Antiretroviral Therapy Anchor-based Trends in Body Mass Index Following Treatment Initiation Among Military Personnel with HIV

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ABSTRACT

Introduction:

Weight gain and obesity in people living with HIV have been associated with increased risk for non-AIDS-related comorbidities, and integrase strand transfer inhibitor (INSTI)-based regimens may lead to comparatively more weight gain than other regimens. We evaluated body mass index (BMI) following antiretroviral therapy (ART) initiation among participants in the U.S. Military HIV Natural History Study (NHS).

Materials and Methods:

NHS participants with available baseline weight and height data initiating ART from 2006 to 2017 were considered for analysis. Antiretroviral therapy was categorized by anchor class to include INSTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Linear growth-curve modeling was used to predict BMI changes from ART initiation through 2 years of follow-up in participants stratified by baseline BMI (<25 vs ≥25 kg/m^2) at ART start and anchor drug class. These models were adjusted for demographic- and HIV-related characteristics.

Results:

Of 961 NHS participants started on initial ART between 2006 and 2017, 491 men who had available baseline BMI data and were virally suppressed (<200 c/mL) at 1 and 2 years of follow-up were included. Overall, the predicted BMI increased at each time point over 2 years regardless of baseline BMI. There was a trend toward less weight gain for non-INSTI regimens regardless of demographic- or HIV-related factors (−0.65 kg/m^2/yr, $P = .070$). In participants with BMI <25, all regimens were associated with BMI gains except in those with high viral load (≥100,000 copies/mL) started on PI regimens (−1.91 kg/m^2/yr, $P = .000$; $n = 13$). For those participants with BMI ≥25, only INSTI- and PI-based regimens were significantly associated with increased BMI (INSTI 0.54 kg/m^2/y, $P = .000$; PI 0.39 kg/m^2/yr, $P = .006$). Non-nucleoside reverse transcriptase inhibitors were not associated with weight gain regardless of race- or HIV-related characteristics. African Americans with BMI ≥25 were more likely to gain weight as compared to Whites (0.99 kg/m^2/yr, $P = .016$). Specific anchor drug-based predictions revealed that only INSTI use among African Americans was significantly associated with BMI gains (1.85 kg/m^2/yr, $P = .007$); NNRTI- and PI-related weight change was not significant as compared to Whites.

Conclusions:

In our cohort of young military members with HIV infection, those with BMI <25 experienced BMI gains across all ART classes. Among those with BMI ≥25, African Americans on INSTI regimens had the greatest BMI gains. Further studies are needed to determine whether NNRTI regimens should be considered in certain individuals at risk for INSTI-associated weight gain.

BACKGROUND

Obesity has reached epidemic proportions in the general population over the recent decades, and military members have not been exempt from this trend. Combined rates of overweight and obesity in active duty personnel have increased from 50.6% in 1995 to 60.8% in 2008, and obesity rates themselves have doubled from 2001 to 2008 with continued increases beyond 2010.[1,2,3] Excess weight has been linked to increased risk for musculoskeletal overuse injuries as well as cardiometabolic illnesses such as hypertension, diabetes mellitus, stroke, and heart disease.[4,5] Weight-related illness in active duty personnel leads to higher absenteeism rates and lower productivity with estimates of nearly 658,000 lost workdays and associated monetary costs over $100 million annually.[5] Additionally, military members are required to

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pass service-specific annual or biannual physical fitness tests to meet retention standards. Given the increasing rates of overweight and obesity diagnoses and the detrimental effects attributed to excess weight, this unsettling trend has become a point of concern for military leadership as relates to mission readiness.[6]

A similar trend is occurring in people living with HIV (PLWH). In contrast to the initial years of the HIV/AIDS epidemic, PLWH now are gaining weight rather than experiencing wasting.[7] Similar to HIV-negative persons, life-limiting comorbidities (e.g., diabetes mellitus and cardiovascular disease) have been associated with obesity in PLWH.[8] Additionally, excess weight acquired within the first few years following start of combination antiretroviral therapy (ART) has been associated with worse cardiometabolic health.[9,10,11] While PLWH in the military have been shown to have improved physical fitness following HIV diagnosis and treatment initiation, there are still concerns regarding excess weight acquired in this group given the trends observed in non-military PLWH and the general population at large.[12]

In previous studies, factors associated with weight gain following ART initiation include lower pretreatment weight or body mass index (BMI), lower baseline CD4 count, higher baseline HIV RNA levels, female sex, and non-White race.[13,14,15,16,17,18,19] While several studies have noted weight gain following ART initiation in general, since the first integrase strand transfer inhibitor (INSTI), raltegravir, became commercially available in 2007, associations between INSTI use and weight gain have been more frequently described. However, data have been conflicting regarding which patients are at highest risk for weight gain and which specific INSTI regimens or ART combinations pose the greatest risk.[11,15,17,18,20,21,22,23,24,25]

Given the increasing concerns for comorbidities related to weight gain and obesity in both the general population and PLWH, optimizing weight gain risk factors is imperative to combating this epidemic. Additionally, given the occupational necessity of fitness in PLWH in the military, weight gain and obesity in this population have potential effects on mission readiness. There are currently numerous effective regimens for controlling HIV. Thus, understanding whether recommended first-line regimens (e.g., INSTIs) are more likely to contribute to excess weight gain compared to alternative regimens is an important step in mitigating this undesired outcome. Therefore, we evaluated trends in BMI after ART initiation in the U.S. Military HIV Natural History Study (NHS) to determine risk factors in this population for ART-related weight gains.

METHODS

We examined data collected within the NHS, a prospective observational cohort of Department of Defense beneficiaries. All participants were ≥18 years of age and provided informed consent for this study approved by the Uniformed Services University of the Health Sciences central Institutional Review Board. Participants are evaluated every 6-12 months at select Military Treatment Facilities throughout the United States.

This retrospective analysis included male active duty NHS participants who were treatment-naïve and initiated ART between January 1, 2006 and December 31, 2017. Participants were required to have baseline weight and height data recorded within 6 months of ART initiation as well as weight measurements from clinical encounters approximately 12 and 24 months after ART initiation.

ART anchor drug classes included INSTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). Integrase strand transfer inhibitor–anchored regimens included dolutegravir, elvitegravir, or raltegravir; NNRTI-anchored regimens included efavirenz or rilpivirine; PI-anchored regimens included lopinavir, atazanavir, or darunavir boosted with either ritonavir or cobicistat.

Exclusion criteria included any of the following non-ART factors that could have impacted changes in weight during the study period: malignancy other than squamous cell or basal cell carcinomas of the skin, newly diagnosed or unstable thyroid disorder, supplemental testosterone use, use of appetite stimulants (e.g., megestrol and dronabinol), history of diabetes mellitus (diagnosed before or during ART therapy) or use of antihyperglycemic therapy, chronic viral hepatitis, congestive heart failure with diuretic use, hemodialysis, pregnancy, diagnosis of CDC-defined opportunistic infection during the study period, and >30 days of systemic corticosteroid use. Additional exclusion criteria included lack of viral suppression defined as viral load (VL) > 200 copies/mL at 1- or 2-year follow-up, and use of multiple anchor drugs or changes in anchor drug during follow-up.

Baseline weight and height measurements were obtained within 180 days of ART initiation and follow-up weights were obtained at clinical visit dates closest to 12 and 24 months following start of therapy. Body mass indexes (kg/m^2) were calculated based on serial weights and baseline height. Given a paucity of participants in this cohort who were underweight or obese at baseline (defined as BMI <18.5 kg/m^2, $n = 1$, or ≥30 kg/m^2, $n = 87$, respectively), baseline BMI categories were dichotomized at the point between normal and overweight (<25 and ≥25 kg/m^2).

Linear growth-curve modeling, a statistical method allowing for the estimation of "between-person differences in within-person change" over time, was used to predict BMI changes from ART initiation through 2 years of follow-up in participants stratified by baseline BMI (<25 vs ≥25 kg/m^2) at ART start and anchor drug class.[26] These models were adjusted for demographic- and HIV-related characteristics (race/ethnicity, baseline CD4 count dichotomized at < or ≥500 c/μL, baseline VL dichotomized at < or ≥100,000 copies/mL). Calendar year of ART initiation

was also analyzed, and unadjusted effects between time and each anchor drug were conducted. All statistical regressions were conducted using STATA 14.

RESULTS

Of the 961 treatment-naïve NHS participants who initiated ART during the study period, 491 met all inclusion criteria and were selected for analysis. Of those participants excluded from the study, 345 did not have available baseline weight/height data. The remaining were excluded based on the aforementioned predefined exclusion criteria. Compared to the excluded patients, included patients were younger (mean age 29.71 years vs. 32.35 years), male (100% vs 92.5%), had higher CD4 counts (≥500 c/μL, 32.4% vs 19.8%), had a higher proportion treated with dolutegravir (21.0% vs 8.8%), and a lower proportion started on efavirenz (45.4% vs 58.5%; all $P < .05$).

The average age at ART initiation was 29.71 ± 7.71 years with 183 (37.1%) participants with baseline BMI <25 kg/m^2 and 308 (62.9%) ≥25 kg/m^2 (Table I). Regarding race, 157 (32.0%) of the participants were White, 215 (43.8%) African American, and 119 (24.2%) non-White, non-African American. CD4 counts before ART initiation were <500 cells/μL and ≥500 cells/μL in 331 (67.3%) and 160 (32.7%) participants, respectively. Baseline VLs were <100,000 copies/mL in 383 (77.8%) and ≥100,000 copies/mL in 108 (22.2%) participants. Integrase strand transfer inhibitors were started on 197 (40.1%), NNRTIs on 249 (50.6%), and PIs on 45 (9.3%) participants. The mean time from HIV diagnosis to ART initiation was 1.52 ± 2.84 years.

Predicted BMIs increased over 2 years regardless of baseline BMI (Table II). In participants with BMI <25, all regimens were associated with BMI gains except for those with high VL (≥100,000 copies/mL) started on PI regimens (−1.91 kg/m^2/yr, $P = .000$; $n = 13$). There were no differences in BMI gains based on demographic- and HIV-related characteristics in those with baseline BMI <25. Additionally, there were no differences between INSTI- versus non-INSTI-anchored regimens.

For participants with BMI ≥25, there was a trend toward less weight gain for non-INSTI regimens regardless of demographic- or HIV-related factors (−0.65 kg/m^2/yr, $P = .070$). Only INSTI- and PI-anchored regimens were significantly associated with increasing BMI over the study period (INSTI 0.54 kg/m^2/yr, $P = .000$; PI 0.39 kg/m^2/yr, $P = .006$). Non-nucleoside reverse transcriptase inhibitors were not associated with weight gain regardless of race- or HIV-related characteristics. African Americans with BMI ≥25 were more likely to gain weight as compared to Whites (0.99 kg/m^2/yr, $P = 0.016$). Specific anchor drug-based predictions revealed that only INSTI use among African Americans was significantly associated with BMI gains (1.85 kg/m^2/yr, $P = 0.007$); NNRTI- and PI-related weight change was not significant as compared to Whites. There was a trend toward larger BMI gains in non-White,

TABLE I. Cohort Baseline Characteristics; $n = 491$

Variables	Frequency (%) or mean ± SD
Baseline/start of ART	
Age (years)	29.71 ± 7.71
BMI (all regimens, kg/m^2)	26.52 ± 3.94
BMI (all regimens, dichotomized)	
<25	183 (37.1%)
≥25	308 (62.9%)
Anchors (all races)	
INSTI	197 (40.1%)
NNRTI	249 (50.6%)
PI	45 (9.3%)
Race/ethnicity	
White	157 (32.0%)
INSTI (% of Whites)	67 (42.7%)
RAL	18
EVG	20
DTG	29
NNRTI (% of Whites)	78 (49.7%)
EFV	73
RVP	5
PI (% of Whites)	12 (7.6%)
DRV	3
ATV	8
LPV	1
African American	215 (43.8%)
INSTI (% of African Americans)	83 (38.6%)
RAL	12
EVG	20
DTG	51
NNRTI (% of African Americans)	118 (54.9%)
EFV	109
RVP	9
PI (% of African Americans)	14 (6.5%)
DRV	3
ATV	11
LPV	0
Other	119 (24.2%)
INSTI	47 (39.5%)
RAL	8
EVG	16
DTG	23
NNRTI	53 (44.5%)
EFV	41
RVP	12
PI	19 (16%)
DRV	5
ATV	12
LPV	2
Baseline CD4 count (cells/μL)	
<500	331 (67.3%)
≥500	160 (32.7%)
Baseline viral load (c/mL)	
<100,000	383 (77.8%)
≥100,000	108 (22.2%)
Time from HIV diagnosis to start of ART (years)	1.52 ± 2.84
One year after ART initiation	
BMI (all regimens)	26.79 ± 3.89
Two years after ART initiation	
BMI (all regimens)	27.26 ± 4.14

Abbreviations: ATV, atazanavir; ART, antiretroviral therapy; BMI, body mass index; c/mL, copies per milliliter; cells/uL, cells per microliter; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; NNRTI, non-nuceloside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir; RVP, rilpivirine; SD, standard deviation.

TABLE II. Linear Growth-Curve Model Predictions for Changes in BMI (kg/m^2) per Year on ART

	All regimens		INSTI		NNRTI		PI	
Independent variables	Predicted change	*P* value	Predicted change	*P* value	Predicted change	*P* value	Predicted change	*P* value
Baseline BMI <25								
Time	0.51	.000	0.54	.000	0.48	.000	0.54	.001
Age	0.03	.067	0.06	.052	0.02	.369	−0.14	.100
Race/ethnicity (ref. White)								
African American	0.27	.298	0.45	.244	0.16	.665	−0.35	.571
Other	0.21	.505	−0.12	.788	0.23	.608	0.60	.262
CD4 (ref. <500 cells/μL)								
CD4 ≥ 500	−0.31	.205	−0.25	.443	−0.43	.274	0.88	.191
Viral load (ref. <100,000 c/mL)								
Viral load ≥100,000	−0.33	.187	−0.3	.392	0.16	.659	−1.91	.000
Time from HIV diagnosis to ART start	−0.02	.776	−0.03	.770	0.01	.905	0.02	.386
Anchor class (ref. INSTI)								
NNRTI or PI	−0.15	.515	-	-	-	-	-	-
Baseline BMI ≥25								
Time	0.29	.000	0.54	.000	0.10	.211	0.39	.006
Age	0.10	.000	0.12	.004	0.09	.008	0.07	.293
Race/ethnicity (ref. White)								
African American	0.99	.016	1.85	.007	0.50	.358	1.53	.186
Other	0.52	.249	0.89	.228	0.36	.572	1.95	.086
CD4 (ref. <500 cells/μL)								
CD4 ≥ 500	0.64	.079	0.98	.083	0.25	.627	0.00	.999
Viral load (ref. <100,000 c/mL)								
Viral load ≥100,000	−0.43	.297	−0.31	.702	−0.69	.202	1.50	.119
Time from HIV diagnosis to ART start	0.09	.139	0.34	.005	0.00	.908	0.44	.037
Anchor class (ref. INSTI)								
NNRTI or PI	−0.65	.070	-	-	-	-	-	-

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cells/uL, cells per microliter; c/mL, copies per milliliter; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

non-African American participants on PIs (1.95 kg/m^2/yr, $P = .086$, $n = 32$).

While increasing age was associated with BMI increases in those on INSTIs and NNRTIs whose baseline BMI $\geq$25, the predicted changes were small (0.12 kg/m^2/yr, 0.09 kg/m^2/yr for INSTI and NNRTI, respectively). Increasing age was not associated with BMI increases in those on PIs. Predicted BMI gains for INSTI- and PI-anchored regimens were also associated with increased time from HIV diagnosis to ART initiation (INSTI 0.34 kg/m^2/yr, $P = .005$; PI 0.44 kg/m^2/yr, $P = .037$). Additionally, there was no association between calendar year of ART initiation and anchor drug-based weight gain ($P > .05$ for all anchor drug classes) regardless of baseline BMI.

There were no differences between particular INSTI anchor drugs (dolutegravir, $n = 103$, vs elvitegravir, $n = 56$, vs raltegravir, $n = 38$) in BMI changes, though this finding may be because of small sample size. Individual NRTI backbone regimen analysis was not performed in this study, though given possible associations with weight gain and tenofovir alafenamide (TAF) analysis excluding participants taking TAF was performed.[17,25] Exclusion of participants on TAF-containing regimens did not yield significant changes to the findings already mentioned above (TAF combined with INSTIs, $n = 10$, with NNRTI, $n = 7$, with PI, $n = 7$).

DISCUSSION

Our study supports the growing evidence that weight gain commonly occurs following ART initiation, particularly with INSTI-based regimens. Previous studies have noted risk factors for weight gain following ART initiation including lower baseline BMI, African American race, female sex, lower CD4 count, and higher pretreatment HIV VL.[7,13,14,16,17,18,19] Our study supports previous literature showing greater absolute weight gain in those with lower baseline BMIs (0.51 vs 0.29 kg/m^2/yr for baseline BMI <25 and $\geq$25, respectively). African Americans also had greater BMI gains than Whites in our study, though only if their baseline BMI was $\geq$25. In contrast to other reports, there were no significant HIV-related characteristics (e.g., baseline CD4 or VL) that were associated with weight gain following ART initiation in our study. However, this may be because of the small number of participants with very low baseline CD4 counts (only 23 participants with CD4 <200 cells/mL) and/or high VLs in our population.

Weight gain following ART initiation is thought potentially to be because of a "return to health" phenomenon in patients with indicators of more advanced disease, namely lower BMI and CD4 counts and higher HIV VLs.[19,22,25] However, as diagnosis and treatment have been progressively occurring earlier in the disease process, rates of overweight and obesity have been rising. A previous study in our cohort showed that 28% of NHS participants were overweight or obese at time of diagnosis from 1985 to 1990 which increased to 53% in 1996-2004.[7] Additionally, PLWH diagnosed in 1985-1990 gained 0.51 kg/m^2 in BMI compared to 0.93 kg/m^2 in 1996-2004 over the follow-up period. A pooled analysis comprising >5,000 treatment-naïve participants from 2003 to 2019 also demonstrated higher baseline weights at time of ART initiation.[19] These findings support that in more recent years, there has been less advanced HIV disease at time of diagnosis and more physiometabolic similarities reflecting the general population at large.[7,14]

Specific ART regimens have been associated with weight gain, though data conflict on which particular classes or drugs within each class play a role. In the prior NHS study noted above, NNRTIs and PIs were not associated with weight gain.[7] A Swiss cohort noted no weight gain difference between NNRTIs and PIs as well.[27] However, in several other studies, PIs were associated with greater weight gains than NNRTIs.[9,16,28] Studies including INSTIs have shown conflicting results. The STARTMRK trial noted lower mean fat gains with raltegravir as compared to efavirenz.[29] However, both the ACTG 5257 and PROGRESS studies noted increased fat-related body measurements in raltegravir-treated participants as compared to several PI-anchored regimens.[30,31] Multivariate analysis of 1118 patients in the SCOLTA cohort revealed no significant weight gain differences between INSTIs and darunavir or rilpivirine.[15]

There exists recently emerging evidence that INSTIs in particular may contribute to weight gain. The aforementioned ACTG 5257 study depicted increased rates of being overweight and obesity in raltegravir-treated participants.[18] In a retrospective analysis, virally suppressed patients switching from efavirenz-based ART to INSTI-anchored regimens gained significantly more weight particularly if switched to dolutegravir.[32] A separate small study ($n = 14$) observed that INSTI use was the most significant risk factor for development of obesity, noting a remarkable >7-fold increase in risk of obesity and more rapid onset from time of ART initiation.[14]

Specific INSTI drug-related weight changes have been noted as well though inconsistently. In a French cohort of 2260 patients, weight gain among patients taking dolutegravir was documented as the reason for discontinuation in up to 7% with BMI increases reaching significance in women.[21] In a Veteran's Affairs cohort, elvitegravir/cobicistat was associated with the greatest BMI changes overall, though in subgroup analysis, women had greater gains on dolutegravir and raltegravir, and African Americans and Hispanics had greater gains on dolutegravir.[23] Another analysis of 22,972 patients noted less weight gain associated with elvitegravir/cobicistat than raltegravir and dolutegravir.[20] In participants switching from non-INSTI-anchored regimens, dolutegravir appeared to be associated with greater weight increases with gains greatest in women, those older than 60 years, and those with baseline obesity.[24] Recently, a South African study showed that weight gain was significantly higher in those treated with dolutegravir versus an efavirenz-anchored regimen. Dolutegravir resulted in significantly more weight gain when paired with TAF as compared to tenofovir disoproxil, with greatest gains in women.[25] Finally, in a pooled analysis evaluating eight randomized controlled trials comprising

treatment-naive participants, weight gain was noted to be most prominent in females as compared to males and in African Americans compared to non-African Americans. Weight gain was noted in NNRTI-, PI-, and INSTI-anchored regimens, but INSTIs were associated with the greatest weight gains. Interestingly, when compared to efavirenz, bictegravir, dolutegravir, elvitegravir/cobicistat, and rilpivirine were associated with increased risk of ≥10% weight gain.[19] As in our study, these data suggest that INSTIs may contribute to excess weight gain as compared with other ART regimens, particularly NNRTIs (and in particular, efavirenz), especially in at-risk populations.

Given the increasing concerns regarding the effect of obesity on military readiness and physical fitness requirements for retention, remaining cognizant of factors that may potentiate obesity risk is imperative to optimizing service member health. Historically, military members with HIV have had limited opportunities for overseas or operational duty assignments. In recent years, as HIV is being treated as a chronic yet controllable disease because of the tolerability and efficacy of modern ART regimens, military members with HIV have increasingly available operational assignments. For example, since 2012, the Secretary of the Navy Instruction 5300.30E has allowed the possibility for shipboard duty and aircraft carrier assignments on a case-by-case basis for service members with HIV. Additionally, Air Force Instruction 44-178 now allows overseas assignments with a waiver. With an average of 350 new HIV diagnoses per year, HIV-infected active duty service members are an important resource to fill mission-related operational roles.[33] Given these increasing roles in military operations, continued control of HIV and mitigation of adverse effects related to therapy such as weight gain and obesity are critical to military readiness.[34] Thus, our data support caution when prescribing INSTIs in at-risk military members with HIV, particularly overweight African American men.

Study limitations included missing weight/BMI data that, if available, may have enhanced the ability to perform subgroup analyses (such as individual INSTI anchor drug analysis) by increasing our sample size. As the NHS predominantly consists of men, our study excluded women; thus, the results are unable to be extrapolated to this population. However, previous studies suggest that inclusion of women may have resulted in higher rates of INSTI-related weight gain. While early weight gain following ART initiation has been associated with worse cardiometabolic outcomes, the fairly short follow-up of 2 years limits conclusions on long-term effects of potential ART or INSTI-related BMI increases and does not allow determination of potentially later-onset weight gain related to therapy. Dichotomizing categories for BMI, CD4 count, and HIV VL may limit further definition of at-risk groups such as those with CD4 <100 cells/μL or BMI <18 or >30. Finally, we did not evaluate NRTI backbone regimens that may have weight-altering effects as well.[17,25]

CONCLUSION

In our cohort of young military members with HIV infection, those with BMI <25 experienced BMI gains across all ART classes following treatment initiation. Among those with BMI ≥25, African Americans started on INSTI regimens had the greatest BMI gains. Further studies are needed to determine whether NNRTI regimens should be considered in certain individuals at risk for INSTI-associated weight gain with potential to impact active duty retention and military readiness.

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CONFLICTS OF INTEREST

None.

REFERENCES

1. Reyes-Guzman CM, Bray RM, Forman-Hoffman VL, Williams J: Overweight and obesity trends among active duty military personnel: a 13-year perspective. Am J Prev Med. 2015; 48(2): 145-53.
2. Rush T, LeardMann CA, Crum-Cianflone NF: Obesity and associated adverse health outcomes among US military members and veterans: findings from the millennium cohort study. Obesity (Silver Spring). 2016; 24(7): 1582-9.
3. Clark LL, Taubman SB: Update: diagnoses of overweight and obesity, active component, U.S. Armed Forces, 2011-2015. MSMR. 2016; 23(9): 9-13.

4. Hruby A, Bulathsinhala L, McKinnon CJ, et al: BMI and lower extremity injury in U.S. Army Soldiers, 2001-2011. Am J Prev Med. 2016; 50(6): e163-e171.
5. Dall TM, Zhang Y, Chen YJ, et al: Cost associated with being overweight and with obesity, high alcohol consumption, and tobacco use within the military health system's TRICARE prime-enrolled population. Am J Health Promot. 2007; 22(2): 120-39.
6. Maxey H, Bishop-Josef S, Goodman B: Unhealthy and unprepared. Mission, Readiness Council for a Strong America, October 2018.
7. Crum-Cianflone N, Roediger MP, Eberly L, et al: Increasing rates of obesity among HIV-infected persons during the HIV epidemic. PLoS One. 2010; 5(4): e10106.
8. Achhra AC, Sabin C, Ryom L, et al: Body mass index and the risk of serious non-AIDS events and all-cause mortality in treated HIV-positive individuals: D:A:D cohort analysis. J Acquir Immune Defic Syndr. 2018; 78(5): 579-88.
9. Achhra AC, Mocroft A, Reiss P, et al: Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardio vascular disease and diabetes: the D:A:D study. HIV Med. 2016; 17(4): 255-68.
10. Herrin M, Tate JP, Akgun KM, et al: Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals. J Acquir Immune Defic Syndr. 2016; 73(2): 228-36.
11. Kerchberger AM, Sheth AN, Angert CD, et al: Integrase strand transfer inhibitors are associated with weight gain in women. Poster presented at Conference on Retroviruses and Opportunistic Infections; March, 2019; Seattle, WA.
12. De A, Xu X, White J, Sunil TS, Okulicz JF: Physical fitness characteristics of active duty US Air Force members with HIV infection. Medicine (Baltimore). 2016; 95(44): e5227.
13. Koethe JR, Jenkins CA, Lau B, et al: Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. AIDS Res Hum Retroviruses. 2016; 32(1): 50-8.
14. Bakal DR, Coelho LE, Luz PM, et al: Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. J Antimicrob Chemother. 2018; 73(8): 2177-85.
15. Taramasso L, Ricci E, Menzaghi B, et al: Weight gain: a possible side effect of all antiretrovirals. Open Forum Infect Dis. 2017; 4(4): ofx239.
16. Lakey W, Yang L-Y, Yancy W, Chow S-C, Hicks C: Short communication: from wasting to obesity: initial antiretroviral therapy and weight gain in HIV-infected persons. AIDS Res Hum Retroviruses. 2013; 29(3): 435-40.
17. Hill A, Waters L, Pozniak A: Are new antiretroviral treatments increasing the risks of clinical obesity?. J Virus Erad. 2019; 5(1): 41-3.
18. Bhagwat P, Ofotokun I, McComsey GA, et al: Predictors of severe weight/body mass index gain following antiretroviral initiation. Poster presented at Conference on Retroviruses and Opportunistic Infections; February, 2017; Seattle, WA.
19. Sax PE, Erlandson KM, Lake JE, et al: Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020; 71(6): 1379-1389.
20. Bourgi K, Jenkins C, Rebeiro PF, et al: Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc. 2020; 23(4): e25484.
21. Menard A, Meddeb L, Tissot-Dupont H, et al: Dolutegravir and weight gain: an unexpected bothering side effect?. AIDS. 2017; 31(10): 1499-500.
22. Bourgi K, Rebeiro PF, Turner M, et al: Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis. 2020; 70(7): 1267-1274..
23. Bedimo R, Li X, Adams-Huet B, et al: Differential BMI changes following PI- and INSTI-based ART initiation by sex and race. Poster presented at Conference on Retroviruses and Opportunistic Infections; March, 2019; Seattle, WA.
24. Lake JE, Wu K, Bares SH, et al: Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy. Clin Inf Dis. 2020; ciaa177. published online ahead of print, 2020 Feb 26.
25. Venter WDF, Moorhouse M, Sokhela S, et al: Dolutegravir plus two different prodrugs of Tenofovir to treat HIV. N Engl J Med. 2019; 381(9): 803-15.
26. Curran PJ, Obeidat K, Losardo D: Twelve frequently asked questions about growth curve modeling. J Cogn Dev. 2010; 11(2): 121-36.
27. Hasse B, Iff M, Ledergerber B, et al: Obesity trends and body mass index changes after starting antiretroviral treatment: the Swiss HIV Cohort Study. Open Forum Infect Dis. 2014; 1(2): ofu040.
28. Tate T, Willig AL, Willig JH, et al: HIV infection and obesity: where did all the wasting go?. Antivir Ther. 2012; 17(7): 1281-9.
29. Rockstroh JK, Lennox JL, Dejesus E, et al: Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. Clin Infect Dis. 2011; 53(8): 807-16.
30. Reynes J, Trinh R, Pulido F, et al: Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study. AIDS Res Hum Retroviruses. 2013; 29(2): 256-65.
31. Ofotokun I, Na LH, Landovitz RJ, et al: Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. Clin Infect Dis. 2015; 60(12): 1842-51.
32. Norwood J, Turner M, Bofill C, et al: Brief report: weight gain in persons with HIV switched from Efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr. 2017; 76(5): 527-31.
33. Okulicz JF, Beckett CG, Blaylock JM, et al: Review of the U.S. military's human immunodeficiency virus program: a legacy of progress and a future of promise. MSMR. 2017; 24(9): 2-7.
34. Stahlman S, Hakre S, Scott PT, et al: Antiretroviral therapy and viral suppression among active duty service members with incident HIV infection—United States, January 2012-June 2018. MMWR Morb Mortal Wkly Rep. 2020; 69(13): 366-70.