, and 96 weeks post ART initiation were analysed. We used Cox mixed-effects model to generate predictions of BMI over time and Generalized Additive Mixed Models (GAMM) to relax the linearity assumptions and generate 95% confidence intervals in the multivariable adjust.

Results: Among 219 (median age 44.0 years, IQR=37.0-53.5; 46 females) participants. Baseline weight mean (SD) was 70.4(13.7)kg without difference between regimens; 66% had a BMI <25 kg/m². The incidence of overweight/obesity was significantly greater in persons starting INSTI-based regimens: 15(36.6%) of 41 patients treated with INSTI vs 30(28.9%) of 104 treated with other ART regimens (HR 2.3, 95%CI, 1.2-4.4; p=0.011). In contrast to other ART regimens, patients treated with INSTI showed a significant increase in systolic BP (SBP) (adjusted increase 7.0 mmHg, 95%CI, 0.3-13.7; p=0.039) that was correlated with weight gain (r=0.13, 95%CI, 0.10-0.16; p<0.001). Patients who reached overweight/obesity in INSTI-based ART showed a significant increase in LDL cholesterol.

Conclusions: INSTI-based ART was associated in the short-term with a greater risk of overweight/obesity and SBP elevation. Patients developing overweight/obesity increased LDL cholesterol with no other metabolic disturbances.

Keywords

1. Integrase Strand Transfer Inhibitors
2. Systolic Blood Pressure
INTRODUCTION

Integrase strand transfer inhibitors (INSTI) have been associated with weight gain [1–3], but it remains unknown if this effect leads to clinically significant changes in body weight or increases the risk of metabolic and cardiovascular diseases. Compared to the general population, in people with HIV (PWH) with traditional cardiovascular risk factors, the rate of acute myocardial infarction has been estimated to be double and the risk of cardiovascular death increases up to 4.5 times[4,5]. Small increments in body mass index (BMI) have been linked to two-fold increase in the risk of developing congestive heart failure in the long-term[6], therefore abrupt increases in BMI, even without reaching obesity, and after change from a normal weight to overweight status, could be considered deleterious and strongly associated with all-cause mortality[7]. In addition, changes in BMI have an independent effect on arterial blood pressure (BP) potentially contributing to the development of major cardiovascular events, specially stroke, which is strongly associated with systolic blood pressure(SBP)[8–12]. Recent observational data suggest that obesity after antiretroviral therapy (ART) initiation may be frequent[3], particularly in women and subjects with lower baseline CD4+ T lymphocyte counts, and lower baseline BMI[13–17]. A number of cohort studies have shown statistically significant increases in body weight and BMI following initiation of ART with different ART regimens[2,3,18] and reported greater weight gains with INSTI compared to non-INSTIT-based regimens, including increased visceral fat[19–21]. Also inflammatory markers have been measured and linked with body weight changes, suggesting that weight gain following ART initiation in overweight/obese population predicts an increase in the inflammatory status[22]. In a Brazilian cohort, the development of obesity was 7-times more likely in PWH who started ART with an INSTI-based regimen than in those who started a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or protease inhibitor (PI)-based ART[3]. In the Vanderbilt cohort, which compared the weight gain in treatment-naïve PWH who started INSTI, NNRTI and PI-based ART, dolutegravir-based regimen was associated with a greater weight gain than the other regimens even amongst INSTI drugs[21]. In the same cohort, within virologically suppressed PWH on efavirenz (EFV)-based regimens, people who
switched to INSTI-based ART gained more weight compared to those remaining on EFV-based ART[2]. Mechanisms explaining the association between INSTI’s and weight gain and its clinical implications, such as the potential metabolic and cardiovascular consequences, are currently unknown.

In this study, we analysed data from patients initiating ART therapy in a single medical center since the introduction of INSTI. The study aimed specifically to compare changes in body weight after ART initiation with different ART regimens and to explore their effects on BP and on different metabolic markers, including fasting blood glucose, lipid panel, and hepatic steatosis indexes.

**METHODS**

We conducted a retrospective database analysis of all treatment-naive HIV-infected adults (age ≥18 years) enrolled in the outpatient clinic of the University General Hospital of Elche (Spain), who initiated ART between January 1st, 2007 and July 11th, 2019. Standard procedures in the clinic throughout the study period included measurement of BMI, BP and metabolic assessment at cohort entry and at each visit.

Collected data included: history of hypertension and diabetes, HIV acquisition mode, date of ART initiation and ART regimen; baseline CD4+ and CD8+ T cell count, plasma HIV-1 RNA, fasting blood glucose (FBG), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), LDL cholesterol, HDL cholesterol and triglycerides before and after ART initiation at every time point, triglyceride and glucose index (TyG) and hepatic steatosis index (HSI). Measurements from 10 weeks before ART initiation to the day of ART initiation were used to define baseline levels and the nearest measurement (with a window period of up to 10 weeks) were used for each time point of analysis. TyG was calculated by the formula Ln [fasting triglyceride (mg/dl) × fasting plasma glucose (mg/dl)/2] and HSI as [8 × (ALT/AST ratio) + BMI (+2, if female; +2, if diabetes mellitus)]. Weight was measured at routine clinic visits using a single measurement on the same mechanical scale and BP by a
validated automatic sphygmomanometer. BMI (defined as weight in kilograms/height in meters squared) was calculated for each patient using the first height and the weight registered within a period from 10 weeks before ART initiation to the day of ART initiation. Net weight gain was defined as the difference between each subsequent weight measurement and the baseline weight; each subsequent weight measurement and baseline height were used to calculate BMI and its changes, defining normal weight as a BMI of 18.5 to 24.9 kg/m² and overweight/obesity as a BMI ≥ 25 kg/m². The absolute change of BP was defined as the difference between each subsequent BP and the baseline BP, both expressed in mmHg. Impaired fasting glucose was defined as FBG > 100 and < 126 mg/dl, insulin resistance was defined as a TyG > 4.68 and nonalcoholic fatty liver disease (NAFLD) when this index was above 8.5 or an HSI > 36.

Demographic, clinic and laboratory information was saved in the same electronic database, including the date of the beginning and the end date of each treatment. Research staff systematically obtained and assessed laboratory and clinical data of each enrolled patient. For all the analyses we excluded patients in which weight, height and BP data have not been collected at least 10 weeks before ART initiation, patients who switched to another ART regimen at any time point of the study, and women who were pregnant or became pregnant during the study period. Patients with diagnosis of hypertension at baseline were excluded from the BP analysis.

To register the change of defined variables in visits at 48, 72, and 96 weeks after the beginning of ART, we used weight and BP variables with a maximum of 10 weeks before and after each visit; as well as for CD4+ and CD8+ T cell count, plasma HIV-1 RNA, FBG, ALT, AST and lipid panel.

The study was approved by Ethics Committee of the University General Hospital of Elche, and the requirement for an informed consent was waived. All patient personal information was anonymized prior to analysis.
Statistical Analysis

We compared demographic variables and baseline characteristics among ART regimens, dividing them into INSTI and non-INSTI groups of treatment. For comparisons between categorical variables in the two groups we used Pearson $X^2$; continuous variables were compared using Student T test for independent samples and Wilcoxon Rank Sum Test as applicable. To contrast the increase in net weight compared to the initial weight and to compare the increase of BP among different ART regimens at 48, 72, and 96 weeks post ART initiation, we used Mann Whitney Wilcoxon U Test for dependent variables; these variables were adjusted by age, sex, HIV acquisition mode, history of hypertension, baseline HIV-1 RNA and CD4 T-cell count, TDF (tenofovir disoproxil fumarate) backbone, baseline weight for weight gain analysis and BMI for BMI change analysis, using Generalized Additive Mixed Models (GAMM) to relax the linearity assumptions and generate 95% confidence intervals. We conducted a subanalysis to compare the weight gain with each NNRTI, PI and INSTI-based regimens and a sensitivity analysis restricting the comparisons to patients who started DTG.

We used Cox mixed-effects model and dependent time covariables to generate risk estimators (hazard ratio, HR) for overweight/obesity adjusted by baseline characteristics mentioned above, and year of ART initiation to eliminate the bias of underlying trends; graphing the cumulative survival function by Kaplan Meir curves. Pearson correlation analysis was used to establish the correlation between weight gain and BP increase and a grade II polynomial model for graphing the predictions of SBP in treatment-time interactions. Significance level was set at 5% ($p< 0.05$). All analyses were conducted in R v. 3.6.0.

RESULTS

Baseline Characteristics

A total of 219 patients were included in the weight analysis; of them, 54(24.7%) persons started ART on INSTI-based regimens; 45(83.3%), 7(13.0%) and 2(3.7%) started dolutegravir, raltegravir and elvitegravir respectively. 165(75.3%) started a different regimen to INSTI, of which, 79(47.9%) started a PI and 86(52.1%) a NNRTI-based regimen. Tenofovir disoproxil fumarate and emtricitabine were
the most frequent nucleoside backbone for NNRTI, IP, raltegravir- and elvitegravir-based ART; for
dolutegravir was abacavir/lamivudine. Most of PI-based regimens were ritonavir-boosted. Tenofovir
alafenamide (TAF) backbone was not used in any regimen during the study period.

Baseline characteristics are presented in Table 1. Patients who started ART in INSTI-based regimens
were younger than those starting with other regimens (mean age[±SD]; 42.7 [11.1] vs 46.8 [11.2]
years) and had lower ALT values. There was no difference among groups in the rest of the baseline
characteristics. Baseline body weight (mean [±SD]) was 70.4 [13.7] kg, without difference among
groups of ART regimens. Patients initiating INSTI-based and non-INSte based regimens started ART
with a similar baseline Log_{10} HIV-1 RNA (mean ± SD), 4.9 (0.6) and 4.9 (0.8) respectively.

**Weight Gain**

A modest increase in body weight was observed in patients starting INSTI and non-INSTE-based ART
regimens which was not statistically different between groups. Patients starting INSTI-based regimens
had a mean (± SD) weight gain of 2.7 (4.5) kg, 3.1 (5.4) kg, and 4.1 (5.7) kg at 48, 72, and 96 weeks
post ART initiation respectively. In the adjusted model, independent factors associated with weight
gain at 48, 72, and 96 weeks after ART initiation, were injection drug use (IDU) as category of HIV
transmission (adjusted weight gain [95%CI] at 48, 72, and 96 weeks, 3.3 [1.0 – 5.7], 3.6 [1.1 – 6.1],
and 4.2 [0.8 – 7.5]); along with HIV-1 RNA >10^5 copies/mL and lower baseline CD4+ T cell count
(Supplemental Table 1). The adjusted weight gain (95%CI) for the INSTI-based regimens at 48, 72,
and 96 weeks post ART initiation was 0.5 (-1.6 – 2.7) kg, 0.3 (-1.8 – 2.4) kg, and 2.0 (-0.7 – 4.7) kg,
respectively.

A subanalysis was performed to assess the weight gain with each class of antiretrovirals: INSTI, PIs
and NNRTIs (Supplemental Table 2). Patients starting INSTI gained greater weight than those
initiating NNRTI-based regimens [mean (±SD) weight gain at 48, 72, and 96 weeks of 2.7 (4.5) kg vs
1.5 (5.6) kg (p= 0.565); 3.1 (5.4) kg vs 1.7 (5.1) kg (p= 0.352); and 4.1 (5.7) kg vs 0.9 (5.1) kg (p=...
0.013), respectively] and non-different than patients starting PIs [mean (±SD) of 4.1 (7.5) kg (p= 0.493), 3.9 (6.2) kg (p = 0.668), and 4.7 (8.2) kg (0.990), respectively]. In the sensitivity analysis patients who started DTG gained greater weight than those initiating NNRT-based regimens [mean (±SD) of 2.3 (4.5) kg (p= 0.986), 2.2 (4.9) kg (p = 0.926), and 3.7 (5.5) kg (0.035), respectively]. (Supplemental Table 3).

**Time to Reach the Overweight/Obesity**

Figure 1 shows survival analysis to reach the overweight/obesity status according to ART regimen at a maximum time of 96 weeks of treatment. The incidence of overweight/obesity was significantly greater in patients starting INSTI-based ART and was reached sooner than with non-INSTI-based regimens (p= 0.011). 66.2% of the total population were enrolled with a BMI <25 kg/m², 41 patients with INSTI-based and 104 with non-INSTI-based regimens, of which, 15(36.6%) and 30(28.9%) respectively, changed their BMI category to overweight/obesity. In the Cox mixed-effects model the risk of becoming overweight/obese was significantly higher among patients starting with INSTI-based regimens (HR [95%CI] 2.3 [1.2 – 4.4];p = 0.011). The results of the adjusted model are shown in Table 2.

A higher risk of overweight/obesity was also seen in the sensitivity analysis (Supplemental Table 4) restricted to patients starting DTG-based regimens (HR [95%CI] 3.6 [1.5 – 8.8];p = 0.006).

**Change in Blood Pressure and Metabolic Parameters**

Patients who started ART with INSTI-based regimens showed a significant increase in SBP in contrast to those who started non-INSTI-based regimens at 48, 72, and 96 weeks post ART initiation with no significant changes in diastolic BP. There was a weak positive linear correlation between weight gain and SBP increase (r = 0.13, 95%CI 0.10-0.16; p< 0.001). In a multivariable model, independent factors significantly associated with elevation of SBP at 96 weeks were baseline BMI, IDU, female sex and starting ART with INSTI-based regimens (Table 3). The adjusted estimated
difference in SBP for starting with INSTI-based compared to non-INSTITI regimens was 7.0 mmHg (95%CI 0.3-13.7; p= 0.039) (Figure 2). Supplemental Table 5 shows the changes in metabolic markers among patients initiating INSTI-based regimens who reached the overweight/obesity category and those who maintained a BMI<25 kg/m². In contrast to those who did not reach the overweight/obesity status with INSTI-based regimens, persons who became overweight/obese had a significant increase in LDL cholesterol. No differences were found in fasting blood glucose, HDL cholesterol, triglycerides, hepatic steatosis index and triglyceride and glucose index.

DISCUSSION

We confirmed a modest increase in body weight following initiation of ART. This is a well-described phenomenon that may be considered as a “return to health” effect of ART, and has been associated with greater HIV disease severity and survival benefits for those who are not initially overweight[23,24]. In our study, the increases in BMI were greater for patients with higher HIV plasma viral load and lower baseline CD4+ T cell count. In contrast to other studies[2,21], the increase in body weight was not statistically different with INSTI and non-INSTITI-based regimens. The mean increase in body weight to week 96 was +4.1 kg with INSTI versus +2.7 kg with non-INSTITI-based regimens. In the multivariate model controlling for age, sex, baseline body weight, CD4 count, plasma viral load, TDF backbone, and HIV transmission category, adjusted average weight gain at 96 weeks was greater with INSTI-based regimens although that difference did not reach statistical significance.

In the subanalysis conducted to establish the differences in weight gain among NNRTI, PI and INSTI-based regimens, we found a greater weight gain in patients initiating INSTI-based ART compared with those starting an NNRTI regimen at 96 weeks, but we could not find any difference between INSTI and PI-based regimens. However, patients starting with INSTI were significantly more likely to become overweight/obese than individuals given non-INSTITI-based regimens. After 3 years on ART, a greater proportion of individuals on INSTI regimens with a normal BMI at baseline had become overweight/obese, supporting the association between use of INSTI and clinically significant weight gain found in recent observational studies[1,3]. Patients starting ART with INSTI-regimens in our study were 2.3 times more likely to become overweight/obese during the study period than those
initiating with non-INSTI-based regimens, and the results were similar when we restricted the analysis to patients starting dolutegravir.

While some observational studies have suggested that weight gain following INSTI-based ART are more likely to occur among women, blacks and persons of older age[25], our adjusted model disclosed injection drug use as an independent factor associated with weight gain, along with immunovirological markers of HIV disease severity. Indeed, after adjusting for multiple covariates, including baseline body weight, the estimated difference in weight gain at 48, 72 and 96 weeks after starting ART was largest in injection drug users. Although increases in BMI at 72 and 96 weeks tended to be greater in women, the differences were not statistically significant.

The greater weight gain observed in injection drug users during ART had not previously been reported and the potential mechanism behind this association is unknown. The use of illicit drugs put PWH at increased risk of weight loss[26] and has been associated with distinct inflammatory profiles in HIV-infected individuals under ART[27]. Therefore, ART might have differential effects in this particular HIV population. Previous studies had reported weight gain in injection drug users of up to 3 kg during the first six months after ART with larger increases in patients with more advanced HIV infection at baseline[28].

Whilst weight gain during ART has been shown to be beneficial among underweight individuals, it may be detrimental for those who are overweight or obese. A number of observational studies have reported an increasing prevalence of overweight and clinical obesity in HIV-infected patients starting ART[3,14,29], raising concerns for obesity-related complications, particularly cardiovascular events[30]. Indeed, in a multinational cohort study, weight gain among overweight/obese persons starting ART heightened systemic inflammation[22] and, in the D.A.D. cohort, short-term gain in BMI after ART in individuals with pre-ART BMI in the normal range increased the longer term risk of cardiovascular events[31]. Nevertheless, it is still unclear whether the modest body weight gains following initiation of ART, as those observed in our study and in other cohorts, are clinically relevant,
particularly if they have cardiometabolic implications. We addressed this critical question by analysing many metabolic parameters, including BP, FBG, lipid panel, and hepatic steatosis indexes. We did find an increase in LDL cholesterol in persons who became overweight/obese with INSTI-based regimens, but no associations of weight gain with other metabolic disturbances nor changes in nonalcoholic fatty liver indicators were found.

Interestingly, the study showed a significant increase in SBP at 96 weeks of ART initiation that was weakly correlated with weight gain, in accordance with a recent report of weight gain and increase of BP found in pretreated women who switched to INSTI-based ART[32]. The interaction of BMI and blood pressure has long been recognized. Changes in BMI have an independent effect on change in systolic and diastolic BP in both women and men, and people who increase their BMI are at increased risk for hypertension[8,33]. The close association between BMI and BP have recently been confirmed in a large study across tens of thousands of individuals where the increase of BP per unit of BMI ranged from 0.8 to 1.7 mmHg/(kg/m²)[9]. Weight gain, however, does not explain completely the SBP elevation observed in our cohort. In addition to BMI, in the adjusted model, female sex (estimated difference in SBP [95% CI], 8.5 [1.1 – 16.0] mmHg), IDU (estimated difference in SBP [95% CI], 11.4 [2.0 – 20.9] mmHg) and initiating INSTI-based ART treatment (estimated difference in SBP [95% CI], 7.0 [0.3 – 13.7] mmHg) were independently associated with SBP elevation. Pathophysiological mechanisms other than weight gain explaining a potential link between exposure to INSTI and high BP are unclear. Available data suggest that the effect of antiretroviral drugs on BP appears to be mediated through an increase in BMI[34], but other mechanisms such as endothelial damage[35] and activation of the renin-angiotensin system[36] could potentially be implicated. Both elevated SBP and excess BMI are established risk factors for cardiovascular disease[6,10], being particularly important in the development of stroke, which is strongly associated with SBP[11,12,33].

The present study does have limitations, including single center and mostly male cohort, that limit the generalizability to other settings. The sample size was relatively small and even though we found a higher incidence of overweight/obesity associated to INSTI, the small number of patients taking INSTI other than dolutegravir prevented comparing the effect of different INSTI drugs and limited the number of analyses and adjustments we could perform. Therefore, our results may only be applicable to patients starting therapy with dolutegravir-based regimens. Finally, several lifestyle factors, such as
nutritional habits, physical activity and drug consumption that may have an effect on weight gain and SBP, were not collected. Unfortunately, neither data on waist circumference, dual-energy absorptiometry or computed tomography nor biochemical markers that could mediate the effect of a specific ART regimen on BMI and SBP were unavailable for the analysis. Despite these limitations, the study informs further on the magnitude of weight changes in patients starting ART and on the lack of effects on several metabolic parameters and is the first to report changes in BP in patients starting with INSTI-based regimens, adding to the clinical relevance of INSTI-associated weight gain.

In summary, our findings highlight that INSTI-based ART among treatment-naïve PWH is associated in the short-term with a greater risk of overweight/obesity than non-INSTI-based regimens, and with an elevation of SBP. Patients developing overweight/obesity increased the LDL cholesterol with no other metabolic disturbances. Further research is needed to confirm our results and to understand the mechanisms and long-term clinical implications of these findings.
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CONFICTS OF INTEREST

The authors report no conflicts of interest related to this work.
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FIGURES

Figure Legends

**Figure 1.** Kaplan-Meier curve of progression to overweight/obesity according to antiretroviral therapy regimen initiation. INSTI: Integrase Strand Transfer Inhibitors; ART: antiretroviral therapy.

**Figure 2.** Predicted systolic blood pressure elevation among antiretroviral therapy regimens at 48, 72, and 96 weeks post treatment initiation. INSTI: Integrase Strand Transfer Inhibitors; ART: antiretroviral therapy; $p$ at 96 weeks = 0.039.
Table 1. Baseline Characteristics by Group of Treatment

| Characteristics                  | INSTI-based Regimen (n= 54) | Non INSTI-based Regimen (n= 165) | p-value |
|----------------------------------|-----------------------------|----------------------------------|---------|
| **Age (y)**                      | 42.7 (11.1)                 | 46.8 (11.2)                      | 0.020   |
| **Sex**                          |                             |                                  |         |
| Male, n(%)                       | 42 (77.8)                   | 131 (79.4)                       | 0.800   |
| Female, n(%)                     | 12 (22.2)                   | 34 (20.6)                        |         |
| **HIV acquisition mode**         |                             |                                  |         |
| IDU, n(%)                        | 5 (9.3)                     | 29 (17.6)                        | 0.143   |
| Other, n(%)                      | 49 (90.7)                   | 136 (82.4)                       |         |
| **History of Hypertension**      | 9 (16.7)                    | 48 (29.1)                        | 0.071   |
| **History of Diabetes**          | 3 (5.7)                     | 14 (8.5)                         | 0.505   |
| **Height (m)**                   | 1.7 (0.1)                   | 1.7 (0.1)                        | 0.282   |
| **Weight(kg)**                   | 70.1 (12.0)                 | 70.5 (14.3)                      | 0.733   |
| **BMI(kg/m²)**                   | 23.5 (3.0)                  | 24.1 (4.5)                       | 0.865   |
| **CD4+ T cell count (cells/µL)** | 276.8 (162.3)               | 263.7 (173.3)                    | 0.408   |
| **CD8+ T cell count (cells/µL)** | 789.2 (395.9)               | 766.7 (441.4)                    | 0.441   |
| **Log_{10} HIV-1 RNA (copies/mL)** | 4.9 (0.6)              | 4.9 (0.8)                       | 0.875   |
| **Fasting Blood Glucose (mg/dL)** | 88.1 (8.6)             | 91.1 (26.9)                     | 0.111   |
| **Triglycerides (mg/dL)**        | 116.5 (57.6)                | 133.6 (87.8)                     | 0.410   |
| **HDL Cholesterol (mg/dL)**      | 40.5 (10.7)                 | 40.7 (14.1)                      | 0.472   |
| **LDL Cholesterol (mg/dL)**      | 96.5 (23.9)                 | 102.0 (36.1)                     | 0.811   |
| **ALT (UI/L)**                   | 29.1 (16.9)                 | 42.5 (38.8)                      | 0.007   |
| **AST (UI/L)**                   | 29.4 (14.5)                 | 36.3 (29.8)                      | 0.097   |
| **TyG**                          | 4.6 (0.2)                   | 4.6 (0.3)                        | 0.504   |
| **HSI**                          | 32.1 (4.6)                  | 33.7 (5.7)                       | 0.157   |
| Systolic Blood Pressure | 131.5 (19.7) | 135.2 (19.9) | 0.216 |
|------------------------|--------------|--------------|-------|
| Diastolic Blood Pressure | 78.4 (12.3) | 82.4 (12.7) | 0.068 |

INSTI: Integrase Strand Transfer Inhibitors; IDU: Injection Drug Use; ALT: serum alanine aminotransferase; AST: serum aspartate aminotransferase. TyG: triglyceride and glucose index calculated using the formula Ln [fasting triglyceride (mg/dl) × fasting plasma glucose (mg/dl)/2]; HSI: hepatic steatosis index calculated using the formula [8 × (ALT/AST ratio) + BMI (+2, if female; +2, if diabetes mellitus)]. *Mean (SD).

| Table 2. Factors Associated with the Development of Overweight/Obesity post Antiretroviral Therapy (ART) initiation |
|-------------------------------------------------|
| **Factor**                                       | **Adjusted HR (95% CI)** | **p-value** |
| INSTI-based ART                                  | 2.3 (1.2 – 4.4)          | 0.011       |
| Baseline HIV-1 RNA >100000 copies/mL            | 1.4 (0.8 – 2.5)          | 0.250       |
| Female                                          | 1.1 (0.7 – 1.8)          | 0.710       |
| IDU                                             | 1.1 (0.6 – 2.0)          | 0.810       |
| Baseline BMI                                    | 1.2 (1.2 – 1.3)          | <0.001      |
| Baseline CD4+ T cell count                      | 1.0 (0.9 – 1.0)          | 0.300       |
| CD4+ T cell count                               | 1.0 (1.0 – 1.1)          | 0.670       |
| CD8+ T cell count                               | 1.0 (1.0 – 1.1)          | 0.063       |
| Baseline CD4+/CD8+ T cell ratio                 | 0.8 (0.3 – 2.4)          | 0.740       |
| Age                                             | 1.0 (1.0 – 1.1)          | 0.430       |
| Year of ART initiation                          | 0.9 (0.8 – 1.0)          | 0.160       |

*INSTI: Integrase Strand Transfer Inhibitors; IDU: Injection Drug Use*
Table 3. Multivariable Model for Factors Associated with Systolic Blood Pressure Elevation (SBP) at 72 and 96 weeks post Antiretroviral Therapy (ART) Initiation

| Factor                        | Estimated difference in SBP (95% CI) 72 weeks | p    | Estimated difference in SBP (95% CI) 96 weeks | p    |
|-------------------------------|----------------------------------------------|------|----------------------------------------------|------|
| INSTI-based ART               | 5.4 (0.4 – 13.1)                             | 0.095| 7.0 (0.3 – 13.7)                             | 0.039|
| Baseline HIV-1 RNA >100000    | 3.7 (-5.8 – 6.9)                             | 0.260| 5.0 (-1.5 – 11.4)                            | 0.130|
| copies/mL                     |                                              |      |                                              |      |
| Female                        | 11.8 (4.2 – 19.7)                            | 0.002| 8.5 (1.1 – 16.0)                             | 0.026|
| IDU                           | 18.1 (-0.7 – 16.7)                           | <0.001| 11.4 (2.0 – 20.9)                            | 0.018|
| Baseline BMI                  | 3.0*                                         | 0.112| 3.4*                                         | 0.047|
| Baseline CD4+ T cell count    | 1.0*                                         | 0.677| 1.0*                                         | 0.406|
| Age                           | 2.4*                                         | 0.162| 1.4*                                         | 0.489|

INSTI: Integrase Strand Transfer Inhibitors; IDU: Injection Drug Use

*Non-linear, adjusted by Generalized Additive Mixed Model
Figure 1

ART Regimen: INSI  Non-INSI

Overweight/Obesity Probability

Adjusted p-value = 0.011

Time (weeks)

Number at risk

|      | INSTI | Non-INSI |
|------|-------|----------|
|      | 41    | 104      |
| 25   | 32    | 97       |
| 50   | 27    | 89       |
| 75   | 23    | 78       |
| 100  | 0     | 0        |
