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Characterizing the Impact of Integrase Strand-Transfer Inhibitors on Metabolic in Women Living with HIV Using Two Modeling Approaches

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By

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Bachelor of Science

Clemson University

2017

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Science in Public Health

in Biostatistics

2019

Abstract

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Background: Integrase strand-transfer inhibitor (INSTI)-based antiretroviral therapy (ART) is recommended first line for HIV treatment. Studies have suggested individuals who switch to INSTI-ART experience increase in body weight. We evaluated the effect of INSTI use on body weight and measurements in women living with HIV (WLHIV) using two separate modeling approaches.

Methods: Data were collected from 2008-2017 from WLHIV enrolled in the Women's Interagency HIV Study (WIHS). Women who switched to or added an INSTI to ART (INSTI group) were compared to women who remained on non-INSTI ART (Control group). Outcomes included changes in body weight; body mass index (BMI); percentage body fat (PBF); circumference of waist, hip, arm, and thigh; blood pressure (BP). Outcomes were measured 6-12 months before and 6-18 months after INSTI switch/add in the INSTI group with comparable time points in the Control group. Linear regression models and mixed-models compared change over time in each outcome by Control/INSTI group, adjusted for age, race, WIHS site, education, income, smoking status, and baseline ART regimen.

Results: 1118 WIHS participants (884 Control and 234 INSTI) were followed for average 2.0 years; mean baseline age was 48.8 years, 61% were Black, and mean CD4 669 cells/mm^3. Using the cross-sectional approach, the INSTI group experienced 2.14 kg greater increase in weight, 0.78 kg/m^2 increase in BMI, 1.35% increase in PBF, and 2.05, 1.87, 0.58, and 0.98 cm increases in waist, hip, arm, and thigh circumference, respectively compared to the Control group. In the longitudinal data approach, the INSTI group experienced 1.01 kg greater increase in weight, 0.37 kg/m^2 increase in BMI, 0.68% increase in PBF, and 1.09, 1.12, 0.31, and 0.54 cm increases in waist, hip, arm, and thigh circumference, respectively compared to the Control group.

Conclusion: In a longitudinal study of WLHIV on ART, a switch to INSTI was associated with significant increases in body weight and measurements, body fat, and blood pressure compared to those remaining on non-INSTI ART. Both modeling approached resulted in the same conclusions. Further research is needed for prevention and management of metabolic effects with INSTI use.

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Acknowledgements

The Department of Biostatistics and Bioinformatics at Emory has provided numerous resources and ongoing support on my thesis. Specifically, I would like to thank C. Christina Mehta, PhD, MSPH who has been a great advisor for me both in the completion of my thesis and academically.

I would like to thank the Women's Interagency HIV Study (WIHS) for approval of this sub-study. This study was made possible by the ongoing commitment of all the WIHS participants whose data was used for this study. This thesis would not have been possible without the guidance and support from Anandi N. Sheth, MD, MS; Cecile D. Lahiri, MD, MS; Anne Marie Kerchberger, M.Eng; Nathan A. Summers, MD; Ighovwerha Ofotokun, MD, MS. It was an honor to work with such dedicated hard-working individuals. I would also like to thank the WIHS site co-investigators who assisted with feedback in preparation of the abstract as well as serving as site liaisons for data collaboration.

I would like to also thank my Biostatistics cohort for making my time at Emory so enjoyable and memorable. Finally, I would like to thank my family and friends for the encouragement and motivation I needed to complete my thesis. The process of completing my thesis has helped me evolve into a more versatile and capable biostatistician.

Table of Contents

Introduction

In the United States it is estimated 1.1 million people are living with HIV. Human immunodeficiency virus (HIV) attacks CD4 cells in the body and weakens a person's immune system over time. When left untreated a person is more susceptible to contracting other infections and illnesses. The final stage of HIV is acquired immunodeficiency syndrome or AIDS. In the United States HIV is primarily contracted from having unprotected vaginal or anal sex with someone who has HIV and through sharing needles for drug injection with someone who is living with HIV. There is currently no known cure for HIV, but it is manageable with antiretroviral therapy (ART). ART is associated with reduced infections and a life expectancy similar to those without HIV.[1]

Integrase strand transfer inhibitors (INSTIs) are used in once daily oral ART regimens and are recommended as first line therapy for persons living with HIV who have never been on an ART. These include the drugs raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG). INSTIs are highly potent anti-HIV medications that have a good safety profile and limited drug interactions. There is however limited research done in the long-term side effects, particularly in women who take these medications. [2]

The prevalence of obesity in the United States has steadily increased since 1999.[3] With the percent of overweight Americans growing, there is also an increase in adverse health-related conditions. Obese people are more at risk to develop hypertension, diabetes, and cardiovascular disease.[4]

Studies have shown that HIV patients are increasingly overweight/obese at diagnosis and during HIV infection. There is currently more research in weight gain among men on ARTs than women.[6] Previous studies showed that men and women who switched to an INSTI-containing regimen had significant increase in weight. In one study, increase in weight was more pronounced in women; however, the small sample size of the study limits the generalizability of the results. In addition, these studies did not evaluate changes in percent body fat (PBF) or body circumferences measurements.[7,8] Additionally considering body circumference measurements with weight and body mass index (BMI) may provide a more accurate representation of non-uniform and uniform weight gain.

In our study, we compared weight and body measurements between women living with HIV (WLHIV) who switched to an INSTI-containing ART with WLHIV who were not on an INSTI-containing regimen. The body measurements we considered were weight, BMI, PBF, waist, hip, thigh, and arm circumference. We hypothesized that women switching to an INSTI would have an increase in their weight as well as BMI, PBF, waist, hip, thigh, and arm circumference compared to women who were not on an INSTI. We also compared systolic and diastolic blood pressure in women who switched to an INSTI compared to women not on an INSTI ART. We again hypothesized that women switching to an INSTI would have an increase in systolic and diastolic blood pressure compared to woman who were not on an INSTI.

The data used was from Women's Interagency HIV Study (WIHS) cohort of WLHIV. WIHS is a longitudinal cohort study of U.S. women with HIV and women at high-risk for acquiring HIV aimed to better understand the progression of HIV in women.

This study aims to compare two analytic approaches for analyzing longitudinal pre/post data by case/control status- a traditional longitudinal data analysis approach and a commonly implemented simplification whereby longitudinal pre/post data are cross-sectionalized by calculating differences and analyzed with linear regression. By changing the data to cross-sectional we ignore the correlation of the outcome within a person over time. Ignoring the correlation leads to overestimation of the variability of the change. It can also lead to less precise estimates of the coefficients.[9,10] To determine if changing the data structure alters the correlation or the estimates we will model both approaches and compare.

Methods

Study Cohort: The Women's Interagency HIV Study

The WIHS is the largest ongoing prospective longitudinal cohort study of WLHIV and at-risk HIV-negative women in the U.S. We retrospectively examined the WIHS observational data from 2008 to 2017, since the FDA approved INSTIs for the treatment of HIV in 2007. In WIHS, after each women's initial baseline visit, follow-up visits occur every six months. These follow-up visits include both clinical and medication history assessment through interviewer-administered survey instruments, physical examinations, and specimen collection depending on the visit cycle. There are currently 9 active clinical sites: San Francisco, California; Chicago, Illinois; Brooklyn, New York; Bronx, New York; Washington, DC; Chapel Hill, North Carolina; Miami Florida; Birmingham, Alabama/Jackson, Mississippi combined site; and Atlanta, Georgia.

Data Acquisition

Women who are enrolled in WIHS participate in twice annual study visits. During these visits, outcome variables are collected on a standard measurement by trained study coordinators, study technicians, nurses, nurse practitioners, and physicians. Participants' weight (kilogram, kg) and height (meters) are measured every visit. This information is then utilized to calculate the BMI. BMI was calculated as $\frac{weight(kg)}{height(meters)^2}$ and reported as $\frac{kg}{m^2}$. Percentage Body Fat (PBF) was calculated using Bioelectrical Impedance Analysis (BIA) as $\frac{BF}{weight(kg)} \times 100$, on the right side of the body unless a participant was pregnant or had a cardiac pacemaker. Electrodes were placed at the right wrist, hand, ankle, and foot. It is reported with displayed resistance and reactance and subsequently PBF is calculated using this information. Women's body measurements include waist, hip, right arm, and right thigh circumference, are taken by a trained study examiner in a standard manner. Each measurement is taken at least two times. If there is a greater than 0.7 cm difference between the first two measurements, then a repeat, third measure and final measurement is taken. For each visit measurement we averaged the available data when multiple measurements were taken. Finally, systolic and diastolic blood pressures are taken at each visit. Blood pressure is collected using an automated monitor (Dinamap Procare Services, GE Medical Systems). Three blood pressure measurements are taken while seated and separated by 5 minutes, and values are averaged for each visit.

Inclusion Criteria

All WIHS participants were assessed for eligibility for the study. Criteria for INSTI group included: 1) History of switching from a non-INSTI ART regimen which could include a nucleoside reverse transcriptase inhibitor (NRTI) backbone plus EITHER non-nucleoside reverse

transcriptase inhibitor (NNRTI) or protease inhibitor (PI) or entry inhibitors (EI) to an INSTI or adding an INSTI to that prior regimen. 2) 5 consecutive WIHS visits where participants were both taking ART and were virologically suppressed, defined as HIV RNA viral load <1000 copies/mL. These 5 visits included the "switch/add" visit (the first visit in which the INSTI switch or add was reported), as well as 2 visits pre-, and 2 visits post switch. 3) Women who switched to an INSTI drug must remain on the same INSTI drug over the subsequent 3 visits. Women who started INSTI-based regimens when they were ART naïve were excluded, because they did not have 2 pre-visits on an ART regimen. Criteria for the Control group included having 5 consecutive WIHS visits with reported history of taking an ART regimen that includes a NRTI backbone, NNRTI, PI, and/or EI and HIV RNA viral load <1000 copies/mL. We chose <1000 copies/mL as a cut-off to confirm adherence to medication while also acknowledging that many patients experience intermittent viral blips (17-18). In addition, all visits from women who were pregnant were excluded from both groups due to the larger expected changes in body weight, BMI, and waist and hip circumference measurements.

The WIHS study protocol was been approved by Institutional Review Boards at all participating sites, and all study participants provided written informed consent for use of their data. Furthermore, this substudy was reviewed and approved by the WIHS Executive Committee (WIHS concept sheet #W17059).

Statistical Analysis: Cross-Sectional Approach

Outcomes of interest included changes in weight, BMI, PBF, circumference of waist, hip, arm, and thigh, and blood pressure. As discussed above, 5 WIHS visits were included in the original

longitudinal data, including 2 pre-visits, one switch/add visit, and 2 post-visits. In order to assess the difference in post- and pre- INSTI change, an average was calculated for each outcome across the 2 pre-visits as well as an average for each outcome across the 2 post-visits. If there was only one pre or one post visit data available for any outcome this was the value used. When multiple measurements were reported in one visit (e.g., blood pressure) an average of those measurements was used. Lastly, the difference between post-visit average and pre-visit average was calculated.

Baseline demographic and clinical characteristics for Control and INSTI groups were compared using chi-square or Fisher's exact tests for categorical variables and two-sample t-tests or Wilcoxon rank sum tests for continuous variables, respectively. Separate linear regression models compared change over time (average post- average pre) in each outcome by Control/INSTI group. These models were adjusted for age, race, WIHS site, education, income, smoking status, and baseline ART regimen. These were determined to be important covariates *a priori* by investigators. Eight participants were removed due to suspected inaccurate data given extreme changes in outcome variables. Model fit was assessed through residual plots.

Statistical Analysis: Longitudinal Approach

In the longitudinal analysis, the same outcomes of interest were considered (weight, BMI, PBF, circumference of waist, hip, arm, and thigh, and blood pressure) but now all time points were included in the analysis. A mixed model was fitted using the 2 baseline visits and the 2 post visits. The model was again adjusted for age, race, WIHS site, education, income, smoking status, and baseline ART regimen. The same eight participants from the cross-sectional analysis

were removed since they were likely inaccurate. The model was fit with a random intercept by subject and an unstructured covariance matrix. Model fit was checked by residual plot.

Results

Demographic and Clinical Characteristics

There were a total of 1118 WIHS participants who meet the inclusion criteria, of which 884 were a part of the Control group and 234 were in the INSTI group (Figure 4). The average overall age of the women was 48.8 (Standard Deviation (SD): 8.8) years. The majority of the participants had completed high school or less (67%), had an income less than $12,000 annually (51%), identified as African American (60%), and had health insurance at baseline (97%) (Table 1). The mean CD4 at baseline was 669 ± 294 $\frac{cells}{mm^3}$. The women in the cohort predominantly self-reported medication adherence greater than 95% of the time (89%) and reported never having used intravenous drugs (80%). The WIHS geographic site distributions was as follows: 333 (29%) from New York sites (Bronx, Brooklyn), 319 (28%) from California sites (Los Angeles, San Francisco), and 187 (16%) from Southern sites (Atlanta, GA, Chapel Hill, NC, Miami, FL, Birmingham, AL, and Jackson, MS). Racial and ethnic distributions among the cohort were as follows: 680 (60%) African American (non-Hispanic), 172 (15%) White (non-Hispanic), and 266 (23%) other race/ethnicity.

At baseline, there was no statistically significant differences between the INSTI and Control groups for age, mean CD4, viral load, medication adherence, WIHS site, race, education level, annual income, insurance status, marital status, residence status, alcohol consumption weekly,

cigarette smoking status, or intravenous (IV) and non-IV drug use status (Table 1). Based on inclusion criteria, these women were followed for average 2 years (SD: 0.1 years).

At baseline, women in the INSTI group were more likely to be on Protease Inhibitor-containing ART: 161 (68%) compared to 411 (46%) of the Control women ($p<0.0001$); this was the only sociodemographic or clinical variable difference observed at baseline between groups. Baseline weight, BMI, PBF, and body circumference measurements were also statistically the same (Table 1).

Weight, Body Mass Index, and Percentage Body Fat: Cross Sectional Approach Model

The average weight of the INSTI group at the baseline visits was 80.84 kg (SD: 25.66) and 80.84 kg (SD: 23.03) in the Control group (Table 2). On average, women in the INSTI group gained 2.36 kg from baseline to follow-up compared to the women in the Control group who gained only 0.21 kg. The difference in the two groups was 2.14 kg (95% CI: 1.21, 3.08) while adjusting for age, site, race, income, smoking status, education, and baseline ART (Table 3).

The baseline mean BMI in the INSTI group was 30.56 kg/m^2 (SD: 8.86) and 30.95 kg/m^2 (SD: 8.25) in the Control group (Table 2). The mean BMI change was 0.94 kg/m^2 in the INSTI group and 0.15 kg/m^2 in the Control group. The difference in INSTI and Control group was 0.78 kg (95% CI: 0.42, 1.14) while continuing to adjust the model for age, site, race, income, smoking status, education, and baseline ART (Table 3).

At baseline the average PBF of the INSTI group was 33.95% (SD: 11.53) and 35.04% (SD: 11.61) in the Control group (Table 2). The change in PBF from follow-up was an increase of 1.84% in the INSTI group compared to 0.49% increase in the Control group. The difference in PBF between the groups in the adjusted covariate model was 1.35% (95% CI: (0.49,2.22)) more in the INSTI group (Table 3).

Weight, Body Mass Index, and Percentage Body Fat: Longitudinal Approach Model

In the longitudinal models, the average weight gain in the INSTI group was 2.73 kg from baseline to follow-up compared to the average weight gain in the Control group of 0.70 kg. The difference in the two groups was 1.01 kg (95% CI: 0.68, 1.35) while adjusting for age, site, race, income, smoking status, education, and baseline ART. The INSTI group had a 0.99 kg/m^2 increase in BMI and the Control group had a 0.25 kg/m^2 during the study. The difference in the two groups was 0.37 kg/m^2 (95% CI: 0.24, 0.50). There was a 1.80% increase in PBF in the INSTI group compared to a 0.44% increase in PBF in the Control group. The difference between the two groups was 0.68% (95% CI: 0.25, 2.22) (Table 4).

Body Circumference & Blood Pressure Measurements: Cross Sectional Approach Model

At baseline the entire cohort's mean (SD) waist, hip, arm, and thigh circumference measurements were 99.49 (16.41), 105.91 (15.05), 32.97 (6.42), and 53.86 (10.07) cm, respectively. The INSTI group had a 2.05 cm (95% CI: 1.06, 3.04) greater increase in waist circumference compared to the Control group. There was a 1.87 cm (95% CI: 0.99, 2.75) greater increase in hip circumference in the INSTI group. After follow-up there was a 0.58 cm (95%CI:

0.25, 0.91) greater increase in arm circumference and a 0.98 cm (95%CI: 0.39, 1.56) greater increase in thigh circumference in the INSTI group (Table 2).

The average systolic and diastolic blood pressure (SD) of the INSTI group at baseline was 119.06 mmHg (14.22) and 73.20 mmHg (8.19) compared to the Control group's 120.84 mmHg (16.21) and 74.19 mmHg (9.03), respectively. There was an average increase in systolic and diastolic blood pressure of 4.47 mmHg and 1.65 mmHg, respectively, in the INSTI group. The Control group had an average increase of systolic and diastolic blood pressures of 2.23 mmHg and 0.48 mmHg, respectively. The difference in the INSTI group and the Control group for the covariate-adjusted model was 2.24 mmHg greater increase in systolic and 1.17 mmHg greater increase in diastolic blood pressure (Table 2).

Body Circumference & Blood Pressure Measurements: Longitudinal Approach Model

The difference between the INSTI and the Control groups body circumference measurements were 1.09 cm, 1.12 cm, 0.31 cm, and 0.54 cm for waist, hip, arm, and thigh respectively. There was an average increase in systolic and diastolic blood pressure of 3.53 mmHg and 1.47 mmHg, respectively, in the INSTI group. The Control group had an average increase of systolic and diastolic blood pressures of 0.80 mmHg and -0.05 mmHg, respectively. The difference in the INSTI group and the Control group for the covariate-adjusted mixed model was 1.36 mmHg greater increase in systolic and 0.76 mmHg greater increase in diastolic blood pressure (Table 4).

The estimates in both the linear and mixed model approach were approximately the same. The outcomes with the biggest discrepancies were weight, BMI, and waist circumference. There was

a 1.13 kg difference in the estimates for weight, 0.41 kg/m^2 difference in BMI, and a 0.96 cm difference in waist circumference (Figure 1-3). The linear model estimate was larger for all outcome variables.

Discussion

Adding or switching to an INSTI medication was associated with a significant increase in weight, BMI, PBF, body circumference measurements, and blood pressure in women with HIV already on an ART from multiple regions in the United States. This is currently the largest study of metabolic body changes following an ART switch or add to and INSTI of women with HIV.

The cross-sectional and longitudinal approaches both resulted in the same conclusions for all of the outcomes of interest- switching to INSTI significantly increases weight and body measurements compared to the control. However, the magnitude of the change did vary between the two approaches with the longitudinal approach generally estimating smaller post-pre differences between INSTI and Control. The longitudinal approach had much more narrow confidence errors compared to the cross-sectional model, suggesting much more precise estimates. The outcome variables weight, BMI, PBF, waist circumference, and hip circumference had similar significance levels for the INSTI/Control difference for both approaches while for the outcomes of arm circumference, thigh circumference, systolic and diastolic blood pressure, INSTI exposure were slightly more significantly associated in the longitudinal approach.

Conclusion

Investigating the effects of switching or adding an INSTI has to the of body weight, BMI, and body circumference is important to better understand how the drug effects women. This could help prevent weight gain in the future as well as better identify those who are at increased risk of weight change.

In this dataset the data was able to be transformed cross-sectional and produce statistically similar results compared to if the data was modeled longitudinally. However, in general it is better to use the longitudinal data in order to account for within person correlation.

Tables and Figures

Table 1: Baseline Demographics and Clinical Characteristics

Variable	Overall Cohort (n=1118)	Control Group (n=884)	INSTI Group (n=234)	p-value
Age(years) - mean (SD)	48.82 (8.78)	48.57 (8.73)	49.78 (8.94)	0.0598
Baseline CD4 Mean of Pre Visits (cells/mm^3) - median {Q1,Q3}	637.5 {479.0, 824.0}	629.5 {473.0, 822.0}	666.25 {500.0, 840.0}	0.1475
Baseline Viral Load (copies/ml) - median {Q1,Q3}	71 {38, 155}	68 {37, 143}	90 {40, 177}	0.2636
Pre-Medication Change Regimens - n (%)				
Nucleoside Reverse Transcriptase Inhibitors	1105 (98.84)	875 (98.98)	230 (98.29)	0.3804
Non-Nucleoside Reverse Transcriptase Inhibitors	555 (49.64)	472 (53.39)	83 (35.47)	<.0001
Protease Inhibitors	572 (51.16)	411 (46.49)	161 (68.80)	<.0001
Entry Inhibitors	5 (0.45)	4 (0.45)	1 (0.43)	0.9591
Medication Adherence - n (%)				0.3289
Self-Reported < 95%	125 (11.19)	103 (11.66)	22 (9.40)	
Self-Reported > 95%	992 (88.81)	780 (88.34)	212 (90.60)	
WIHS Site - n (%)				0.0954
New York (NYC Bronx & Brooklyn)	333 (29.79)	256 (28.96)	77 (32.91)	
Washington, D.C.	133 (11.90)	96 (10.86)	37 (15.81)	
California (LA & SF)	319 (28.53)	261 (29.52)	58 (24.79)	
Chicago, IL	146 (13.06)	116 (13.12)	30 (12.82)	
Southern Sites	187 (16.73)	155 (17.53)	32 (13.68)	
Race - n (%)				0.0863
White (Non-Hispanic) & Other	172 (15.38)	126 (14.25)	46 (19.66)	
African-American (Non- Hispanic)	680 (60.82)	540 (61.09)	140 (59.83)	

Hispanic	266 (23.79)	218 (24.66)	48 (20.51)	
Education - n (%)				0.1477
Completed High School or Less	741 (66.64)	595 (67.69)	146 (62.66)	
Completed More than High School	371 (33.36)	284 (32.31)	87 (37.34)	
Income - n (%)				0.4778
<$12000 per year	555 (51.15)	441 (51.64)	114 (49.35)	
$12001-24000	254 (23.41)	193 (22.60)	61 (26.41)	
> $24000	276 (25.44)	220 (25.76)	56 (24.24)	
Insurance - n (%)				0.4058
Currently has insurance	1079 (97.03)	851 (96.81)	228 (97.85)	
Does not currently have insurance	33 (2.97)	28 (3.19)	5 (2.15)	
Marital Status - n (%)				0.4524
Married/Partnered	348 (31.75)	282 (32.64)	66 (28.45)	
Divorced/Widowed/Separated	328 (29.93)	257 (29.75)	71 (30.60)	
Never married	420 (38.32)	325 (37.62)	95 (40.95)	
Alcohol use - n (%)				0.5594
Abstainer	706 (63.60)	557 (63.44)	149 (64.22)	
>0-7 drinks/week	324 (29.19)	254 (28.93)	70 (30.17)	
>7 drinks/week	80 (7.21)	67 (7.63)	13 (5.60)	
Current Cigarette Smoking Status - n (%)				0.1108
Not Currently Smoking	728 (65.47)	564 (64.16)	164 (70.39)	
Currently Smoking	382 (34.35)	314 (35.72)	68 (29.18)	
Drug use- n (%)				
Injection Drug Use				0.3995
Current	2 (0.18)	1 (0.11)	1 (0.43)	
Former	220 (19.82)	177 (20.16)	43 (18.53)	
Never	888 (80.00)	700 (79.73)	188 (81.03)	
Non-injection drug use				0.1045

Current	205 (18.49)	164 (18.70)	41 (17.67)
Former	571 (51.49)	438 (49.94)	133 (57.33)
Never	333 (30.03)	275 (31.36)	58 (25.00)

Notes: p-values for categorical variables were calculated using Chi-Square, Fisher's exact tests, or Wilcoxon, p values for continuous values were calculated using two-sided t-test or Wilcoxon test based on the variables distribution.

Table 2: Baseline Outcome Variable Measurements

Outcome Variable	Mean (SD) INSTI Baseline	Mean (SD) Control Baseline
Mean Weight (kgs)	80.84(25.66)	80.84(23.02)
Mean BMI (kg/m^2)	30.56(8.86)	30.95(8.25)
Mean Body Fat (%)[b]	33.95(11.53)	35.04(11.61)
Body Measurements		
Waist Circumference (cm)	99.19(17.07)	99.57(16.23)
Hip Circumference (cm)	104.48(15.53)	106.29(14.90)
Arm Circumference (cm)	32.84(6.64)	33.01(6.37)
Thigh Circumference (cm)	53.11(10.64)	54.06(9.91)
Mean Systolic BP (mmHg)	119.06(14.22)	120.84(16.21)
Mean Diastolic BP (mmHg)	73.20(8.19)	74.19(9.03)

[b] *Using Bioelectrical Impedance Analysis [(body fat/ weight_kg)*100] = (%)*

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval

Table 3: Cross Sectional Model-adjusted change over time in outcome variables in INSTI and Control groups

Outcome Variable	Mean (95% CI) Change in INSTI[a]	Mean (95% CI) Change in Control[a]	Difference Between Means, INSTI-Control (95% CI)[a]
Mean Weight (kgs)	2.36(1.45, 3.26)	0.21(-0.37, 0.79)	2.14(1.21, 3.08)****
Mean BMI (kg/m^2)	0.94(0.60, 1.27)	0.15(-0.04, 0.35)	0.78(0.42, 1.14)****
Mean Body Fat (%)[b]	1.84(1.04, 2.65)	0.49(0.02, 0.96)	1.35(0.49, 2.22)**
Body Measurements			
Waist Circumference (cm)	2.62(1.69, 3.55)	0.57(0.03, 1.12)	2.05(1.06, 3.04)****
Hip Circumference (cm)	1.68(0.86, 2.51)	-0.19(-0.67, 0.30)	1.87(0.99, 2.75)****
Arm Circumference (cm)	0.72(0.41, 1.03)	0.14(-0.04, 0.32)	0.58(0.25, 0.91)***
Thigh Circumference (cm)	1.04(0.49, 1.58)	0.06(-0.26, 0.38)	0.98(0.39, 1.56)**
Mean Systolic BP (mmHg)	4.47(2.52, 6.43)	2.23(1.09, 3.38)	2.24(0.14, 4.35)*
Mean Diastolic BP (mmHg)	1.65(0.61, 2.69)	0.48(-0.13, 1.09)	1.17(0.05, 2.29)*

[a] Models adjusted for age, site, race/ethnicity, income, smoking status, education, baseline antiretroviral therapy

*[b] Using Bioelectrical Impedance Analysis [(body fat/ weight_kg)*100] = (%)*

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval

** <0.05, **p<0.01, ***p<0.001, ****p<0.0001*

Table 4: Longitudinal Mixed Model-adjusted change over time in outcome variables in INSTI and Control groups

Outcome Variable	Mean (95% CI) Change in INSTI[a]	Mean (95% CI) Change in Control[a]	Difference Between Means, INSTI-Control (95% CI)[a]
Mean Weight (kgs)	2.73(2.09, 3.37)	0.70(0.32, 1.09)	1.01(0.68, 1.35)****
Mean BMI (kg/m^2)	0.99(0.75, 1.23)	0.25(0.12, 0.40)	0.37(0.24, 0.50)****
Mean Body Fat (%)[b]	1.80(1.04, 2.57)	0.44(0.01, 0.86)	0.68(0.25, 1.11)**
Body Measurements			
Waist Circumference (cm)	2.40(1.65, 3.16)	0.23(-0.19, 0.65)	1.09(0.67, 1.50)****
Hip Circumference (cm)	1.65(0.97, 2.33)	-0.59(-0.97, -0.21)	1.12(0.75, 1.50)****
Arm Circumference (cm)	0.90(0.65, 1.15)	0.28(0.13, 0.42)	0.31(0.17, 0.45)****
Thigh Circumference (cm)	1.14(0.71, 1.57)	0.05(-0.19, 0.29)	0.54(0.31, 0.78)****
Mean Systolic BP (mmHg)	3.53(1.84, 5.22)	0.80(-0.09, 1.69)	1.36(0.42, 2.31)**
Mean Diastolic BP (mmHg)	1.47(0.56, 2.38)	-0.05(-0.53, 0.43)	0.76(0.25, 1.27)**

[a] Models adjusted for age, site, race/ethnicity, income, smoking status, education, baseline antiretroviral therapy

*[b] Using Bioelectrical Impedance Analysis [(body fat/ weight_kg)*100] = (%)*

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval

** <0.05, **p<0.01, ***p<0.001, ****p<0.0001*

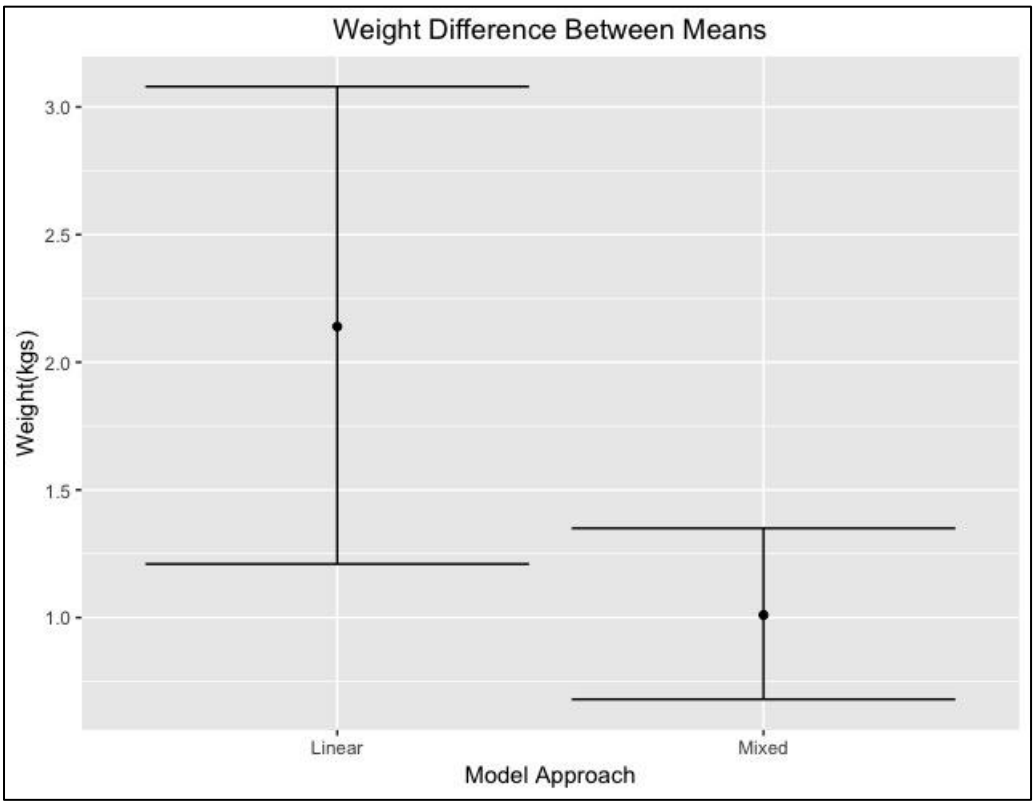

Figure 1: Comparison of Linear and Mixed Model in estimating change in weight from post-pre visits change between INSTI group – Control group.

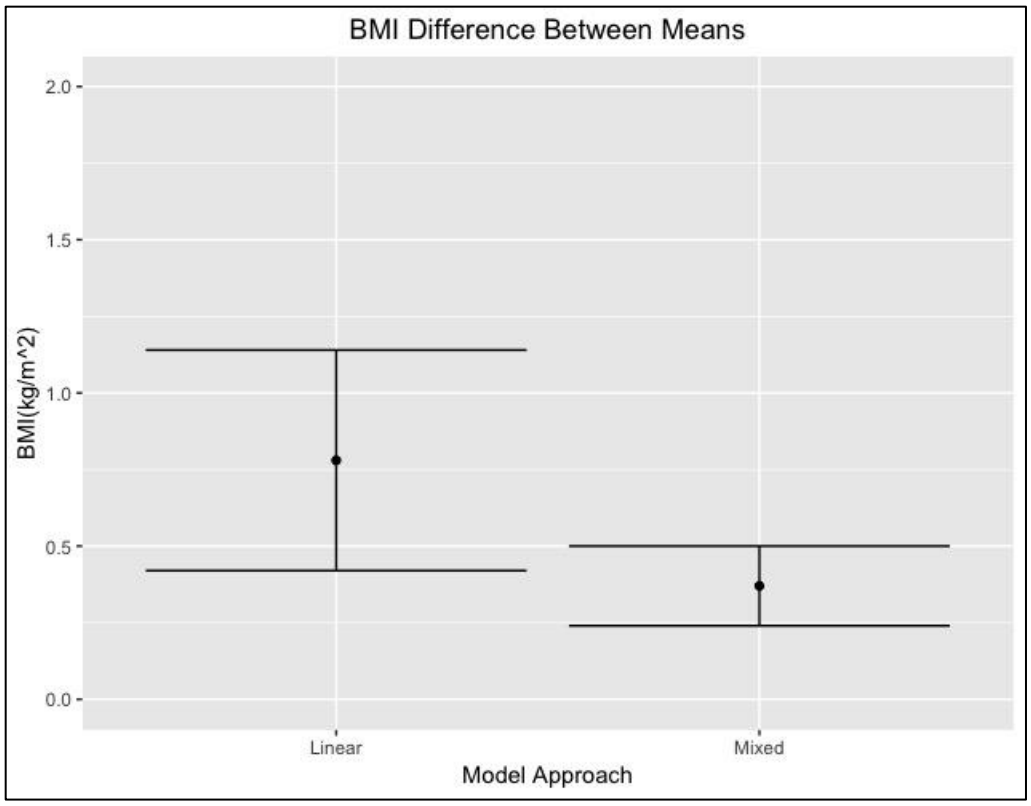

Figure 2: Comparison of Linear and Mixed Model in estimating change in BMI from post-pre visits change between INSTI group – Control group.

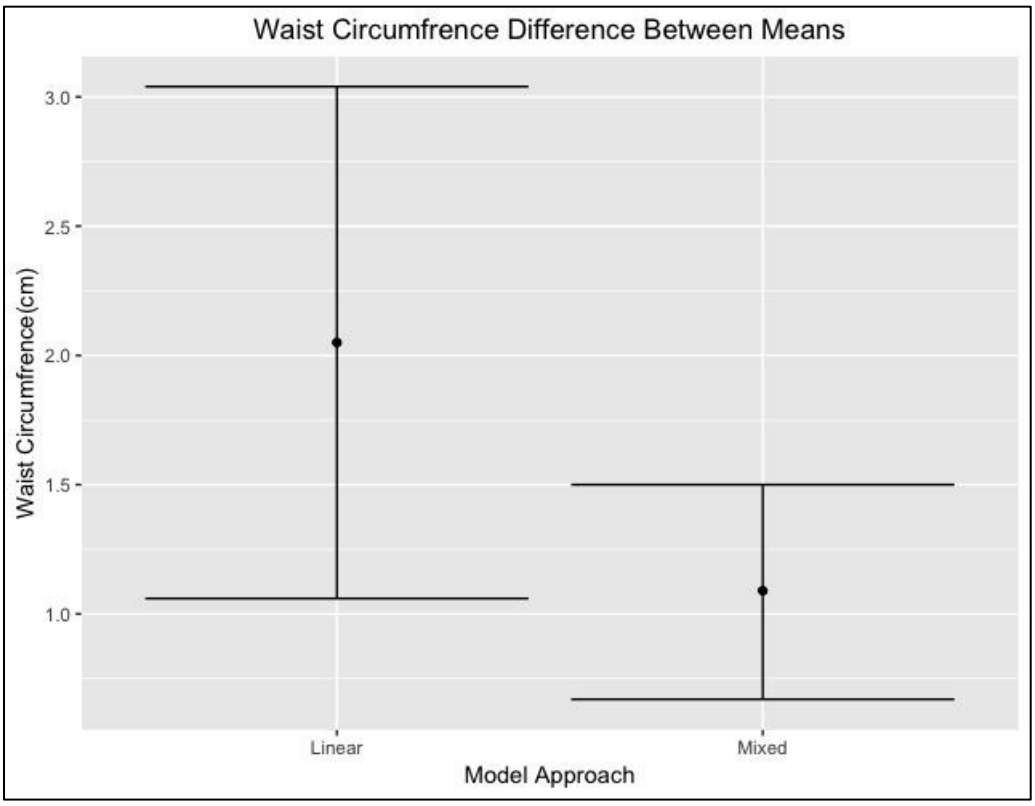

Figure 3: Comparison of Linear and Mixed Model in estimating change in waist circumference from post-pre visits change between INSTI group – Control group.

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