HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

AIDS. 2023 October 01; 37(12): 1819–1826. doi:10.1097/QAD.0000000000003635.

Physical activity is associated with adiposity in older adults with HIV in the modern HIV era

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Abstract

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Authorship Contribution Statement:

All authors on this paper meet the four criteria for authorship as identified by the International Committee of Medical Journal Editors (ICMJE); all authors have contributed to the conception and design of the study, drafted or have been involved in revising this manuscript, reviewed the final version of this manuscript before submission, and agree to be accountable for all aspects of the work. Specifically, using the CRediT taxonomy, the specific contributions of each author is as follows: Conceptualization & Methodology: AR Webel, C Horvat Davey, V Oliveira, D. Cleveland, HM Crane BM Gripshover, D. Long, J Fleming, TW Buford and AL Willing Formal Analysis: D Cleveland & D. Long; Funding acquisition: AR Webel & AL Willig; Investigation: AR Webel, C Horvat Davey, HM Crane BM Gripshover, J Fleming, and AL Willing; Project administration: AR Webel & AL Willig; Supervision: AR Webel, C Horvat Davey, HM Crane BM Gripshover, J Fleming, and AL Willing; Writing AR Webel, C Horvat Davey, V Oliveira, D. Cleveland, HM Crane BM Gripshover, D. Long, J Fleming, TW Buford and AL Willing

Conflicts of Interest: None

Registration number: NCT03790501

Objectives: People with HIV (PWH) are aging and are experiencing higher rates of abdominal adiposity. Physical activity is an effective non-pharmacological strategy to reduce adiposity in the general aging population. Yet, the relationship between physical activity and adiposity in people with well-controlled HIV is unclear. Our objective was to describe the association between objectively-measured physical activity and abdominal adiposity in PWH.

Methods: As part of the multisite, observational PROSPER-HIV study, virologically suppressed, adult PWH wore an Actigraph accelerometer for 7–10 days and completed duplicate waist and hip circumference measures. Demographic and medical characteristics were abstracted from the CFAR Network of Integrated Clinical Systems dataset. Descriptive statistics and multiple linear regressions were used to analyze the data.

Results: On average, our 419 PWH were 58 years of age (IQR: 50, 64), male (77%), Black (54%), and currently taking an integrase inhibitor (78%). PWH completed a mean of 7.06 (±2.74) days of total actigraphy wear time. They took an average of 4,905 (3233, 7140) steps per day and engaged in 5.4 hours of sedentary time per day. Controlling for age, sex, employment and integrase inhibitor use, the number of steps taken per day was associated with reduced abdominal adiposity ($F= 3.27$; $p<0.001$) and the hours of daily sedentary time was associated with increased abdominal adiposity ($F= 3.24$; $p<0.001$).

Conclusions: Greater physical activity is associated with reduced abdominal adiposity in aging PWH. Future work should investigate how to tailor the amount, type and intensity of physical activity needed to reduce adiposity in PWH taking contemporary HIV medication.

Keywords

Physical Activity; Aging; HIV; Antiretroviral Therapy; Adiposity

People with HIV (PWH) are living longer and developing chronic comorbidities at higher rates than those without HIV. Today the average PWH on stable antiretroviral therapy (ART) lives into their mid-seventies, [1] a significant increase since the beginning of the HIV epidemic. [2] While this increased longevity represents a monumental success over what was once the largest global health problem, we are only starting to understand the interacting clinical impact of aging, HIV infection and HIV treatment on this growing population. [3–5]

Aging and HIV are each associated with increased abdominal adiposity – a modifiable risk factor for cardiovascular disease, diabetes mellitus, chronic kidney disease, and frailty. [6,7] Recent scholarship has revealed that PWH have an approximately 2 fold increased risk for developing cardiovascular disease, [8] diabetes mellitus, [9] chronic kidney disease, [10] and frailty[11] compared to the general population. These trends have been observed across clinical and geographic settings, yet effective strategies acceptable to PWH across these settings are limited. [7]

While offering superior virological effects, safety profile and simplification for PWH, some newer antiretroviral therapies have also been associated with increased abdominal adiposity that levels off, but does not decrease after 48 weeks of treatment. [12] Though these clinical effects are well documented and thoroughly debated, [13–17] their impact on the quality of life and physical functioning of PWH is less described. Studies report an increased risk of

diabetes mellitus and hypertension with integrase inhibitor use, [18–20] however the extent to which these are direct effects of integrase inhibitors versus the associated weight gain remains unclear. This underscores the importance of moving beyond describing the risk of increased abdominal adiposity, [21] but also examining strategies to help mitigate it without compromising the gains observed in these novel therapeutics.

In the general aging population, regular physical activity is one of the few non-pharmacological interventions that can help reduce central adiposity, even though this population presents with aging-related reduced metabolic demands. The mechanisms by which physical activity support reducing adiposity include release of adipokines that help to balance weight gain, and stimulating in lipid hydrolysis thereby increasing the body's use of energy stores such as fat. [22] Yet, the relationship between physical activity and abdominal adiposity in people with well-controlled HIV is unclear. This lack of clarity can be attributed to a limitation in the common assessment of physical activity – specifically much of the assessment of physical activity in this population has relied on self-reported measures which have various limitations and usually do not precisely document the amount, frequency, intensity and duration of physical activity in PWH. [23,24] However an alternative exists. Accelerometry has been widely used to accurately measure physical activity for almost 20 years and the public health impact of these studies have been significant. [25–27] HIV care and treatment have entered a new era, one that emphasizes aging well with HIV and that data informing this era must also evolve. These data need to be more precise, collected and analyzed using rigorous and reproducible methods, and drawn from a heterogenous sample of PWH. To help meet this need, our aim was to describe the association between objectively-measured physical activity and abdominal adiposity (i.e., waist circumference and waist-to-hip ratio) in aging PWH throughout the United States.

METHODS

The PROSPER-HIV study is an ongoing 4-year, prospective, observational study of 707 participants from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS). [28] The overall goal of the PROSPER-HIV study is to describe the precise, longitudinal relationship between physical activity and dietary intake on symptom burden in a diverse sample of PWH in the United States. Enrollment began at four CNICS sites (i.e., Boston, Massachusetts; Birmingham, Alabama; Cleveland, Ohio; and Seattle, Washington) in spring of 2019 and concluded in summer 2022. Enrolled participants complete standardized assessments of objectively-measured physical activity, dietary intake, and physical fitness (including hip and waist circumference) approximately once a year for 3 years. Participants also complete a standard CNICS patient-reported outcome assessment, medical chart abstraction, and clinical assessment procedures. [29] The PROSPER-HIV study is approved (#00013048) by the University of Washington Institutional Review Board (IRB), the IRB of record, and the IRBs at the other three sites have sanctioned the study protocol allowing it to adhere to a single IRB policy. The PROSPER-HIV study is registered at ClinicalTrials.gov #NCT03790501.

Setting and Participants

PROSPER-HIV sites.—The PROSPER-HIV study is being conducted at four academic medical centers (University of Alabama at Birmingham 1917 Clinic, Case Western Reserve University Special Immunology Unit, Fenway Health Institute, and University of Washington Madison Clinic) that provide HIV specialty and primary care for PWH throughout their lifespan. These four sites are longstanding members of CNICS and have dedicated space and technological infrastructure for research visits. Most PROSPER-HIV procedures occur in this existing research space, with some adjustments allowed for COVID-19 related institutional policies.

PROSPER-HIV participants.—To be eligible to participate in PROSPER-HIV, interested individuals had to be (a) an active CNICS participant (i.e., they must have a CNICS consent and have completed the current patient reported outcome assessment); (b) at least 18 years of age; (c) prescribed ART as part of CNICS care; and (d) HIV Viral Load less than 200 copies/mL at time of enrollment. Participants were excluded from enrollment if they (a) did not complete the *HIV Symptom Index* in a recent assessment; (b) were pregnant, breast-feeding, or planning a pregnancy during the study period; (c) did not have telephone or Internet access to complete 24-hour diet recalls; or (d) planned to move out of the area in the next 36 months.

PROSPER-HIV timeline.—The original timeline for enrollment and baseline visits was planned for March 2019-December 2020. However, local and institutional policies limiting access to potential participants were initiated in March 2020 due to the COVID-19 pandemic and continued through December, 2021, thus necessitating an extended enrollment period. The PROSPER-HIV final participants were enrolled in July 2022.

Measures

Adiposity.—Our measures of adiposity included waist (cm) and hip circumference (cm) and waist to hip ratio. Waist circumference is an established and widely used clinical surrogate of visceral adipose tissue when gold-standard imaging techniques (i.e., computed tomography (CT) and Magnetic Resonance Imaging (MRI)) are not feasible.[48,49] We measured waist and hip circumference in duplicate and then averaged the two measures provided they were less than 2.54 cm apart. [30] If the first two measures were more than 2.54 cm apart, a third measurement was taken and the average of those computed. Waist circumference was measured at the top of the iliac crest and hip circumference using a flexible tape measure to the nearest 0.1 cm. To standardize assessment of these measures research staff collecting waist and hip measures were trained using a standardized training protocol prior to collecting these data on participants. We computed waist to hip ratio from these measurements. Excess adiposity was defined as: (1) waist circumference > 94 cm in a currently identifying male-sex participant; (2) waist circumference > 80 cm in a currently identifying female-sex participant; or (3) a waist/hip ratio > 0.9 in males or 0.85 in females. In modeling the associations between physical activity and adiposity, the outcome was waist circumference as a continuous variable.

Physical activity.—Physical activity was measured with the wGT3X-BT ActiGraph accelerometer (ActiGraph, LLC, Fort Walton Beach, FL). All participants were instructed to wear the activity monitor during waking hours for 7-to-10 consecutive days on their non-dominant hip, except for while they were in water (*i.e.*, showering or swimming). A valid wear cycle was determined if the participant recorded data for a minimum of 10 hours per day for at least 4 days including one weekend day. [31,32] Participants not meeting wear time standards were asked to re-wear the ActiGraph. Data was sampled at 30 Hz, using 60-second epochs, and the normal frequency filter. [32] Consistent with recent changes in public health guidance, [33] no minimum threshold was used to analyze bouted physical activity time. All valid wear time consisting of any physical activity was included in our analysis. At the time of analysis, 419 participants met all wear time criteria at baseline and were included in this analysis. The primary exercise endpoints were (a) time spent in moderate-to-vigorous physical activity; (b) number of steps per day; and (c) sedentary time per day. These endpoints were selected for their established clinical and public health significance[33,34] and set with the Sasaki et al. (2011) cut points which for moderate-to-vigorous physical activity was set as a minimum of 2690 counts per minute and for light activity was set if there were 1–2689 counts per minute. Actigraphy data were analyzed using the ActiLife software (ActiGraph, LLC, Fort Walton Beach, FL). [35] Sedentary behavior was defined as 10 or more minutes with 100 or fewer counts per minute. Non-wear time was defined as at least 60 consecutive minutes of zero counts.

Clinical Characteristics.—All clinical data, including the length of time on ART, medication classifications, and current and historical comorbid conditions were abstracted from the participant's electronic medical record with quality control completed according to all CNICS data quality standards. [29]

Analyses

We conducted an analysis of PROSPER-HIV participants who had complete data on age, sex, current gender, employment status, integrase inhibitor use, study site, physical activity, and hip and waist and circumference. Descriptive characteristics were reported as n (%) or median (25%, 75%), and compared by sex using chi-square tests or *t*-tests. Due to the small number of participants self-reporting race besides Black or White, these individuals were combined into one "other" category consisting of 0.24% American Indian, 0.73% Asian/Pacific Islander, and 0.73% multiracial. Linear regression was used to evaluate the relationship between the variables hypothesized to predict waist circumference, while controlling for study site. Separate models were analyzed to evaluate the independent associations of different physical activity measures (i.e., steps per day, sedentary time, MVPA) with abdominal adiposity. Investigation of model residuals did not reveal any indications of poor fit. As our focus was on factors associated with waist circumference all variables were entered simultaneously and none were removed due to non-significance. All data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) with a significance level of $p<0.05$.

RESULTS

Demographic and Clinical Characteristics.

On average participants were 58 years of age (25%,75%: 50 years, 64 years), male (77%) and Black /African American (54%). Thirty-eight percent of participants reported full time employment, 23% reported receiving disability and 16% were retired. Participants had been taking HIV antiretroviral medications a median of 14.1 years (8.9 21.5). Overall, 77% were currently taking an antiretroviral therapy regimen containing integrase inhibitors (Table 1).

Adiposity and Physical Activity Characteristics.

The median waist circumference for men was 107.5 (93.8, 121.5) cm and for women was 98.4 (89.5, 108.8) cm. The waist-to-hip ratio of men was 0.9 and for women was 1.0 and 368 (88%) participants had excess abdominal adiposity. Many participants reported comorbidities including hypertension (77%), renal disease (39%), diabetes (33%) and cardiovascular disease (22%). Participants completed a mean of 7.06 (±2.74) days of total actigraphy wear time. These data revealed that 229 (55%) of PROSPER-HIV participants met the DHHS Physical Activity Guidelines of 150 minutes of non-bouted moderate-to-vigorous physical activity or 75 minutes of vigorous physical activity per week in any duration. On average participants completed approximately 4,906 steps per day (3233, 7140), spent a median of 5.4 hours/day being sedentary and engaged in 168 minutes moderate-to-vigorous physical activity per week (72.8, 319.7; Table 1).

Relationship between physical activity, sedentary behavior, and abdominal adiposity.

After controlling for sex, employment status, study site, age, and current integrase inhibitor use, more steps per day was associated with a significantly smaller waist circumference in PROSPER-HIV participants ($F= 3.27$; $p<0.001$; $R^2= 0.095$). Specifically, each additional 1,000 steps/day was associated with a decrease of 0.77 centimeters in waist circumference (Table 2). In examining the relationship between moderate-to-vigorous physical activity and waist circumference, we found that time spent in moderate-to-vigorous physical activity was not associated with waist circumference ($F= 2.72$; $p=0.001$; $R^2= 0.08$ (Table 3)). Finally, to help understand the impact of sedentary time on waist circumference we found that controlling for sex, employment status, study site, age, and current integrase inhibitor use more sedentary time was associated with a larger waist circumference in PROSPER-HIV participants ($F= 3.24$; $p<0.001$; $R^2= 0.109$; (Table 4)).

DISCUSSION

We employed precise, rigorous, gold standard methods to examine the association between objectively-measured physical activity and abdominal adiposity (i.e., waist circumference) in a large, heterogenous, contemporary sample of aging PWH in the United States. In doing so, we observed several key findings that help to advance the field of healthy aging in PWH.

We observed that although half of PWH engage in enough physical activity to meet recommended guidelines, over 87% experience high adiposity, but steps per day is likely an effective mode of physical activity to reduce waist circumference. While a landmark

review confirmed that PWH engaged in relatively low levels of physical activity and that 50% of PWH met the recommended 150 minutes of moderate physical activity; these data were collected prior to 2016 and were mostly self-reported levels of physical activity. [24] Studies examining the relationship between self-reported recall of physical activity and objectively-measured physical activity in real world settings has demonstrated that these are often divergent data. [36,37] Yet as population health, including among PWH, has grown in importance, the need for precise, rigorous data on population risk (or protective) factors has also grown. This study provides critical insight into the association of physical activity with abdominal adiposity due to the enhanced rigor and reproducibility embedded in the standardized accelerometry data collection and analysis protocol adhered to by all PROSPER-HIV participants and investigators.

We observed relatively high levels of unbouted physical activity in PWH and also high adiposity in both male and female PWH, but particularly among women. [38–41] As these are consistently observed relationships, coupled with their negative impact on health; it is reasonable to suggest that we must elevate our investment in evidence-based clinical strategies to increase and sustain the amount, intensity and diversity of physical activity in PWH. These strategies may include walking groups, [42] supervised exercise training, [43] community group exercise programs such as Enhance®Fitness, [44] as well as better integration of physical activity assessment and exercise prescriptions into HIV and primary care visits. [45] Given the pleiotropic effects of physical activity on a wide range of aging-related outcomes including frailty, falls, cognitive function, obesity, cardiometabolic diseases, among others we are long overdue to reimagine the U.S. HIV health care system delivery to meaningfully include exercise as a key benchmark of HIV medicine.

Most importantly, we demonstrated that the number of steps per day are associated with decreased adiposity in PWH and increased sedentary time was associated with increased adiposity. While not surprising, these are among the first data to demonstrate these relationships in a large, geographically diverse sample of PWH, most of whom were on integrase inhibitors. Integrase Inhibitor initiation has been independently associated with increased body weight and subcutaneous fat mass gain, [46,47] thus strategies that can reduce weight gain when using this ART regimen are needed. In our analyses, Integrase Inhibitor use was not associated with increased waist circumference when controlling for total steps per day. Improvements in affordable accelerometry technology has made implementing daily step goals a feasible option for patient populations. Thus, clinical implications of these data include implementing physical activity prescriptions at the time of initiating ART with integrase inhibitors, and monitoring and documenting their progress during routine healthcare visits. Healthcare providers can also refer PWH to a catalog of evidence-based physical activity sites and/or interventions as they consider initiating or switching their ART regimen. However, none of these strategies have been examined in PWH initiating ART with integrase inhibitors; future research should prospectively explore these strategies and their impact on adiposity in aging PWH and on the healthcare delivery system.

Finally, we did not observe a relationship between moderate-to-vigorous physical activity and adiposity in PWH. A likely explanation for this finding is that our participants often engaged in extremely short bouts of moderate or vigorous physical activity (<10 minutes

at a time) which, while important for overall health may not be sufficient enough to meaningfully impact adiposity in this population. Additional evidence on the variation in types, intensities, and duration of physical activity in this population in real world settings are needed to understand how physical activity can impact important clinical indicators such as adiposity.

We observed and confirmed several important, novel findings which are bolstered by the PROPSER-HIV study's strengths. These include a large, heterogenous sample; objectively measured physical activity with significant accelerometry wear time; careful and standardized ascertainment of waist and hip circumference; and a representative proportion of female PWH. Despite these strengths, there are several study features that may limit to whom these findings can be generalized. All PROSPER-HIV participants are in the CNICS cohort of PWH in clinical care. Consequently, these findings should not be extrapolated to those PWH who are not in routine clinical HIV care. Also, participants were virally suppressed and our findings may not apply to those who have a detectable HIV viral load. In addition, we chose to measure adiposity using waist circumference. While waist circumference is a recommend, widely-used, validated clinical surrogate of visceral adipose tissue,[48, 49] it lacks the precision of imaging techniques (e.g., CT, MRI). Future work among aging PWH should replicate and expand upon these findings by incorporating imaging techniques if possible. Future work should also consider additional factors that may confound the relationship between physical activity and adiposity in PWH including current alcohol use and volume, co-occurring hepatic diseases, and prior use of older HIV antiretroviral medications.

In conclusion, we found that among the PROSPER-HIV participants physical activity is associated with abdominal adiposity in aging PWH. Specifically, the number of steps per day is an effective physical activity strategy to reduce burdensome adiposity in a mostly sedentary population. Future work should investigate how to effectively tailor the amount, type, duration and intensity of physical activity needed to reduce adiposity in PWH in the settings in which they live, work and play. Future work must be centered on the voices of aging PWH in order to meaningfully support them in their physical activity journey.

Acknowledgements

This study was funded by the National Institutes of Nursing Research #R01 NR018391 (PIs: Webel and Willig) and by the National Institute of Allergy and Infectious Diseases #R24 AI067039 (PI: Saag). An abstract based on this work was presented at AIDS2022 in July 2022.

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Table 1:

Participant Characteristics (n=419)

	Frequency (%)
Age[1] (years)	58.0 (50.0, 64.0)
Current Gender	
Female	95 (22.7)
Male	324 (77.3)
Sex at Birth	
Female	92 (22.0)
Male	327 (78.0)
Race	
Black	219 (53.5)
White	179 (43.8)
Other	11 (2.7)
Employment Status	
Disabled	97 (23.2)
Full time employee	157 (37.5)
Part time employee	45 (10.7)
Retired	67 (16.0)
Student or Keeping House	11 (2.6)
Unemployed or on leave	25 (6.0)
Other	17 (4.1)
Years Taking HIV Medications [1]	14.1 (8.9, 21.5)
Integrase Inhibitor Regimen	
ABC/3TC/DTG	63 (15.0)
TAF 25 mg/FTC/BIC	94 (22.4)
TAF 10 mg/FTC/COBI/EVG	57 (13.6)
Other	114 (27.2)
Clinical Characteristics	
Height (cm)	175.3 (168.9, 180.6)
Weight (kg)	85.7 (74.6, 98.2)
BMI (kg/m2)	28.1 (24.5, 32.2)
Waist Circumference (cm)	100.0 (90.0, 110.5)
Waist : Hip Ratio	1.0 (0.9, 1.0)
Excess Adiposity[2]	368 (87.8)
Physical Activity Characteristics	
Total Actigraph Wear Time (days)	7.06 (5,8)
Currently Meet Physical Activity Guidelines	229 (54.7)

Steps per Day [1]	4,905.6 (3,233.0, 7,139.8)
Sedentary Time per Day (hours) [1]	5.4 (3.5, 7.8)
Moderate-to-Vigorous Physical Activity per Week [1]	168.0 (72.8, 319.7)
Select Comorbidities	
Cardiovascular	59 (21.8)
Diabetes	90 (33.2)
Hypertension	209 (77.1)
Renal	106 (39.1)

[1]: Data presented as median and 25% and 75%

[2]: Defined as waist circumference > 35 inches or a waist/hip ratio > 0.9 in a currently identifying male-sex participant; waist circumference > 40 inches or a waist/hip ratio > 0.85 in a currently identifying female-sex participant

Table 2:

Steps Count is Associated with Reduced *Waist Circumference* in People Living with HIV

Parameter	Estimate	Std Error	*p* value	Lower CI	Upper CI
Age	0.235	0.086	<0.001	0.066	0.404
Female	6.495	2.024	0.001	2.516	10.475
Current Integrase Inhibitor Use	1.301	2.709	0.631	−4.025	6.627
Employment Status					
Disabled	2.917	3.790	0.441	−4.533	10.367
Full time employee	3.753	3.558	0.292	−3.242	10.748
Other	2.751	5.191	0.596	−7.453	12.955
Part time employee	5.695	4.128	0.169	−2.420	13.809
Retired	−2.929	4.205	0.486	−11.195	5.336
Student or Keeping House	10.981	5.985	0.067	−0.785	22.747
Unemployed or on leave	.	.	.	.	.
Site					
Case Western Reserve University	4.181	1.961	0.034	0.326723	8.036
Fenway	3.711	2.620	0.157	−1.439	8.861
University of Washington	3.115	3.026	0.304	−2.833	9.063
University of Alabama at Birmingham	.	.	.	.	.
Per 1000 Steps Per Day	−0.772	0.275	0.005	−1.312	−0.232

Table 3:

Moderate-to-Vigorous Physical Activity is Not Associated with Waist Circumference in PWH

Parameter	Estimate	Std Error	*p* value	Lower CI	Upper CI
Age	0.254	0.0871	0.0038	0.083	0.425
Female	6.694	2.041	0.001	2.683	10.705
Current Integrase Inhibitor Use	1.999	2.720	0.465	−3.359	7.336
Employment Status					
Disabled	3.352	3.820	0.381	−4.157	10.862
Full time employee	3.178	3.582	0.376	−3.863	10.218
Other	2.845	5.236	0.587	−7.447	13.138
Part time employee	5.32234	4.160	0.201	−2.855	13.500
Retired	−2.6325	4.241	0.535	−10.969	5.704
Student or Keeping House	11.1251	6.035	0.066	−0.739	22.989
Unemployed or on leave	.	.	.	.	.
Site					
Case Western Reserve University	4.267	1.979	0.032	0.377	8.157
Fenway	3.605	2.690	0.181	−1.683	8.894
University of Washington	3.111	3.070	0.312	−2.924	9.146
University of Alabama at Birmingham	.	.	.	.	.
Moderate-to-Vigorous Physical Activity Time per week	−0.005	0.004	0.271	−0.013	0.004

Table 4:

Sedentary Time is Associated with Increased *Waist Circumference* in PWH

Parameter	Estimate	Std Error	*p* value	Lower CI	Upper CI
Age	0.229	0.085	0.007	0.062	0.396
Female	7.321	2.010	0.000	3.369	11.272
Current Integrase Inhibitor Use	.	.	.	.	.
Employment Status	2.265	2.668	0.396	−2.980	7.509
Disabled	.	.	.	.	.
Full time employee	4.178	3.756	0.267	−3.205	11.560
Other	5.139	3.563	0.150	−1.865	12.143
Part time employee	3.380	5.154	0.512	−6.752	13.513
Retired	6.235	4.102	0.129	−1.828	14.298
Student or Keeping House	−1.127	4.181	0.788	−9.346	7.093
Unemployed or on leave	12.539	5.948	0.036	0.847	24.231
Site	.	.	.	.	.
Case Western Reserve University	5.228	1.966	0.008	1.364	9.093
Fenway	4.857	2.634	0.066	−0.321	10.036
University of Washington	3.442	3.005	0.253	−2.466	9.350
University of Alabama at Birmingham	.	.	.	.	.
Hours of Sedentary Time Per Day	1.082	0.286	<0.001	0.520	1.645