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Weight Gain among Treatment-naïve Persons with HIV Receiving Dolutegravir in Kenya

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Abstract

Background—Several recent studies have linked integrase strand transfer inhibitors (INSTI) with increased weight gain.

Setting—The effects of sex on weight gain with dolutegravir (DTG) based antiretroviral therapy (ART) among treatment-naïve participants in a lower income, sub-Saharan population with high rates of pre-ART underweight and tuberculosis (TB) co-infection are unknown.

Methods—Our analysis included treatment-naïve participants in Kenya, and starting their first treatment regimen between January 1, 2015, and September 30, 2018. Participants were grouped into 2 cohorts based on initial treatment regimen (DTG vs. non-nucleoside reverse transcriptase inhibitors (NNRTI)). We modelled weight changes over time using a multivariable non-linear mixed effect model, with participant as a random effect. Logistic regression models were constructed to evaluate the association between different variables with extreme increase in body mass index (≥10% increase).

Results—17,044 participants met our inclusion criteria. 62% of participants were females, 6% were receiving active tuberculosis (TB) therapy and 97% were on NNRTI-based regimens. Participants starting DTG-based regimens were more likely to gain weight when compared to participants starting NNRTI-based regimens. Females starting DTG-based regimens experienced the highest weight gain compared to other participants (mean gain of 6.1 kgs at 18-months). Females receiving DTG-based regimens, along with participants with lower CD4 cell counts,

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underweight at baseline and those receiving active TB therapy were also at higher risk for extreme BMI increase.

Conclusion—Our study in a lower income sub-Saharan African population confirms higher weight gain with DTG-based regimens compared to traditional ART for treatment-naïve patients.

Keywords

Weight Gain; Dolutegravir; Sub-saharan Africa

BACKGROUND

The advent of highly effective antiretroviral therapy (ART) has led to dramatically improved survival among persons with HIV (PWH) (1). The decrease in HIV disease morbidity and mortality has been associated with parallel increases in the rate of non-communicable diseases in this population, including metabolic disorders (2). In PWH, the traditional risk factors of smoking, rising obesity and genetic predisposition intersect with HIV-specific risk factors including metabolic perturbations related to ART (3). Initiation of ART among treatment naïve PWH is often associated with an initial period of weight gain, especially among patients with a low baseline body mass index (BMI) and those with profound depletion of CD4 cells (4).

Currently integrase strand transfer inhibitors (INSTI) comprise an increasingly used class of ART due to its tolerability and high efficacy (5, 6). Recent large-scale rollout of dolutegravir (DTG) has been expanded to low- and middle-income countries, in hopes that the drug's clinical and programmatic advantages will help them advance toward the UNAIDS 90–90-90 targets (7). Kenya is one of 11 countries in sub-Saharan Africa that have introduced DTG into their national HIV treatment guidelines.

Several recent studies have evaluated the association between weight gain and the use of INSTI among treatment-naïve patients, especially women (8–10). However, the population of PWH in Kenya is distinctively different compared to North America and South Africa where there are high rates of obesity in the general population (11). PWH starting ART in Kenya have significantly more advanced HIV disease, characterized by lower CD4 counts (12) and lower baseline body mass index (BMI) (13) at treatment initiation compared to those starting treatment in North America or South Africa. Moreover, unlike the case in North America, the majority of PWH are women (12) and there is a significantly higher prevalence of HIV/TB (14) co-infection. Decreased appetite is more common among patients with HIV/TB coinfection compared to TB mono-infection (15) and treatment for tuberculosis itself is associated with significant weight gain (12, 13, 16).

In our study, we aimed to assess the impact of starting DTG-based ART regimens on weight gain in a study population from a lower middle-income east African country with high prevalence of HIV, HIV/TB co-infection, and food insecurity (17).

METHODS

We conducted our analysis using a longitudinal cohort of PWH in western Kenya enrolled in the Academic Model Providing Access to Healthcare (AMPATH) care and treatment program. AMPATH is the flagship for the East Africa International epidemiology Databases to Evaluate AIDS (EA-IeDEA). Clinical and demographic data were collected at baseline and follow-up visits using standardized instruments, which were either transcribed into an electronic medical record (EMR) system by trained data clerks or recorded directly in the EMR. These data are pooled from multiple facilities, harmonized, and undergo quality control procedures for accuracy and completeness. This analysis was approved, as part of East Africa IeDEA, by the Indiana University Institutional Review Board (IRB) and the Moi University Research and Ethics Committee (IREC). These regulatory bodies did not require written informed consent for the use of these de-identified, routinely collected patient-level data of public health significance.

For this analysis, we identified adult treatment-naïve participants who started their first treatment regimen between January 1, 2016, and September 30, 2018. Data were available until February 6, 2020. Participants were considered treatment-naïve if there was no prior recorded ART exposure. We included participants whose first recorded regimen on the reported ART start date or within six months following was a non-nucleoside reverse transcriptase inhibitor (NNRTI-) based (Efavirenz or Nevirapine) regimen with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) drugs or a DTG-based regimen with 2 NRTI drugs.

Weights of females who were pregnant at any time during the study period were censored at the estimated date of conception. Weights of participants were censored at the time of switch from NNRTI to dolutegravir or at first virologic failure. Virologic failure was defined as a plasma HIV-1 RNA >1000 copies/mL after having reached viral suppression (viral load < 400 copies/mL).

Baseline height was the first recorded height for each participant at or after age 18. Baseline weight was the most recently recorded weight in the six months prior to or on ART start date. Baseline BMI was calculated using baseline weight (in kg) divided by baseline height squared (m2). Participants with baseline BMI < 18.5 kg/m2 were considered underweight, while participants were considered to have normal BMI if BMI ≥ 18.5 kg/m2 and < 25 kg/m2. Participants were considered overweight or obese if they have a BMI of 25.0 – 29.9 kg/m2 or BMI ≥ 30 kg/m2, respectively. Baseline CD4 count was the value closest to ART initiation within a window of −180 days to +7 days. Additionally, participants were evaluated for active tuberculosis infection, identified as receiving TB therapy within a window of 60 days prior to and up to 30 days following ART start date.

Participants were grouped based on initial treatment regimen (DTG vs. NNRTI). Demographic and clinical characteristics for each group were summarized using median (Interquartile range [IQR]) or percent with frequency, as appropriate. Wilcoxon rank sum tests were used to test for group differences in the distributions of continuous variables; Pearson chi-square tests assessed differences in group size in categorical variables.

The primary aim of this analysis was to assess the relationship between ART regimen and weight over time among ART-naïve participants. We modelled weight at ART start date and later using a multivariable non-linear mixed-effect model, with participant as a random effect. Weight increase was modeled as an inverted exponential function to allow for an initial increase which then leveled off over time. We entered treatment group (DTG vs. NNRTI) and sex at birth into three parts of the model: the intercept (baseline weight), the asymptote (ending weight) and the slope (rate of weight change) and included the interaction of treatment group and sex in the asymptote which allowed us to see group differences for males and females in mean weight at 18 months. As an extension of this model, we further included a term for active TB therapy in each part and the interaction of treatment group and active TB therapy in the asymptote.

In secondary analyses, we aimed to explore the association of specific variables, including initial ART regimen, with time to extreme BMI increase, defined as a 10% or more increase in BMI as compared to baseline BMI (BMI at ART start). Patients were included in the extreme BMI increase analysis if they had both baseline and follow-up BMI, thereby leading to fewer participants in this secondary analysis. Cox proportional hazards models were used to model time to extreme BMI increase. Time to event for participants who did not experience a 10% increase was censored at their last visit date. The Cox model allowed us to estimate hazard ratios (measures of the risks) of extreme BMI increase with sex, ART regimen and with age category (<29 years, 30–45 years, >45 years), CD4 count category (<200 cells/mm3, 200 – 350 cells/mm3, >350 cells/mm3), BMI category (underweight, normal, overweight, obese), and active TB therapy at ART start. The interaction of treatment group and sex was also included. Since we had substantial missing data for baseline CD4 count (66% missing), we fit this model with and without that variable. Results were similar; so, we only present the analysis from the model which included CD4 count.

RESULTS

A total of 17,044 participants met our inclusion criteria. Table 1 highlights baseline clinical and demographic characteristics for all participants categorized by treatment regimen. Most of our cohort were female (62%), had normal BMI (54%) and had CD4 counts ≥ 200 cells/mm3 (64%) at ART start. Median age at time of ART initiation was 36.8 years and median baseline weight was 58.0 kg. A small number of participants (6%) were receiving active TB therapy at the start of ART. We had significantly more participants initiating NNRTI-based (97%) compared to DTG-based regimens (3%).

Participants initiating DTG-based regimens tended to be older at the time of ART start, were more likely to be males and a greater percentage were underweight. Median baseline weight and CD4 count were not different between groups. Additionally, both groups had similar prevalence of baseline CD4 count < 200 cells/mm3 and active TB therapy. Baseline characteristics of all participants and participants starting DTG-based regimens categorized by sex are shown in Supplemental Table 1 and Supplemental Table 2, respectively.

Model estimated mean changes in weight over time are highlighted in Figures 1 and 2. Males starting NNRTI-based regimens gained 2.0, 2.6, and 2.8 kgs at 6, 12, and 18 months,

respectively. In contrast, females starting NNRTI-based regimens gained 1.3, 2.1 and 2.6 kgs during the same period. Males starting DTG-based regimens gained 3.5, 4.0, and 4.1 kgs gained at 6, 12, and 18 months, respectively. Females starting DTG gained at 6 months (3.4 kgs), 12 months (5.2 kgs), and 18 months (6.1 kgs). Comparison of mean weights at 18 months revealed that NNRTI men gained significantly more weight than NNRTI women (2.8 kgs vs 2.6 kgs, p-value = 0.0006), DTG females gained significantly more weight than NNRTI females (6.1 kgs vs 2.6 kgs, p=<.0001) and DTG males gained significantly more weight than NNRTI males (4.1 kgs v 2.8 kgs, p=0.0129). Weight gain between DTG males and DTG females was not significantly different (4.1 kgs vs 6.1 kgs, p-value = 0.5704).

Patients coinfected with TB at the time of ART start had a significantly lower baseline weight compared to those without evidence of TB coinfection (females, age 29–45, starting NNRTI: 51.6 kg vs. 59.1 kg, p-value < 0.001). Additionally, participants with TB-coinfection gained significantly more weight than those without presumptive TB co-infection (females, age 29–45, starting NNRTI: 9.3 kg vs. 3.5 kg, p-value <0.001). There was no significant interaction between active TB treatment and antiretroviral drug group. Differences in weight gain by TB-coinfection status are shown in Figure 3.

Figure 4 is a forest plot highlighting the risk (adjusted hazard ratios) of extreme weight gain (≥10% increase in BMI from baseline). This analysis included 13,454 participants from the NNRTI group and 426 participants from the DTG group.

In this model, the interaction between ART-regimen and sex was not statistically significant (p= 0.060) but was included to allow estimation of the hazard ratio for the DTG group relative to the NNRTI group for each sex. Compared to females on NNRTI-based regimens, female participants receiving DTG-based regimens experienced extreme BMI increase at twice the rate (adjusted Hazard Ratio [aHR]: 2.1 (95% Confidence Interval [CI]: 1.5 – 3.0). The hazard ratios of extreme BMI increase did not vary by age category at ART initiation. Additionally, our results highlighted that participants who were underweight at baseline and participants with CD4 count < 200 cells/mm3 experienced extreme BMI increase at significantly higher rates than those with normal BMI at baseline or with CD4 counts >350 cells/mm3 (p-values <0.001 in all cases). Meanwhile, participants who were overweight or obese at baseline experienced extreme BMI increase at significantly lower rates than those with normal BMI. Those who were underweight had 2.2 times greater rate of extreme BMI increase than those with normal weight. Lastly, we noted that participants actively receiving TB therapy had 1.6 times the hazard rate of extreme BMI increase.

DISCUSSION

In our study, we demonstrated that most treatment-naïve PWH in the Kenyan AMPATH cohort experienced some weight gain after starting ART, with participants starting DTG-based regimens gaining on average more weight than those starting NNRTI-based regimens. It appeared that females starting DTG gained on average the most weight, compared to the least amount of weight gain experienced by females starting NNRTI-based regimens. In our analyses of extreme weight gain, several factors were associated with increased risk

of extreme weight gain, including sex, low CD4 count, and weight at baseline, along with receipt of active TB treatment at the start of therapy.

Weight gain after ART initiation was often regarded as a 'return to health' phenomenon earlier in the HIV epidemic. More recently, with markedly extended survival having become routine among ART-treated PWH, an increasing proportion of ART-treated PWH ultimately become overweight or obese – a phenomenon associated with increased risk for several cardiometabolic diseases (18–22). Among ART-naïve patients, weight gain after ART initiation tends to be greater among persons with lower baseline BMI, higher HIV-1 viral load and lower CD4 count (18). We noted similar findings in our study, with the increased risk of extreme BMI gain experienced by participants with more advanced disease at baseline (lower CD4 count and weight).

The origin of this weight gain is multifactorial and may result from a reduction in inflammation-related catabolism, lower basal energy expenditure, changes in dietary habits or other behaviors (e.g., access to smoking cessation treatment) among other factors (23, 24). Importantly, findings from our study and from similar smaller studies indicate that initial ART agents also exert independent effects on weight gain over time as well.

Increased weight gain has previously been documented among female and Black PWH receiving INSTI-based initial ART regimens in the prospective ACTG study A5257 (25) and ACTG participants in protocols A5001 and A5322 (26). Additionally, in a pooled analysis of weight gain across 8 randomized phase III clinical trials of first-line ART initiation occurring in 2003–2015, weight gain was highest among Black females on INSTI (27). Similar results were noted in studies from Africa in the ADVANCE trial (10). In this multicentre, randomized, open-label phase III trial conducted in South Africa, ART-naïve participants receiving DTG-based regimens experienced higher weight gain compared to those receiving efavirenz (EFV-) based regimens (10). The highest weight gain was experienced by women who gained, on average at 96-weeks, 3 kg on EFV with Emtricitabine/Tenofovir Disoproxil (TDF/FTC), 5 kg with DTG and TDF/FTC, and a significantly higher 10-kg weight gain with DTG and Tenofovir alafenamide and Emtricitabine (TAF/FTC) (10). Moreover, while in general participants gained more fat than lean mass, it was noted that women gained significantly more fat than men (10). Another study from Africa including adults with HIV infection starting or switching ART at 12 President's Emergency Plan for AIDS Relief (PEPFAR-) supported clinics in Uganda, Kenya, Tanzania, and Nigeria, highlighted those participants receiving DTG-based regimens had almost two-fold increased odds of developing a higher BMI compared to participants receiving other ART (28). This latter study, however, did not account for differences by sex or TB co-infection as our current analysis has done.

Our study highlights that the phenomenon of increased weight gain among women receiving INSTI is not unique to the developed world and South Africa. On the contrary, our results demonstrate that similar weight gain is seen in Kenya, a country with lower prevalence of baseline obesity, higher food insecurity, and more advanced baseline HIV disease (12, 13, 16). We should note that in our study none of the participants were on TAF, and the weight

gained by women on DTG at 18-months is comparable to the weight gained by women on DTG and TDF at week 96 in the ADVANCE trial.

In our study, we also found that participants with HIV/TB coinfection experienced higher rate of extreme BMI gain. Patients with tuberculosis often present with severe wasting and experience significant weight gain during treatment (16). Additionally, participants with HIV/TB co-infection tend to have more advanced disease and are therefore more likely to gain excessive weight as part of their return to health phenomenon while being treated for both HIV and TB.

This is the largest observational study to date evaluating associations between use of various ART regimens and subsequent weight gain among ART-naïve PWH in East Africa. Our study includes over 17,000 treatment-naïve participants with over 1,300 participants with presumptive HIV/TB co-infection. However, some caution is warranted in interpreting the findings from this study. As our observational cohort was drawn from sites in Kenya, our results may therefore not be generalizable to all PWH, particularly populations outside the East Africa region. Additionally, based on the date of DTG approval and change in treatment guidelines in Kenya, we had appreciably fewer participants on DTG compared to NNRTI-based regimens. In addition, a lower number of women were treated with DTG, possibly the result of concerns of congenital abnormalities assigned to DTG treatment (29). This may have infused some bias in the results given how important age and sex are with respect to weight gain after ART initiation. Moreover, we did not account for concomitant medication usage that may have caused weight changes (ie, metformin, psychiatric medications) as such information was not recorded. Another limitation of our study was the lack of complete documented baseline data as 9% of the participants did not have baseline data to estimate BMI while 65% of participants did not have baseline CD4 count. Finally, we did not assess clinical outcomes, such as metabolic or cardiovascular disease incidence or progression, and so future studies will be needed to assess the impact of the observed weight changes on the overall health of PWH.

Further studies are needed to evaluate the mechanism of weight gain among patients starting INSTI-based regimens. Several mechanisms have been proposed including rapid reduction of viremia seen with INSTI and therefore lower resting energy expenditure (30). Moreover, some studies demonstrated larger decreases in inflammation and immune activation with INSTI (31, 32). Dolutegravir also affects the activity of melanocortin 4 receptor which is involved with energy expenditure (33). However, the mechanism of higher weight gain with INSTI among women, compared to men, remains unclear. Moreover, the finding that weight gain with NNRTI was greater in men than in women was unexpected and requires confirmation in future studies. At this time, despite evidence that INSTI, and particularly DTG, is associated with significantly higher weight gain, it remains unclear whether the weight gain is secondary to off-target effects of these drugs and a drug toxicity, or if it is simply due to better drug tolerability (e.g., less gastrointestinal upset) and virologic effectiveness.

In summary, our multisite cohort study demonstrates higher weight gain on average with DTG-based regimens compared to NNRTI-based regimens. While not statistically

significantly different, it appears that the risk of extreme weight gain is not uniform, with female participants receiving DTG being at higher risk than men on DTG of extreme weight increase relative to same sex participants on NNRTI-based regimens. With increasing prevalence of obesity and cardiometabolic diseases among PWH globally, weight gain amongst treatment naïve DTG PWH needs to be closely monitored and scrutinized for any associated cardiometabolic risks. Additionally, our results highlighted that participant who were underweight at baseline, participants who had CD4 depletion, and participants with HIV/TB coinfection experienced higher risk of extreme BMI gain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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https://researchscholars.gilead.com/en/hiv_portal/award-recipients

Prior Presentation:

A prior version of this work was presented during CROI 2021 (virtual) as a Scientific Spotlight (March 6 - 10, 2021).

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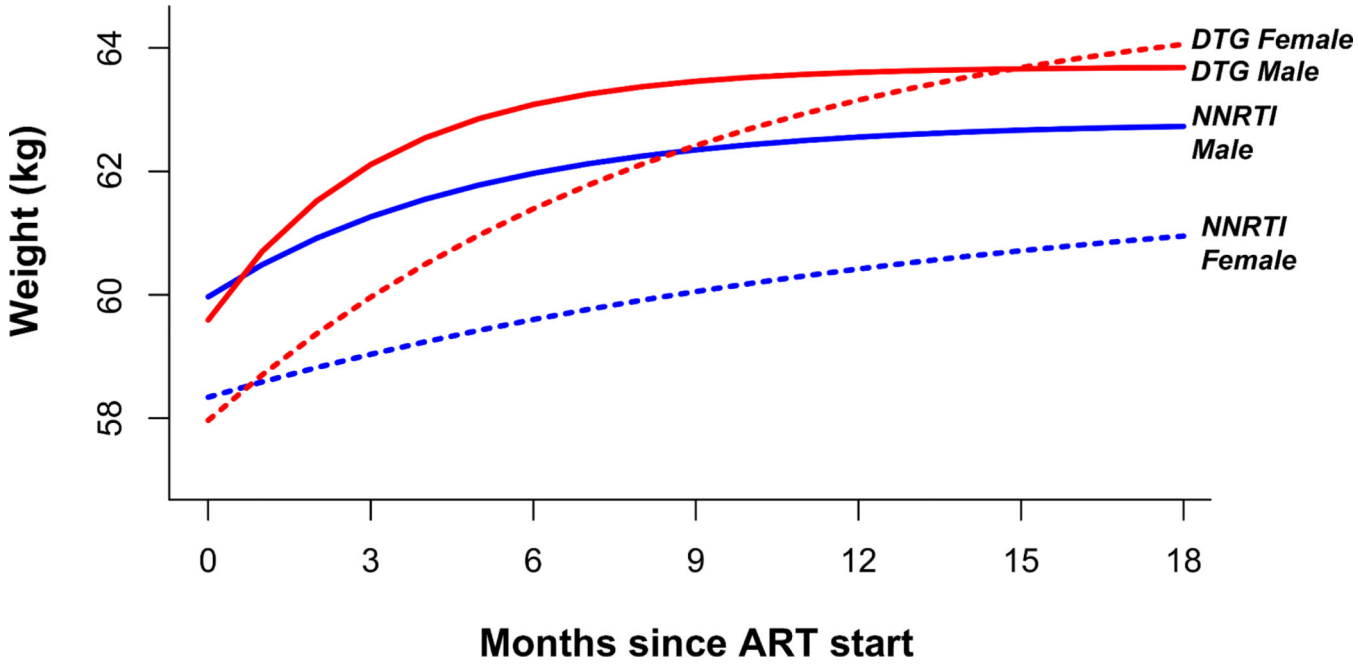

Figure 1.

Changes in weight over time by sex and treatment regimen. NNRTI: Non-nucleoside reverse-transcriptase inhibitor; DTG: Dolutegravir.

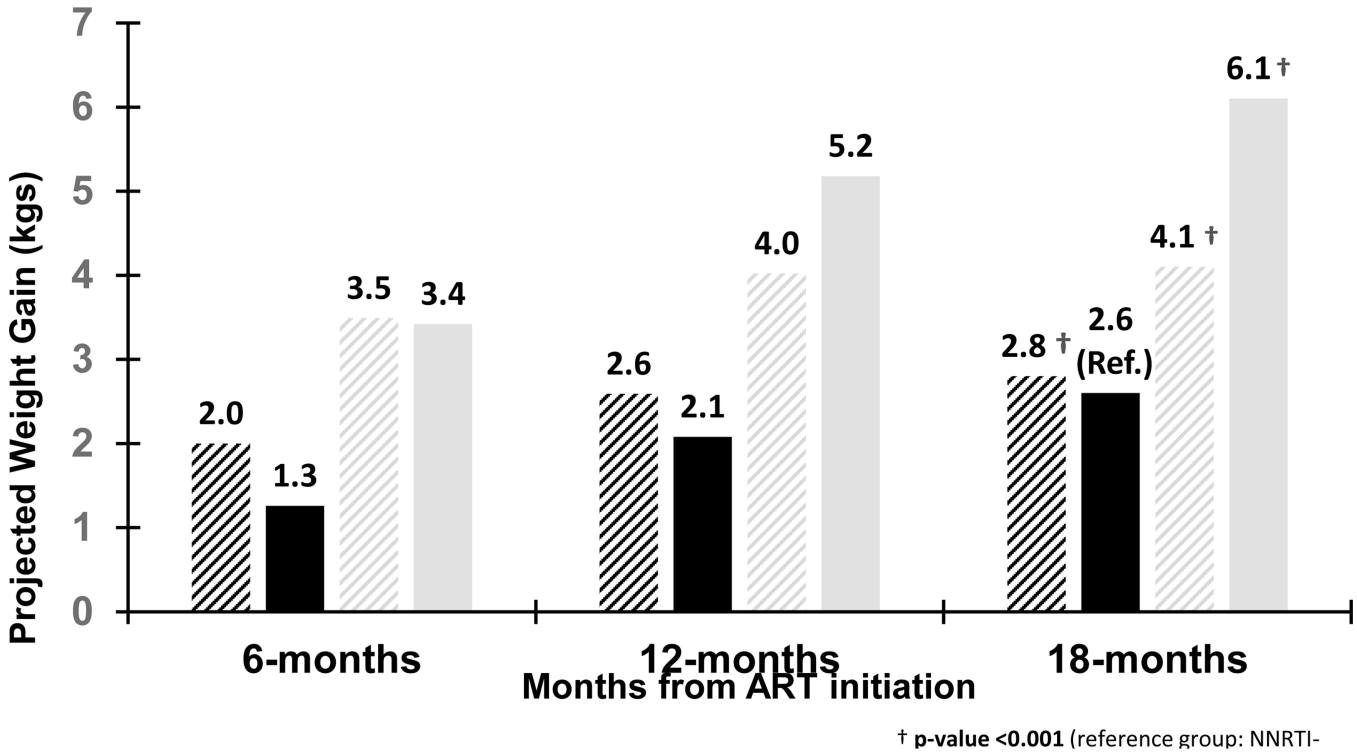

Figure 2.

Projected weight gain by sex and treatment regimen at 6-, 12- and 18-months. NNRTI: Non-nucleoside reverse-transcriptase inhibitor; DTG: Dolutegravir. (NNRTI Male = dashed black column, NNRTI Female = solid black column, DTG Male = dashed gray column, DTG Female = solid gray column).

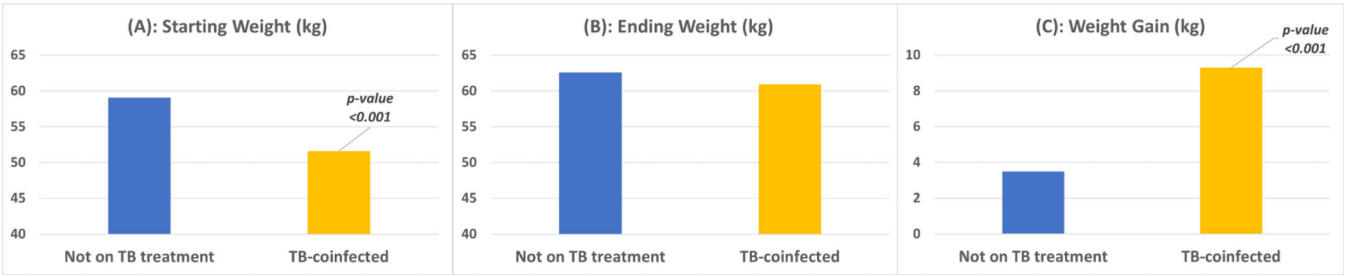

Figure 3.

Difference in weight gain among participants starting antiretroviral therapy by tuberculosis coinfection status. Weight estimates standardized for female participants, ages 29 – 45, starting NNRTI-based therapy. (A): Starting weight, (B): Ending weight, and (C): Weight gain by TB co-infection status. TB: Tuberculosis.

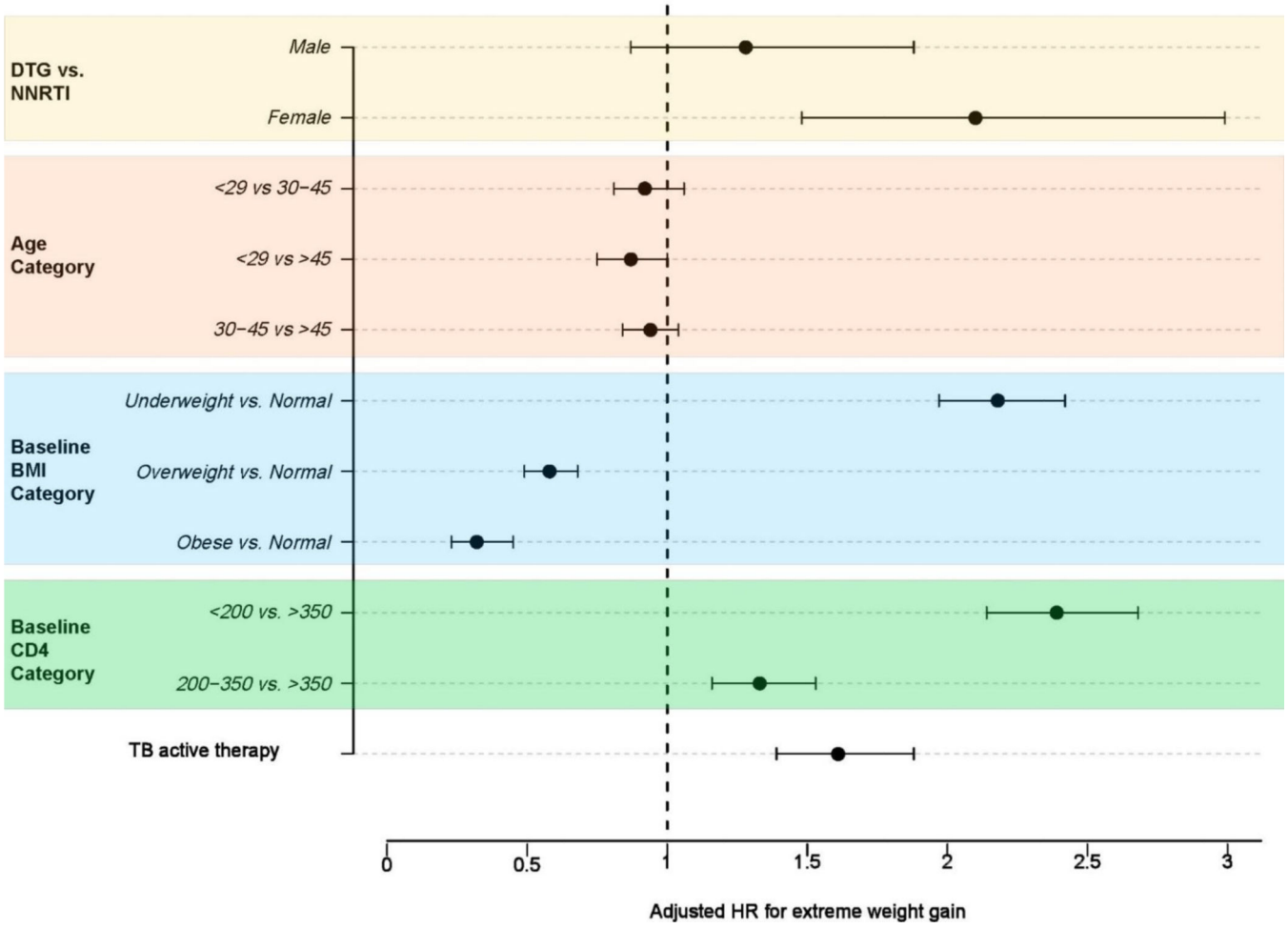

Figure 4.

Adjusted hazard of extreme weight gain, defined as more than 10% increase in BMI compared to baseline, among participants starting ART. NNRTI, Non-nucleoside reverse-transcriptase inhibitor; DTG, Dolutegravir; BMI, Body Mass Index.

Table 1.

Baseline clinical and demographic characteristics of all participants included in the analysis, and characteristics by treatment group. ART: Antiretroviral Therapy; DTG: Dolutegravir; NNRTI: Non-nucleoside reverse-transcriptase inhibitor. BMI: Body mass index (body mass in kg divided by square of body height in m^2).

		All ART regimens	NNRTI-based regimens	DTG-based regimens	p-value
Total, N (%)		17,044	16,517 (97%)	527 (3%)	*NA*
Year ART Start	2016	7295 (43%)	7295 (44%)	0 (0%)	*<0.001*
	2017	5654 (33%)	5630 (34%)	24 (5%)	
	2018	4095 (24%)	3592 (22%)	503 (95%)	
Age in years, median (IQR)		36.8 (30.0, 45.2)	36.8 (29.9, 45.1)	38.7 (31.6, 47.0)	*<0.001*
Sex at birth, N (%)	Female	10,518 (62%)	10,268 (62%)	250 (47%)	*<0.001*
	Male	6,526 (38%)	6,249 (38%)	277 (53%)	
Participants with available baseline BMI, N (%)		15,555 (91%)	15,080 (91%)	475 (90%)	*0.35*
Baseline weight (kg), median (IQR)		58.0 (51.0, 65.0)	58.0 (51.0, 65.0)	59.0 (50.5, 65.0)	*0.81*
Baseline BMI (kg/m^2), median (IQR)		20.8 (18.7, 23.5)	20.8 (18.7, 23.5)	20.4 (18.2, 23.1)	*0.01*
Baseline BMI Category, N (%)	Underweight (BMI < 18.5)	3,570 (21%)	3,436 (21%)	134 (25%)	*0.02**
	Normal (18.5 ≤ BMI < 25)	9,232 (54%)	8,960 (54%)	272 (52%)	
	Overweight (25 ≤ BMI < 30)	2,027 (12%)	1,972 (12%)	55 (10%)	
	Obese (BMI ≥ 30)	726 (4%)	712 (4%)	14 (3%)	
	Missing	1,489 (9%)	1,437 (9%)	52 (10%)	
Participants with available baseline CD4 count, N (%)		5,401 (35%)	5,240 (35%)	161 (34%)	*0.57*
Baseline CD4 count ($cells/mm^3$), median (IQR)		298.0 (125.0, 493.0)	299.0 (125.0, 493.0)	262.0 (130.0, 506.0)	*0.88*
Baseline CD4 count range (in $cells/mm^3$), N (%)	< 200, N (%)	1974 (11.6)	1916 (11.6)	58 (11.0)	*0.40**
	200 – 350, N (%)	1121 (6.6)	1081 (6.5)	40 (7.6)	
	>350, N (%)	2306 (13.5)	2243 (13.6)	63 (12.0)	
	Missing	11643 (68.3)	11277 (68.3)	366 (69.4)	
Active Tuberculosis Therapy, N (%)		1,056 (6%)	1,016 (6%)	40 (8%)	*0.18*
Number of Viral Loads Measured, median (IQR)		3.0(2.0,4.0)	3.0(2.0,4.0)	2.0(1.0,2.0)	<0.001
Length of Follow-Up (months), median (IQR)		14.0(3.0,26.0)	14.0(3.0,26.0)	15.0(7.0,18.0)	*<0.001*

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* missing not included in statistical comparison