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Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors

Running Title: Obesity following ART initiation

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Abstract

Introduction

Obesity rates are increasing among HIV-infected individuals, but risk factors for obesity development on ART remain unclear. In a cohort of HIV-infected adults in Rio de Janeiro, Brazil, we aimed to determine obesity rates before and after ART initiation, and to analyze risk factors for incident obesity on ART.

Materials and methods

We retrospectively analyzed data from individuals initiating ART between 2000 and 2015. BMI was calculated at baseline (time of ART initiation). Participants who were non-obese at baseline and had ≥90 days of ART exposure were followed until the development of obesity or the end of follow-up. Obesity incidence rates were estimated using Poisson regression models and risk factors were assessed using Cox regression models.

Results

Of participants analyzed at baseline (n=1,794), 61.3% were male, 48.3% were white, and 7.9% were obese. Among participants followed longitudinally (n=1,567), 66.2% primarily used a NNRTI, 32.9% a PI and 0.9% an integrase inhibitor (INSTI); 18.3% developed obesity, and obesity incidence was 37.4 per 1000 person-years. In multivariable analysis, the greatest risk factor for developing obesity was the use of an INSTI as the primary ART core drug (adjusted hazard ratio 7.12, $p<0.0001$); other risk factors included younger age, female sex, higher baseline BMI, lower baseline $CD4^+$ T lymphocyte count, higher baseline HIV-1 RNA, hypertension, and diabetes mellitus.

Discussion

Obesity following ART initiation is frequent among HIV-infected adults; key risk factors include female sex, HIV disease severity and INSTI use. Further research regarding the association between INSTIs and the development of obesity is needed.

Introduction

Advancements in ART have led to vast improvements in the general health and life expectancy of HIV-infected individuals.[1–3] Among individuals on suppressive ART, wasting has become less common, and recent studies from both upper- and lower-income countries report weight gain irrespective of ART type.[4–8] Additionally, many countries have reported an increasing prevalence of overweight and obese states in HIV-infected persons even prior to ART initiation, consistent with trends in the general population.[6,9] As obesity rates rise, so does the risk for obesity-related complications.[10–13] This is particularly worrisome as, even in the absence of obesity, HIV-infected individuals are already at high risk of non-AIDS events such as cardiovascular and fatty liver disease.[14–16]

Among HIV-infected individuals initiating ART, female sex,[4,17] lower baseline $CD4^+$ T lymphocyte counts[4,17,18] and a lower baseline BMI[4,6] have been associated with subsequent weight gain. However, associations between specific ART regimens and weight gain/obesity remain controversial.[5,17–19]

In a large cohort of HIV-infected, ART-treated adults in Rio de Janeiro, Brazil, we aimed to calculate the prevalence of obesity prior to ART initiation and the incidence of obesity after ART initiation. Additionally, we aimed to determine specific risk factors associated with the development of obesity after ART initiation, including associations between weight gain and the use of specific ART drugs and classes.

Materials and methods

Ethics

This study was approved by the ethics committee of the Evandro Chagas Clinical Research Institute of the Oswaldo Cruz Foundation (INI/FIOCRUZ, CAAE 0032.0.009.000-10) and was conducted according to the principles expressed in the Declaration of Helsinki. All patient records/information was de-identified prior to analysis. The study was exempt from additional review by the Office of the Human Research Protection Program of the University of California, Los Angeles.

Study population

The HIV clinical cohort of INI/FIOCRUZ in Rio de Janeiro, Brazil includes a database of socio-demographic and clinical information on patients receiving HIV care. Trained extractors input information from medical records and laboratory results into the database biannually. Complete procedures regarding cohort data collection have been described elsewhere.[20]

Inclusion and exclusion criteria

Participants included in the baseline obesity prevalence analysis were HIV-infected adults ≥18 years of age who started their first ART regimen between January 1, 2000 and December 31, 2015. Women who became pregnant while on ART were excluded. In addition, participants without height data and without a weight recorded within 180 days prior to and 30 days after ART initiation were excluded. For participants with multiple eligible height and weight records, the height/weight recorded closest to the date of ART initiation was used to calculate the baseline BMI (defined as weight in kilograms divided by the square of height in meters). Participants from the baseline obesity prevalence analysis were included in the longitudinal obesity incidence analysis if they were non-obese (BMI <30 kg/m^2) at the time of ART initiation and had ≥90 days of cumulative exposure to at least one NRTI and at least one ART core drug class (NNRTI, PI, or integrase strand transfer inhibitor [INSTI]).

Study design

In this retrospective cohort study, participants included in the baseline analysis were assessed for the presence of obesity (BMI ≥30kg/m^2) prior to ART initiation. Participants included in the longitudinal analysis were retrospectively followed for the development of obesity after ART initiation. In order to determine whether a participant developed obesity, all recorded weights after baseline and prior to December 31, 2015 were compiled into a list and the amount of time between sequential weight measurements was calculated. Every post-baseline weight was required to have been measured within two years of the previously recorded weight in order to be included. Weights that were recorded after a gap of greater than two years, and any subsequent measurements, were excluded from the analysis. These data were excluded because significant weight changes occurring within these large time intervals could have occurred but not been captured, and exclusion ensured that the weights being analyzed provided an accurate longitudinal depiction of weight changes over the course of follow-up.

Follow-up for each participant started on their date of ART initiation. For participants who developed obesity, follow-up ended on the date of obesity diagnosis. For participants who did not develop obesity, follow-up ended on the date of their last clinic visit, date of death, two years after their last recorded weight measurement, or December 31, 2015, whichever occurred first. Loss to follow-up (LTFU) was defined among participants whose last clinic visit was earlier than any of the above-mentioned dates.

Baseline BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) or obese (≥30 kg/m^2). Age at ART initiation was calculated by subtracting the participant's date of birth from their ART start date. Self-reported sex/gender was grouped as "male," "female," or "transgender woman (TW)." Self-reported race/skin color was categorized as "white," "black," or "mixed/other." Education was self-reported and dichotomized as 0-8 years or >8 years. Baseline $CD4^+$ T lymphocyte count and HIV-1 RNA were defined as the values recorded closest to the date of ART initiation (within 180 days before and 30 days after ART initiation). Time from HIV diagnosis to ART start was calculated by subtracting the participant's date of HIV diagnosis from their ART start date. History of hypertension was defined as any of the following recorded up to 30 days after ART initiation: diagnosis of hypertension, use of antihypertensive medication, systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg. History of diabetes mellitus was defined as any of the following recorded up to 30 days after ART initiation: history of diabetes mellitus, diabetes on treatment, fasting glucose level ≥126 mg/dL, or hemoglobin A1c >6.5%. History of dyslipidemia was defined as any of the following recorded up to 30 days after ART initiation: history of dyslipidemia, use of lipid-lowering therapy, low-density lipoprotein cholesterol >159 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, total cholesterol >239 mg/dL, or triglycerides >199 mg/dL. History of an AIDS-defining illness was defined as any of the diagnoses included in the Centers for Disease Control and Prevention 1993 definition diagnosed up to 30 days after ART initiation.[21] Participants were classified as "ever smoker" if they indicated any smoking history on cross-sectional survey.[22] Those missing data from the cross-sectional survey were classified as "ever smoker" if their medical chart indicated a history of tobacco use.

The summation of an individual's time on ART during follow-up was calculated for the following drugs/classes: tenofovir, zidovudine, NNRTI, PI and INSTI. Time spent on abacavir was categorized with time on tenofovir, and time on didanosine, zalcitabine and stavudine were categorized with time on zidovudine. This was done due to the low frequency of use of these agents for ≥90 days (abacavir n=111, didanosine n=89, zalcitabine n=1, stavudine n=104). Each participant was classified according to the NRTI (tenofovir versus zidovudine) and core drug class (NNRTI versus PI versus INSTI) used for the greatest cumulative time during their follow-up.

Statistical analysis

Descriptive statistics were compared using Chi-squared tests for categorical variables and Kruskall-Wallis tests for continuous variables. Obesity incidence was estimated per 1000 person-years of follow-up (PYFU) using Poisson regression models. Cox competing risk models (accounting for death and LTFU as competing events) were used to assess factors associated with incident obesity after ART initiation. Multivariable modeling was performed by including all covariates with p-value ≤0.20 in bivariate models and sequentially removing variables with the highest p-value until only variables with p-value ≤0.05 remained. Age at ART initiation and most-used NRTI were forced into the final model. Date of ART initiation and end of follow-up date were both accounted for in the final model. Multiple imputation for missing data was performed for missing values of baseline $CD4^+$ T lymphocyte count (n=125) and log of HIV-1 RNA (n=229). Continuous variables that were not linearly correlated with obesity (baseline BMI and baseline $CD4^+$ T lymphocyte count) were included in the models using restricted cubic splines to relax linearity assumptions.[23] R (version 3.1.1) and libraries "survival", "mi", "rms" and "mstate" were used for the analyses.

Results

Baseline characteristics and obesity prevalence

A total of 1794 individuals met inclusion criteria for the baseline analysis (Figure 1). At the time of ART initiation, 251 participants (14.0%) were underweight, 1012 (56.4%) were normal weight, 390 (21.7%) were overweight and 141 (7.9%) were obese. Median age at ART initiation was 36.3 years (IQR: 29.5-

44.1). The majority of participants were male, white, and had greater than eight years of schooling. Median baseline $CD4^+$ T lymphocyte count was 226 cells/mm^3 (IQR: 79-350) and the median log HIV-1 RNA was 4.8 (IQR: 4.0-5.4). Median time from the date of HIV diagnosis to ART initiation was 0.6 years (IQR: 0.2-2.7). Participants had the following histories of comorbid disease: 12.9% hypertension, 4.9% diabetes mellitus, 27.0% dyslipidemia, 38.8% AIDS-defining illness, and 51.0% ever smoker. The prevalence of obesity at ART initiation increased over the study period (4.9% in 2000-2003, 6.2% in 2004-2007, 6.4% in 2008-2011 and 12.0% in 2012-2015) (Table 1).

Factors associated with incident obesity after ART initiation

Of the 1794 individuals analyzed at baseline, 1567 were non-obese and had ≥90 days of cumulative exposure to at least one NRTI and one core drug class, thus meeting inclusion criteria for the obesity incidence analysis. These individuals contributed 7657 PYFU with a median follow-up time of 4.1 years (IQR: 2.1-7.0). The median time to obesity diagnosis was 1.9 years (IQR: 0.9-3.6), while the median follow-up time for participants who did not develop obesity was 4.7 years (IQR: 2.5-7.4). A total of 1198 individuals (76.5%) gained weight over the study period, 688 (43.9%) increased their BMI category, and 286 (18.3%) developed obesity. From baseline to end of study, the median BMI increased from 22.3 to 24.7 kg/m^2 ($p<0.0001$), with a median annual increase of 0.4 kg/m^2/year.

Table 2 shows longitudinal changes in BMI stratified by baseline BMI. For those underweight at baseline, the median BMI increased from 17.1 to 20.3 kg/m^2, with a median annual increase of 0.6 kg/m^2/year. A total of 65.9% of those underweight at baseline were classified into a higher BMI category at study end. For those of normal weight at baseline, the median BMI increased from 21.9 to 24.2 kg/m^2, with a median annual increase of 0.4 kg/m^2/year. A total of 40.3% of those of normal weight at baseline were categorized as overweight or obese at study end. For those overweight at baseline, the median BMI increased from 26.9 to 28.6 kg/m^2, with a median annual increase of 0.3 kg/m^2/year. A total of 40.0% of those overweight at baseline had become obese by the end of follow-up.

Table 3 shows characteristics of participants who developed obesity after starting ART compared to those who remained non-obese, as well as the unadjusted hazard ratios for incident obesity. Participants who became obese were more likely to have the following characteristics: female sex (24.4% females

developed obesity versus 16.7% males and 13.1% TW, p=0.0005), higher baseline BMI (median 25.3 versus 21.8 kg/m^2, p<0.0001), lower baseline $CD4^+$ T lymphocyte count (median 152 versus 233 cells/mm^3, p<0.0001), higher baseline log HIV-1 RNA (median 5.0 versus 4.8, p=0.0100), use of zidovudine as the most-used NRTI (zidovudine 21.3% versus tenofovir 16.1%, p=0.0104), use of an INSTI as the most-used ART core drug class (INSTI 42.9% versus NNRTI 17.3% and PI 19.4%, p=0.0346), and a history of hypertension (hypertension 30.1% versus no hypertension 16.8%, p<0.0001). Of note, all variables listed in Table 3 were considered for inclusion in the final multivariable model.

The overall incidence rate of obesity was 37.4 per 1000 PYFU. Patients who were overweight at baseline had a higher incidence of obesity (106.6 per 1000 PYFU) than those who were underweight and normal weight (5.2 and 25.5 per 1000 PYFU, respectively). Females had a higher incidence of obesity (49.8 per 1000 PYFU) compared to males and TW (34.5 and 25.5 per 1000 PYFU, respectively) (Table 2). In addition, those who started ART between the years 2000-2003 had a lower incidence of obesity (20.1 per 1000 PYFU) than those who started ART between 2004-2007, 2008-2011 and 2012-2015 (39.7, 44.1 and 43.2 per 1000 PYFU, respectively) (Supplementary Table 1).

In individuals primarily using an INSTI (n=14), obesity incidence was higher than those primarily using an NNRTI (n=1038) or PI (n=515) (incidence of 370.7 versus 36.0 and 37.8 per 1000 PYFU, respectively). In addition, those using an INSTI as their most-used ART core drug had greater annual BMI change versus NNRTI and PI (median gain of 1.6 versus 0.4 and 0.4 kg/m^2/year, respectively, p=0.1569) and shorter time to obesity diagnosis (median 1.0 versus 1.9 and 1.9 years, respectively, p=0.1850). Among those classified under INSTI (10 men, 3 women, 1 TW), obesity incidence was higher for women than men (1073.2 versus 344.4 per 1000 PYFU, respectively), and women experienced greater annual BMI gain than men (median of 5.0 versus 0.5 kg/m^2 per year) (Supplementary Table 2, Supplementary Table 3).

In multivariable models accounting for competing risks, the following variables were associated with the development of obesity after ART initiation: younger age at ART initiation (adjusted hazard ratio [aHR] 0.82 per ten year increase, p=0.0048), female sex (aHR 1.66, p=0.0003), higher baseline BMI (using restricted cubic splines), lower baseline $CD4^+$ T lymphocyte count (using restricted cubic splines),

higher baseline HIV-1 RNA (aHR 1.16, p=0.0275), use of an INSTI as the ART core drug (aHR 7.12, p<0.0001), and baseline diagnoses of hypertension (aHR 1.54, p=0.0136) and diabetes mellitus (aHR 1.92, p=0.0238) (Figure 2).

Discussion

We aimed to characterize obesity rates and risk factors in HIV-infected adults before and after ART initiation. We observed that at the time of ART initiation, 7.9% of participants were obese, and this prevalence increased over the study period (2000-2015). This trend can likely be attributed to a combination of increasing obesity incidence worldwide[24] and 2012-2013 international guidelines recommending earlier initiation of ART.[25,26] While the prevalence of obesity at ART initiation observed in our cohort was lower than that reported in the Brazilian general population, where the prevalence of obesity steadily rose from 11.9% in 2006 to 17.9% in 2014,[27] the prevalence of obesity at ART initiation increased by calendar year in our cohort, as did the incidence rate of obesity after ART initiation.

Among non-obese individuals initiating ART, 18.3% developed obesity with a rapid median time of 1.9 years from ART initiation to obesity diagnosis. The greatest risk factor for developing obesity after ART initiation was having an INSTI as the most-used ART core drug class. Other risk factors included younger age, female sex, higher baseline BMI, lower baseline $CD4^+$ T lymphocyte count, higher baseline HIV-1 RNA, and baseline diagnoses of hypertension and diabetes mellitus.

The observed associations between female sex and weight gain after ART initiation have been previously documented.[5,17] Individuals who were overweight at baseline had a greater risk of developing obesity because their starting BMI was closer to the obesity threshold; however, underweight individuals had the greatest annual change in BMI. This may be explained in part by the extreme relative immune reconstitution that can occur in individuals with more advanced HIV disease after ART initiation.[4] This same explanation can be used to justify associations between obesity development and lower baseline $CD4^+$ T lymphocyte counts and higher baseline HIV-1 RNA levels. This explanation may also help clarify why younger participants were more likely to develop obesity after ART use, as younger participants may have more robust immunologic response to ART, making them more susceptible to weight gain. Finally,

associations between obesity development and baseline hypertension and diabetes mellitus likely results from the fact that these conditions were more prevalent in individuals who were overweight at baseline compared to those who were of normal weight.

Importantly, the greatest risk factor for developing obesity in our cohort was having an INSTI as the most-used ART core drug class. Compared to those who primarily used an NNRTI and PI, participants who primarily used an INSTI had ten-fold higher obesity incidence, four-fold greater annual BMI gain and nearly twice as rapid time to obesity. Of note, females classified under INSTI had remarkably high rates of obesity and annual BMI gain. When adjusted for potential confounding, having an INSTI as the most-used ART core drug was associated with over seven times the risk of developing obesity. Although the sample size of those classified under INSTI was small (n=14), the magnitude of this association is impressive and has only recently been described in the literature. Menard *et al* looked at weight changes in 462 individuals prescribed dolutegravir plus abacavir/lamivudine or tenofovir/emtricitabine and found that after one year of therapy, mean weight gain was 3 kg. This weight gain was significant for women and showed a tendency toward significance for men.[28] Similarly, Norwood *et al* found that, in individuals with ≥2 years of exposure to efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC), those who were switched to an INSTI-containing regimen (dolutegravir/abacavir/lamivudine or raltegravir/TDF/FTC or elvitegravir/cobicistat/TDF/FTC) gained 2.9 kg after 18 months, compared to a 0.7 kg gain in those switched to a PI-containing regimen and a 0.9 kg gain in those who remained on EFV/TDF/FTC.[29]

Potential mechanisms explaining the association between weight gain and INSTI use are currently unknown. One possible explanation is that INSTIs cause an especially rapid drop in HIV-1 RNA,[30] and HIV-1 RNA is positively correlated with resting energy expenditure.[31] Thus, individuals taking INSTIs may experience greater short-term decreases in resting energy expenditure, predisposing them to weight gain. This hypothesis was unable to be assessed in our cohort as we did not have sufficient HIV-1 RNA data post-ART initiation to explore if decreases in HIV-1 RNA correlated with weight gain. A second possible explanation is that raltegravir has higher levels of tissue penetration compared to other

classes of ART,[32] which could result in yet unidentified mechanisms of metabolic change that drive weight gain.

It should be noted that of the 14 individuals who had an INSTI as their most-used ART core drug, 50% had a baseline diagnosis of tuberculosis compared to 24% in the total cohort. The longitudinal multivariable analysis accounted for TB in the variable "History of AIDS defining illness." When forcing TB into the final multivariable analysis, INSTIs were still associated with an increased risk of obesity (aHR 5.5, p=0.0002) (Supplementary Table 4). Additionally, when repeating the multivariable analysis in exclusively TB-infected individuals (n=383), the association between INSTIs and an increased risk of obesity remained (aHR 6.9, p=0.0006) (Supplementary Table 5). Thus, even when adjusting for the potential confounding effect of TB, INSTIs were still associated with an increased risk of developing obesity.

This study has several limitations. First, we did not have data regarding caloric intake, alcohol use, menopausal status, concomitant medication usage that may have caused weight changes (i.e. metformin, psychiatric medications), or physical activity levels in participants, as would be ideal. Second, we were forced to rely on BMI as the sole marker of obesity because we did not have data from other anthropomorphic measurements, such as waist circumference and waist-to-hip ratio. Third, since this was an observational study, participants did not have weights recorded at regularly scheduled intervals. In order to account for this, each participant was screened to ensure that they did not have a period of greater than two years where they did not have a weight recorded. Another limitation is that NRTI usage and ART core drug usage were classified into mutually exclusive categories. While this categorization allowed for the comparison of obesity rates between NRTIs and core drug classes, it could not account for the overlap effects of using combination ART. However, it should be noted that 79% (n=1231) of the participants had exposure to only one ART core drug class for ≥90 days during follow-up, and associations between the specific NRTIs and obesity were not observed. In addition, of the six individuals who took an INSTI as their most-used ART core drug and developed obesity, five (83%) had no exposure to an NNRTI- or PI-based regimen for ≥90 days. Finally, due to the years of study follow-up included, overall low numbers of participants had INSTI exposure. However, this also makes the effect size and statistical significance

more striking. Additionally, of the participants who took an INSTI as their most-used ART core drug, 92.9% (n=13) used raltegravir. Thus, it is unknown whether our results will be applicable to the more recent generations of INSTIs.

A major strength of this study is the high number of female and TW participants, which allowed for the determination of sex/gender-specific risk factors. Other strengths included the diversity of the cohort in terms of race and education, the high median follow-up time and the number of years that the study spanned.

Conclusions

Obesity is a major concern in the HIV-infected population before and after ART initiation. Both the prevalence of obesity in HIV-infected, ART-naive individuals and the incidence of obesity after ART initiation continue to increase. Obesity prevention should be discussed at the time of ART initiation in order to reduce incidence and minimize long-term sequelae. Further research with a larger number of INSTI-exposed individuals is needed in order to validate the association between INSTIs and obesity and to elucidate potential mechanisms of weight gain in INSTI-treated individuals.

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Transparency declarations

None to declare.

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Table 1. Study Population Characteristics at ART Initiation by Baseline BMI Category, INI/FIOCRUZ, 2000-2015.

	Underweight (<18.5kg/m^2) n=251 (14.0%)	**Normal Weight** (18.5-24.9kg/m^2) n=1012 (56.4%)	**Overweight** (25-29.9kg/m^2) N=390 (21.7%)	**Obese** (≥30kg/m^2) n=141 (7.9%)	**Total** n=1794	**P value**
Age ART Initiation (years)						
median (IQR)	34.0 (27.9,43.2)	35.7 (29.0,43.7)	37.4 (31.5,44.8)	39.8 (33.2,44.7)	36.3 (29.5,44.1)	< 0.0001
<30	86 (34.3%)	290 (28.7%)	79 (20.3%)	22 (15.6%)	477 (26.6%)	< 0.0001
30-39	84 (33.5%)	361 (35.7%)	143 (36.7%)	50 (35.5%)	638 (35.6%)	
40-49	55 (21.9%)	251 (24.8%)	114 (29.2%)	55 (39.0%)	475 (26.5%)	
≥ 50	26 (10.4%)	110 (10.9%)	54 (13.8%)	14 (9.9%)	204 (11.4%)	
Sex Category						0.0009
Male	149 (59.4%)	648 (64.0%)	243 (62.3%)	60 (42.6%)	1100 (61.3%)	
Female	81 (32.3%)	241 (23.8%)	102 (26.2%)	67 (47.5%)	491 (27.4%)	
Transgender Women	21 (8.4%)	123 (12.2%)	45 (11.5%)	14 (9.9%)	203 (11.3%)	
Race/skin color						0.0002
White	90 (35.9%)	489 (48.3%)	224 (57.4%)	63 (44.7%)	866 (48.3%)	
Black	69 (27.5%)	194 (19.2%)	56 (14.4%)	33 (23.4%)	352 (19.6%)	
Mixed/Other	92 (36.7%)	329 (32.5%)	110 (28.2%)	45 (31.9%)	576 (32.1%)	
Education level						< 0.0001
0-8 years	177 (70.5%)	505 (49.9%)	148 (37.9%)	73 (51.8%)	903 (50.3%)	
>8 years	74 (29.5%)	507 (50.1%)	242 (62.1%)	68 (48.2%)	891 (49.7%)	
Year ART Initiation						< 0.0001
2000-2003	34 (13.5%)	128 (12.6%)	33 (8.5%)	10 (7.1%)	205 (11.4%)	
2004-2007	33 (13.1%)	217 (21.4%)	69 (17.7%)	21 (14.9%)	340 (19.0%)	
2008-2011	114 (45.4%)	400 (39.5%)	157 (40.3%)	46 (32.6%)	717 (40.0%)	
2012-2015	70 (27.9%)	267 (26.4%)	131 (33.6%)	64 (45.4%)	532 (29.7%)	
CD4$^+$ T lymphocyte count (cells/mm^3)						
median (IQR)	88 (29,207)	212 (71,334)	292 (185,400)	323 (224,439)	226 (79,350)	< 0.0001
< 100	117 (46.6%)	291 (28.8%)	57 (14.6%)	13 (9.2%)	478 (26.6%)	< 0.0001
100-249	62 (24.7%)	261 (25.8%)	93 (23.8%)	29 (20.6%)	445 (24.8%)	
250-500	31 (12.4%)	316 (31.2%)	160 (41.0%)	69 (48.9%)	576 (32.1%)	
>500	9 (3.6%)	77 (7.6%)	61 (15.6%)	23 (16.3%)	170 (9.5%)	
Missing	32 (12.7%)	67 (6.6%)	19 (4.9%)	7 (5.0%)	125 (7.0%)	
Viral Load (copies/mL)						
median log10 (IQR)	5.2 (4.5,5.7)	4.8 (4.1,5.4)	4.4 (3.8,5.2)	4.4 (3.7,5.0)	4.8 (4.0,5.4)	< 0.0001
< 100,000	88 (35.1%)	505 (49.9%)	247 (63.3%)	94 (66.7%)	934 (52.1%)	< 0.0001
≥ 100,000	117 (46.6%)	372 (36.8%)	105 (26.9%)	37 (26.2%)	631 (35.2%)	
Missing	46 (18.3%)	135 (13.3%)	38 (9.7%)	10 (7.1%)	229 (12.8%)	
Median Years from HIV diagnosis to ART start (IQR)	0.3 (0.1,1.0)	0.5 (0.2,2.2)	1.7 (0.4,4.2)	1.7 (0.6,5.0)	0.6 (0.2,2.7)	< 0.0001
History of Hypertension	17 (6.8%)	94 (9.3%)	74 (19%)	46 (32.6%)	231 (12.9%)	< 0.0001
History of Diabetes	14 (5.6%)	38 (3.8%)	20 (5.1%)	16 (11.3%)	88 (4.9%)	0.0013
History of Dyslipidemia	53 (21.1%)	247 (24.4%)	126 (32.3%)	58 (41.1%)	484 (27.0%)	< 0.0001
History of AIDS-defining illness	180 (71.7%)	425 (42.0%)	72 (18.5%)	19 (13.5%)	696 (38.8%)	< 0.0001
Ever smoker	137 (54.6%)	524 (51.8%)	189 (48.5%)	65 (46.1%)	915 (51.0%)	0.2733

Table 3. Factors Associated with the Development of Obesity in HIV-Infected Individuals on ART

	Remained Non-Obese (BMI < 30kg/m^2) n=1281 (81.7%)	**Developed Obesity** (BMI ≥ 30kg/m^2) n=286 (18.3%)	**Total** n=1567	**Crude Hazard Ratio (95% CI)**		**P value**
Follow Up Time, median years (IQR)	4.7 (2.5,7.4)	1.9 (0.9,3.6)	4.1 (2.1,7.0)			
Age ART Initiation						
median (IQR)	35.7 (29.0,43.8)	36.5 (30.9,43.5)	36.0 (29.3,43.8)	1.02[b] (0.91, 1.15)		< 0.0001
<30	365 (28.5%)	64 (22.4%)	429 (27.4%)		%)	
30-39	450 (35.1%)	114 (39.9%)	564 (36.0%)		9%)	
40-49	325 (25.4%)	75 (26.2%)	400 (25.5%)		2%)	
≥ 50	141 (11.0%)	33 (11.5%)	174 (11.1%)		3%)	
Sex Category					.9,24.9)	< 0.0001
Male	815 (63.6%)	163 (57.0%)	978 (62.4%)	Ref	.9,28.1)	< 0.0001
Female	307 (24.0%)	99 (34.6%)	406 (25.9%)	1.48 (1.15, 1.90)	1.0)	0.0039
Transgender Women	159 (12.4%)	24 (8.4%)	183 (11.7%)	0.80 (0.52, 1.23)	.3, 41.9)	< 0.0001*
Race/skin color					.6, 40.2)	< 0.0001*
White	633 (49.4%)	140 (49.0%)	773 (49.3%)	Ref	.9, 60.6)	< 0.0001*
Black	241 (18.8%)	57 (19.9%)	298 (19.0%)	1.27 (0.93, 1.73)	.1, 38.0)	< 0.0001*
Mixed/Other	407 (31.8%)	89 (31.1%)	496 (31.7%)	1.12 (0.86, 1.46)		
Education level						
0-8 years	626 (48.9%)	155 (54.2%)	781 (49.8%)	Ref		
>8 years	655 (51.1%)	131 (45.8%)	786 (50.2%)	0.94 (0.74, 1.18)		
Baseline BMI (kg/m^2)						
median (IQR)[a]	21.8 (19.4,24.0)	25.3 (22.3,27.7)	22.3 (19.9,24.9)	1.15 (1.04, 1.28)		
Underweight (< 18.5)	217 (16.9%)	6 (2.1%)	223 (14.2%)			
Normal Weight (18.5-24.9)	839 (65.5%)	130 (45.5%)	969 (61.8%)			
Overweight (25-29.9)	225 (17.6%)	150 (52.4%)	375 (23.9%)			
Baseline CD4$^+$ T lymphocyte count (cells/mm^3)						
Median (IQR)[a] *	233 (90,355)	152 (48,287)	222 (78,343)	0.74[c] (0.61, 0.90)		
< 100	319 (24.9%)	102 (35.7%)	421 (26.9%)			
100-249	331 (25.8%)	72 (25.2%)	403 (25.7%)			
250-500	428 (33.4%)	68 (23.8%)	496 (31.7%)			
>500	122 (9.5%)	16 (5.6%)	138 (8.8%)			
Missing	81 (6.3%)	28 (9.8%)	109 (7.0%)			
Baseline Viral Load (copies/mL)						
median log10 (IQR)*	4.8 (4.0,5.4)	5.0 (4.2,5.5)	4.8 (4.1,5.4)	1.09 (0.96, 1.23)		
< 100,000	681 (53.2%)	119 (41.6%)	800 (51.1%)			
≥ 100,000	452 (35.3%)	115 (40.2%)	567 (36.2%)			
Missing	148 (11.6%)	52 (18.2%)	200 (12.8%)			
Median Years from HIV diagnosis to ART start (IQR)	0.6 (0.2,2.5)	0.5 (0.2,2.3)	0.6 (0.2,2.5)	0.98 (0.94, 1.02)		
Most-Used NRTI						
TDF	767 (59.9%)	147 (51.4%)	914 (58.3%)	Ref		
AZT	514 (40.1%)	139 (48.6%)	653 (41.7%)	0.86 (0.68, 1.09)		
Most-Used ART Core Drug Class						
NNRTI	858 (67.0%)	180 (62.9%)	1038 (66.2%)	Ref		
PI	415 (32.4%)	100 (35.0%)	515 (32.9%)	1.04 (0.82, 1.33)		
INSTI	8 (0.6%)	6 (2.1%)	14 (0.9%)	8.57 (3.77, 19.47)		
History of Hypertension	121 (9.4%)	52 (18.2%)	173 (11.0%)	1.92 (1.42, 2.60)		
History of Diabetes	47 (3.7%)	16 (5.6%)	63 (4.0%)	1.74 (1.05, 2.88)		
History of Dyslipidemia	329 (25.7%)	70 (24.5%)	399 (25.5%)	1.03 (0.78, 1.34)		
History of AIDS defining illness	489 (38.2%)	125 (43.7%)	614 (39.2%)	1.11 (0.88, 1.40)		
Ever smoker	676 (52.8%)	145 (50.7%)	821 (52.4%)	0.84 (0.66, 1.06)		

Abbreviations: *CI* confidence interval, *TDF* tenofovir, *AZT* zidovudine, *INSTI* integrase strand transfer inhibitor.

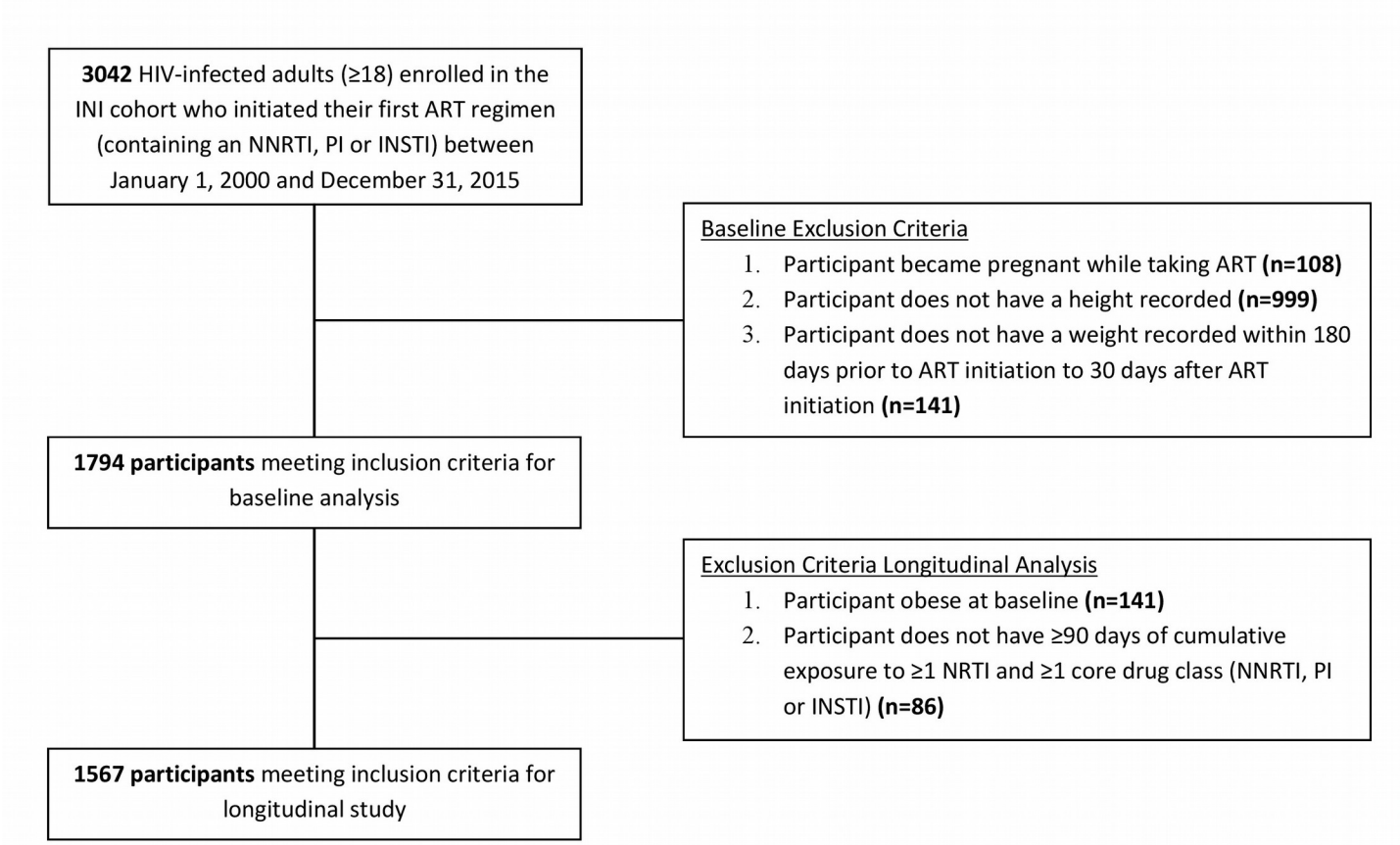
[a] variable included in model using restricted cubic spline

[b] crude HR per 10 year increase in age

[c] crude HR per 100 cell increase in CD4$^+$ T lymphocyte count

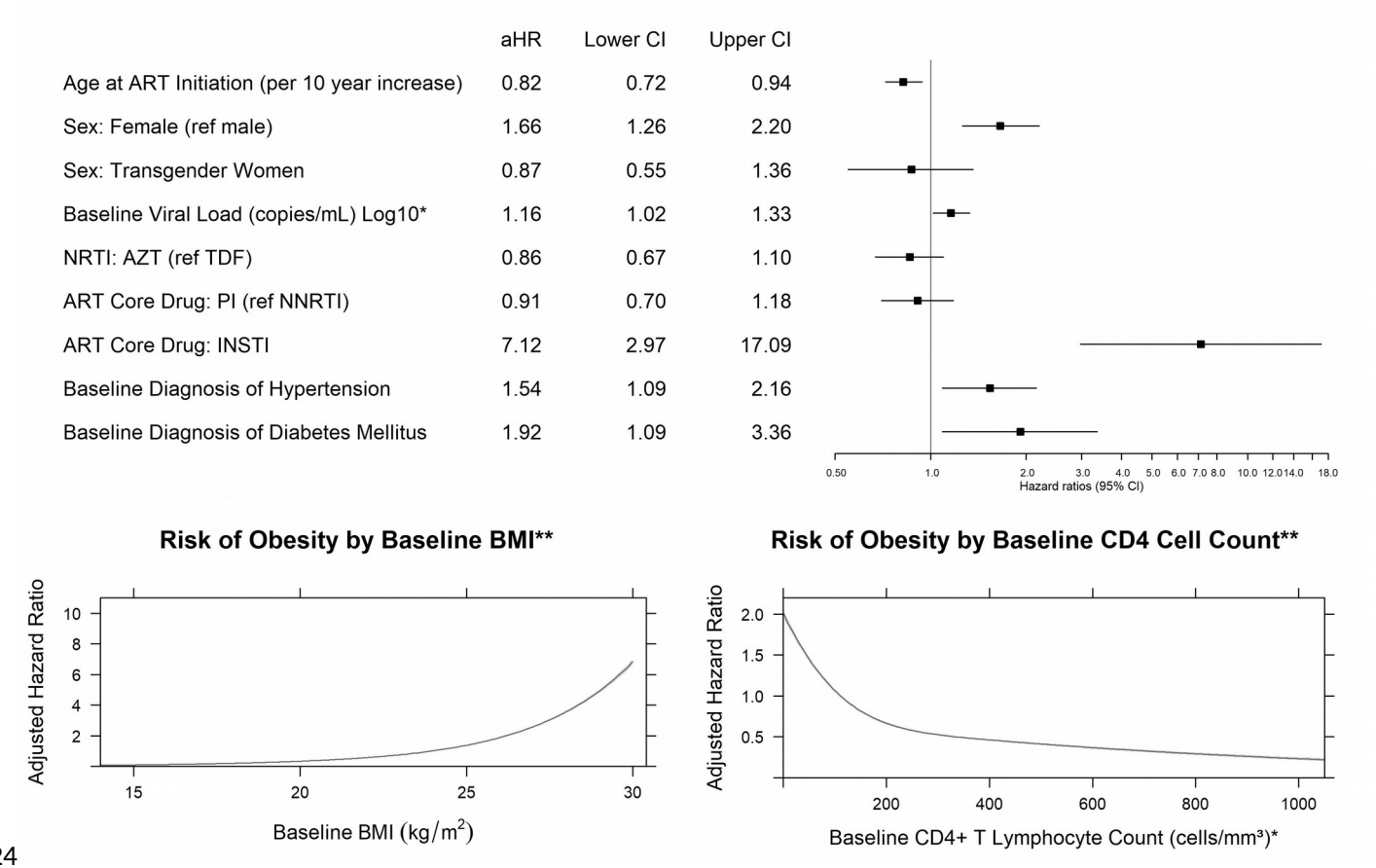
*missing values imputed in the models

Figure 1. Study Participant Flowchart



Abbreviations: *INI* Instituto Nacional de Infectologia Evandro Chagas, *INSTI* integrase strand transfer inhibitor.

Figure 2. Factors Associated with Incident Obesity after Multivariable Analysis



Note: date of ART initiation and end of follow-up date were accounted for in multivariable analysis.
Abbreviations: *AZT* zidovudine, *TDF* tenofovir, *INSTI* integrase strand transfer inhibitor, *aHR* adjusted hazard ratio, *CI* confidence interval.
*missing values imputed in the models.
**variables included in the models using restricted cubic splines.