No overall impact on rate of weight gain with integrase inhibitor-containing regimens in antiretroviral naïve adults

Running head title: No rate of weight gain impact if starting an INSTI

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Abstract

Objectives: Integrase strand transfer inhibitors (INSTIs) are commonplace in modern antiretroviral therapy (ART). Increased weight gain with their use is increasingly scrutinised. We evaluated weight changes in treatment-naïve adults with HIV-1 attending a UK centre who started regimens including raltegravir or dolutegravir.

Methods: A retrospective cohort study of adults prescribed an INSTI between January-2015 and March-2020 were categorised as having started an ART regimen containing raltegravir, dolutegravir, a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. Individuals with ≥1 weight measurement ≤5 years both pre- and post-ART-initiation, who started a three-drug regimen with ≥6 months duration and achieved virological suppression (<50 copies/ml) within 6 months were included. A random effects model with linear slope pre- and post-ART was used, adjusting for: age; gender; ethnicity; ART regimen, backbone, and year of initiation.

Results: The cohort included 390 adults, 88.7% male, 66.4% of white ethnicity, median age 40 years, with a median of six weight measurements, 2.2 years from diagnosis to ART-initiation, 2.9 years from ART to last weight, and weight and body mass index at initiation of 75kg and 24.1kg/m^2 respectively. 254 (65%) started an INSTI. Average pre-ART rate of weight gain was 0.44kg/year (95% CI 0.19-0.70), increasing to 0.88kg/year (0.63-1.10, p=0.04) after ART-initiation. Our adjusted model found no evidence of an association between ART regimen and rate of weight gain.

Conclusion: Weight increased in the cohort both pre- and post-ART; we found no evidence of a higher rate of weight gain following ART-initiation with an INSTI compared to other regimens.

Keywords: integrase inhibitors, weight gain, antiretroviral therapy, naïve

Introduction

Integrase strand transfer inhibitors (INSTIs) are one of the recommended third agents for initial antiretroviral therapy (ART) regimens (1). Raltegravir (RAL) and dolutegravir (DTG) remain the most widely used INSTI in the UK (2). 'Excessive' weight gain with INSTI-based regimens has been reported in a variety of settings, although the magnitude of the weight gain impact attributable to INSTIs, and what level of change should be considered significant, remains unclear.

In ART-naïve cohorts, weight gain after ART-initiation is seen as part of a "return-to-health" phenomenon, particularly in individuals with advanced immunosuppression. This is a manifestation of reduced immune activation, and the associated high metabolic turnover, following viral suppression (3). In contrast, more recent cohorts are typically started on treatment earlier, therefore, weight change may be more reflective of an effect of the ART regimen and/or obesogenic environments that similarly influence the general population.

We conducted a retrospective analysis of an adult, ART-naïve HIV-1 cohort in London, UK to evaluate the rate of weight change after starting a RAL- or DTG-containing regimen relative to other regimens.

Methods

Data were extracted from clinic records of people living with HIV (PLWH) who were prescribed INSTI-containing regimens between January-2015 and March-2020. The inclusion criteria were: ART-naïve, started a three-drug regimen containing DTG or RAL, initial regimen duration of ≥6 months, evidence of viral load (VL) suppression (<50copies/ml) within 6 months of ART initiation, ≥1 weight measurement ≤5years before (or at) ART-initiation, and ≥1 weight measurement ≤5years post-ART initiation. If consecutive VL 'blips' (>50, <200copies/ml) or

viral failure (>200copies/ml) occurred after suppression, only weights before that point were included. There were no restrictions on year of ART-initiation.

The analysis was restricted to individuals with dual nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbones comprised of abacavir/lamivudine (ABC/3TC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Tenofovir alafenamide fumarate (TAF) was excluded because of low use. On-ART weight measurements were only included for participants remaining on their initial ART regimen.

The comparator group were the identified ART-experienced individuals who previously started a non-INSTI-containing initial regimen; all other inclusion criteria were the same. Weight/height measurements were performed in outpatient clinics; devices were presumed to have undergone regular calibration in compliance with local standard operating procedures. Pregnant women and individuals with reported adherence issues or treatment interruptions were completely excluded from the analysis. Elvitegravir, bictegravir, and cabotegravir were excluded because use as initial therapy was limited during the study period. Previous HIV pre-exposure prophylaxis (PrEP) use was not an exclusion criterion.

Statistical Analysis

A random effects model with linear slope before and after ART-initiation was used to analyse weight change. Person-level correlated random effect terms were incorporated for intercept and pre- and post-ART slopes. The model parameters were defined in terms of the average weight at ART-initiation, annual rate of weight gain pre-ART, and change in rate of weight gain post-ART. This approach was replicated for BMI. Categorical weight change (e.g. 5% gain) was not adopted because of the heterogeneity in when weight measurements were recorded.

Associations with age, gender, ethnicity (Black African or other non-white/unknown vs. white), baseline CD4, baseline VL, initial ART regimen, and year of ART-initiation were evaluated. Control ART regimens were grouped into those containing a protease inhibitor (PI) vs. non-nucleoside reverse transcriptase inhibitor (NNRTI). Associations between continuous variables at ART start and weight/BMI trajectory characteristics were modelled using 4-knot natural cubic splines (2.5^{th}, 33^{rd}, 66^{th}, and 97.5^{th} centiles). A sensitivity analysis was conducted with additional adjustment of each model term for co-morbidities of depression, renal impairment, high cholesterol/lipids, hypertension and non-alcoholic fatty liver disease (NAFLD). Models were fitted using the *nlme* package (4) in *R* (5).

Results

Of 682 identified ART-naïve individuals, 492 were started on regimens meeting the inclusion criteria, of whom, 486 received this regimen for ≥6 months. In 424/486 participants, an undetectable VL was observed ≤6 months after ART-initiation. A further 25 were excluded because pre- and post-ART weight measurements were outside the specified timeframe; nine were excluded due to no baseline HIV-1 VL and CD4 T-cell data. The final sample for analysis included 390 individuals with 926 pre-ART and 1415 post-ART weights. The median number of measurements was 2 (1-3) pre-ART and 3 (IQR 2-5) post-ART. There was a median of 2.2 years (IQR 0.3-4.7) from HIV-1 diagnosis to ART-initiation, and 2.9 years (IQR 1.3-4.1) between ART-initiation and last weight.

The cohort was predominantly male (n=346, 89%), of white ethnicity (n=259, 66%), Centres for Disease Control category A (n=345, 89%), with a median age at ART initiation of 40 years (IQR 34-46), and a median pre-ART CD4 count and viral load of 390cells/μl (290-528) and 4.5Log_{10}copies/ml (3.9-5.1) respectively. The median weight and BMI at ART initiation were 75.0kg (IQR 68.0-83.0) and

24.1kg/m^2 (IQR 22.2-26.8) respectively. Of the 254 (65%) starting an INSTI, 196 (77%) started RAL and 58 (23%) DTG. 122 (48%) started TDF/FTC and 132 (52%) started ABC/3TC. None had received PrEP. Additional cohort characteristics are presented in the supplementary materials (Supplementary Digital Content 1).

The unadjusted mixed effects model showed higher weights at initiation in the INSTI groups (NNRTI 75.5kg [95% CI 73.2-77.7], PI 73.9kg [70.1- 77.7], DTG 77.1kg [74.0-80.1], RAL 78.9kg [76.7 to 81.0]), an average pre-ART rate of weight gain of 0.44kg/year (0.19-0.70) with an increase to 0.88kg/year (0.63-1.10, p=0.04) after ART-initiation (Supplementary Digital Content 2). The adjusted model spline plots show trends of greater weight loss per year prior to ART initiation with lower CD4, higher baseline viral load, and higher age (Figure 1b,f,j, predicted average rates of change are shown for CD4, whilst differences in the predicted average rate of change relative to a reference value are shown for age and VL). Characteristics associated with weight loss prior to ART initiation were associated with a greater relative change in the rate of weight loss/gain at ART initiation (Figure 1d,h,l), with low CD4 and high VL at baseline associated with the larger absolute rates of weight gain on ART (Figure 1c,g).

Overall, when adjusting for the characteristics in Table 1, individuals had a higher rate of weight gain pre-ART for all other regimens compared to those starting an NNRTI, though not to a significant degree. The change in rate of weight gain after starting ART is positive where the rate of gain increased and negative where it decreased (e.g. Black Africans, rate increased by 0.49kg/year from a loss of -0.3kg/year to a gain of 0.46kg/year). This did not significantly differ by ART regimen relative to NNRTI (RAL –0.76kg/year [-2.36-0.84, p=0.36], DTG -1.01kg/year [-2.97-0.95, p=0.32], PI -0.45kg/year [-1.97-1.07, p=0.57],

NNRTI [reference], Table 1). Similar findings were seen for BMI (Table 1, Supplementary Digital Content 3). There was some evidence that individuals starting ART more recently had higher baseline weights (2007-10 -0.82kg [-6.82-5.18, p=0.79], 2011-13 -0.13kg [-5.29-5.03, p=0.96], 2014-16 [reference], 2017-20 +2.57kg [-0.99-6.13, p=0.16]).

Further adjustment for patient co-morbidities showed an increased rate of weight gain post-ART in those with depression (+1.29kg/year, 95% CI 0.32-2.26, p=0.01) and greater weight at ART initiation for those with hypertension (+8.07kg, 95% CI 3.24-12.91, p=0.001) and NAFLD (+9.48kg, 95%CI 5.04-13.91, p<0.0001), without any other statistically significant findings. This did not affect the overall conclusions from the analyses regarding ART regimens.

Discussion

Our real-world cohort was on average gaining weight both pre-and post-ART in our unadjusted analysis. However, we did not observe a difference in the rate of weight or BMI gain after starting an ART regimen containing RAL or DTG compared to a PI- or NNRTI-based regimen. Our study is novel in that we incorporated weights before baseline to assess pre-ART trends. We analysed the rate at which weight is gained (or lost), not the absolute weight change. Our aim was to identify whether the inclusion of INSTIs within the ART regimen was associated with an acceleration in the rate of weight gain as opposed to quantifying absolute weight change.

Observations of absolute weight gain after starting INSTIs in other treatment-naïve cohorts and a pooled analysis of randomised studies have been reported (6, 7), though contrasting findings have been reported in switch cohorts (8). Whilst ART-naïve individuals may experience gains in absolute weight after starting ART,

the cause is likely to be multifactorial. One hypothesis to explain the variability of effect could be that INSTIs sensitise PLWH to gaining weight, the melanocortin-4 receptor pathway being one proposed mechanism (9). However, absolute gains are likely influenced by lifestyle (10), cultural attitudes to weight (11), the individual's perception of their weight (12), and host genetics/microbiome (13). This may explain why weight gain is not a universal phenomenon for all individuals on ART and for all regimens (14). Improved tolerability of modern regimens could also be a factor and is more easily identified when full adverse event data from studies are reported (7). For individuals who undergo extremely rapid weight gain with ART, host/genetic factors, yet to be elucidated, could amplify or synergise such an effect.

Individuals with a more recent year of ART initiation were heavier at initiation. This likely reflects that PLWH are now diagnosed and started on treatment earlier, with fewer patients with advanced disease and the associated weight loss. However, it may also reflect the increasingly obesogenic environment that equally affects the general population; 64% of adults in England are overweight or obese (36% and 28% respectively) (15), with a similar prevalence observed in comparable countries (16). Increased rate of weight gain was observed in those starting treatment with lower CD4, higher viral load, and older age, likely associated with a return-to-health. Both findings have been observed in other HIV cohorts (6).

Our study is limited by being a relatively small, single-centre cohort comprised predominantly of white males. This restricts the generalisability of our findings to other groups taking INSTI-containing regimens, particularly black females who are thought to be susceptible to weight gain. Similarly, TAF was excluded due to small numbers (n=4), precluding assessment of the potential effect of TAF as

noted in other studies (7, 17). We were also unable to include other INSTIs (cabotegravir, elvitegravir, and bictegravir) due to low use.

Our study will not have captured extremely rapid changes in weight that may have occurred during the six months after ART-initiation if this caused a regimen switch. However, only a small number of individuals were excluded on this basis (n=6) and our primary focus was the rate of weight change across the whole cohort following a longer period of INSTI exposure. This approach allowed for sufficient time to determine if any immediate acceleration of weight gain is maintained.

Conclusion

Weight change after ART initiation is likely a complex, multifactorial process. These data suggest that RAL- and DTG-containing regimens in treatment-naïve individuals are not associated with an acceleration in weight gain compared to other ART regimens, beyond that expected following viral suppression, within the limitations specified. Research incorporating assessment of general weight gain factors such as diet and exercise would be beneficial, mitigating the under-reporting and recording bias with diet recall, though this is often logistically challenging (18). Comorbidities also need to be considered; depression was associated with increased rate of weight gain, a condition with high prevalence (19) where both the disease and the treatment can affect weight (20).

Caution should be shown in attributing weight gain as a causal effect of INSTI use in the absence of adequate follow-up and monitoring. More data are needed to evaluate individuals switching away from INSTIs because of weight gain. This should include capturing obesogenic factors; whether the weight gain continues, plateaus, or reverses; weight distribution, and whether any clinical or metabolic sequelae manifest.

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Contributions: JB, SLP, DD, and OS developed the research question and study. JB completed electronic clinical record reviews and data collection, data cleaning, and drafted the initial manuscript. OS performed the statistical analyses and contributed towards the initial draft manuscript of the article. All authors were involved in the final interpretation of the results and finalised manuscript.

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Conflicts of Interest and Sources of Funding

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References

1. European AIDS Clinical Society. EACS Guidelines version 10.1. 2020.
2. El Bouzidi K, Jose S, Phillips AN, Pozniak A, Ustianowski A, Gompels M, et al. First-line HIV treatment outcomes following the introduction of integrase inhibitors in UK guidelines. *AIDS*. 2020;**34**(12):1823-31.
3. Mave V, Erlandson KM, Gupte N, Balagopal A, Asmuth DM, Campbell TB, et al. Inflammation and Change in Body Weight With Antiretroviral Therapy Initiation in a Multinational Cohort of HIV-Infected Adults. *J Infect Dis*. 2016;**214**(1):65-72.
4. Pinheiro J BD, DebRoy S, Sarkar D, R Core Team. nlme: Linear and Nonlinear Mixed Effects Models. R package. 3.1-151 ed2020.
5. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2013.
6. Sax PE, Erlandson KM, Lake JE, McComsey GA, Orkin C, Esser S, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. *Clin Infect Dis*. 2020;**71**(6):1379-89.
7. Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, Mashabane N, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020;**7**(10):e666-e76.
8. Burns JE, Stirrup OT, Dunn D, Runcie-Unger I, Milinkovic A, Candfield S, et al. No overall change in the rate of weight gain after switching to an integrase-inhibitor in virologically suppressed adults with HIV. *Aids*. 2020;**34**(1):109-14.

9. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? *J Virus Erad*. 2019;**5**(1):41-3.
10. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in Diet and Lifestyle and Long-Term Weight Gain in Women and Men. *New England Journal of Medicine*. 2011;**364**(25):2392-404.
11. Pradeilles R, Holdsworth M, Olaitan O, Irache A, Osei-Kwasi HA, Ngandu CB, et al. Body size preferences for women and adolescent girls living in Africa: a mixed-methods systematic review. *Public Health Nutr*. 2021:1-22.
12. Hurley E, Coutsoudis A, Giddy J, Knight SE, Loots E, Esterhuizen TM. Weight evolution and perceptions of adults living with HIV following initiation of antiretroviral therapy in a South African urban setting. *S Afr Med J*. 2011;**101**(9):645-50.
13. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;**518**(7538):197-206.
14. Orkin C, Elion R, Thompson M, Rockstroh JK, Alvarez Bognar F, Xu ZJ, et al. Changes in weight and BMI with first-line doravirine-based therapy. *AIDS*. 2021;**35**(1):91-9.
15. NHS Digital. Health Survey for England 2019: Overweight and obesity in adults and children. 2020.
16. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. *National Center for Health Statistics*. 2020.
17. Wohl DA, Yazdanpanah Y, Baumgarten A, Clarke A, Thompson MA, Brinson C, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2019;**6**(6):e355-e63.
18. St George SM, Van Horn ML, Lawman HG, Wilson DK. Reliability of 24-Hour Dietary Recalls as a Measure of Diet in African-American Youth. *Journal of the Academy of Nutrition and Dietetics*. 2016;**116**(10):1551-9.
19. Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. *Curr Psychiatry Rep*. 2015;**17**(1):530.
20. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;**67**(3):220-9.

Figure 1 Estimates of average (a) weight at ART-initiation, (b) pre-ART rate of weight gain, (c) post-ART rate of weight gain, and (d) post-ART change in rate of weight gain in relation to CD4 at ART-initiation. (e)-(l) show the difference (delta) in the predicted weight/rate of change relative to (a)-(d), in relation to age at ART-initiation for (e)-(h), and in relation to viral load at ART-initiation for (i)-(l). These estimates are derived from models with adjustment for the demographic and treatment characteristics listed in Table 1. The plots relate to a white male individual starting a raltegravir-based regimen. Dotted lines show pointwise 95% CI. Plot (c) represents a summation of the functions in (b) and (d), (g) is a summation of (f) and (h), and (k) is a summation of (j) and (l). ART=antiretroviral therapy, init=initiation, SQRT=square root, VL=viral load,

Supplementary Digital Content 1: Summary of cohort characteristics

Supplementary Digital Content 2: Summary of unadjusted rate of weight change estimates, overall and by ART regimen

Supplementary Digital Content 3: Figure showing adjusted model for body mass index

Figure SDC3 Estimates of average (a) BMI at ART-initiation, (b) pre-ART rate of BMI gain, (c) post-ART rate of BMI gain, and (d) post-ART change in rate of BMI gain in relation to CD4 at ART-initiation. (e)-(l) show the difference (delta) in the predicted BMI/rate of change relative to (a)-(d), in relation to age at ART-initiation for (e)-(h) and in relation to viral load at ART-initiation for (i)-(l).. These estimates are derived from models with adjustment for the demographic and treatment characteristics listed in Table 1. The plots relate to a white male individual starting a raltegravir-based regimen. Dotted lines show pointwise 95% CI. Plot (c) represents a summation of the functions in (b) and (d), (g) is a summation of (f) and (h), and (k) is a summation of (j) and (l). ART=antiretroviral therapy, BMI=body mass index, init=initiation, SQRT=square root, VL=viral load

No impact on weight gain rate if starting an INSTI

Table 1 Associations between demographic/treatment characteristics and weight/BMI trajectories

		n (%)	*Weight/BMI at ART initiation*		*Pre-ART rate of weight/BMI gain (per year)*		*Change in rate of weight/BMI gain after starting ART (per year)*	
			ΔEst. (95%CI)	*P*-value	ΔEst. (95% CI)	*P*-value	ΔEst. (95% CI)	*P*-value
Weight results (kg)								
Gender	Men	346 (89)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	Women	44 (11)	-7.04 (-11.87 to -2.21)	0.005	0.21 (-0.63 to 1.05)	0.63	0.37 (-1.07 to 1.82)	0.62
Ethnicity	White	259 (66)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	Black African	42 (11)	3.61 (-1.39 to 8.61)	0.16	-0.3 (-1.14 to 0.55)	0.49	0.49 (-0.99 to 1.97)	0.52
	Other non-white	89 (23)	1.72 (-1.53 to 4.96)	0.30	-0.46 (-1.04 to 0.12)	0.12	0.26 (-0.72 to 1.24)	0.60
ART regimen type	NNRTI	95 (24)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	PI	41 (11)	-0.41 (-5.33 to 4.51)	0.87	0.36 (-0.57 to 1.29)	0.46	-0.45 (-1.97 to 1.07)	0.57
	DTG	58 (15)	2.58 (-3.55 to 8.71)	0.41	0.69 (-0.51 to 1.88)	0.26	-1.01 (-2.97 to 0.95)	0.32
	RAL	196 (50)	3.23 (-1.7 to 8.15)	0.20	0.93 (-0.06 to 1.92)	0.07	-0.76 (-2.36 to 0.84)	0.36
NRTI backbone	TDF+FTC	233 (60)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	ABC+3TC	157 (40)	-2.05 (-5.23 to 1.13)	0.21	-0.08 (-0.64 to 0.48)	0.78	0.32 (-0.64 to 1.28)	0.52
Year of ART initiation	2007-2010	49 (13)	-0.82 (-6.82 to 5.18)	0.79	0.41 (-0.7 to 1.51)	0.48	-0.8 (-2.68 to 1.07)	0.41
	2011-2013	63 (16)	-0.13 (-5.29 to 5.03)	0.96	0.45 (-0.63 to 1.54)	0.42	-0.87 (-2.57 to 0.84)	0.32

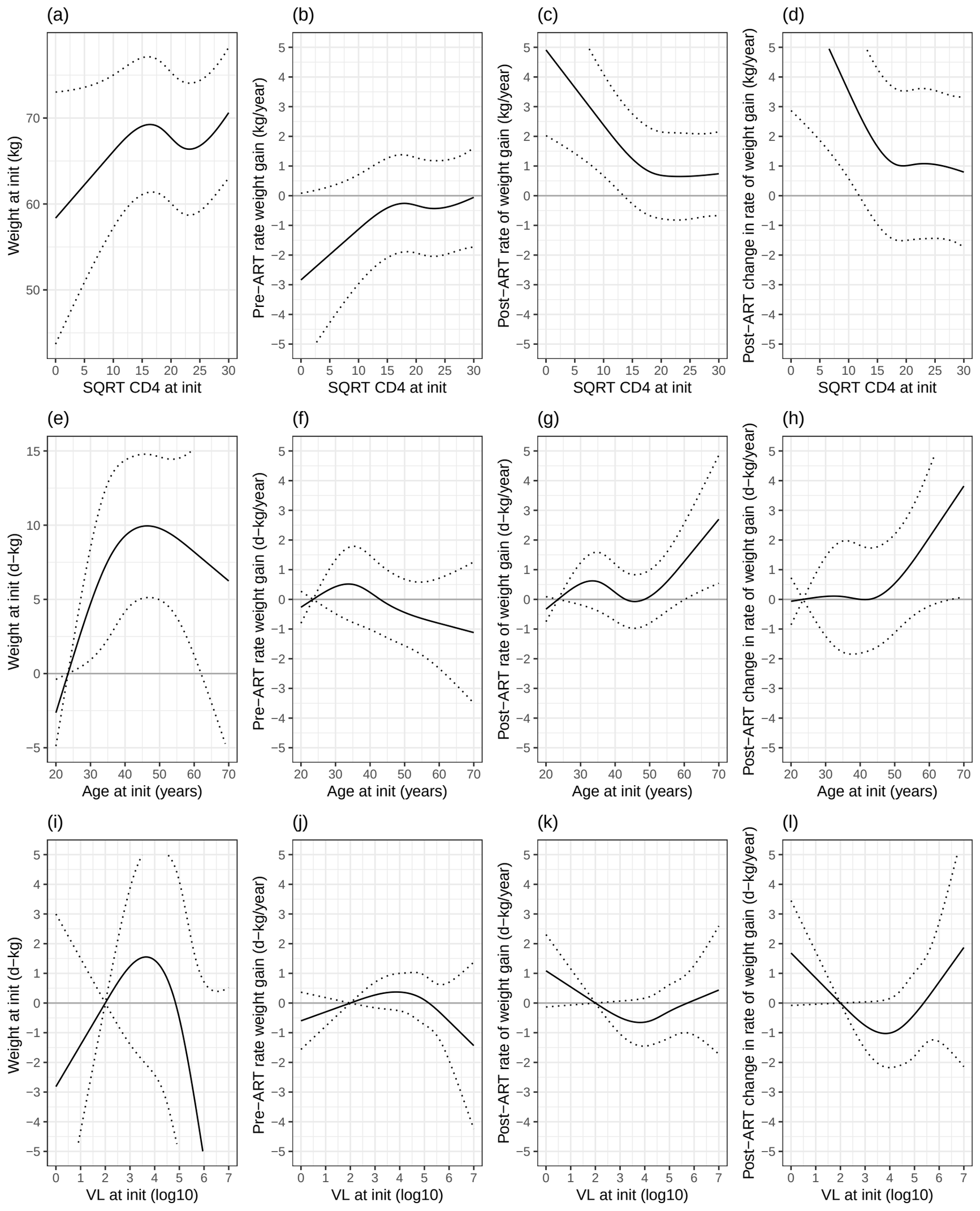
No impact on weight gain rate if starting an INSTI

	2014-2016	195 (50)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	2017-2020	83 (21)	2.57 (-0.99 to 6.13)	0.16	0.72 (0.03 to 1.41)	0.04	-0.82 (-1.99 to 0.34)	0.17
BMI results (kg/m²)								
Gender	Men	346 (89)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	Women	44 (11)	1.29 (-0.23 to 2.8)	0.10	0.16 (-0.13 to 0.45)	0.29	0 (-0.48 to 0.47)	0.99
Ethnicity	White	259 (66)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	Black African	42 (11)	2.54 (0.96 to 4.13)	0.002	-0.07 (-0.36 to 0.22)	0.65	0.07 (-0.42 to 0.57)	0.77
	Other non-white	89 (22)	1.38 (0.34 to 2.43)	0.01	-0.14 (-0.33 to 0.05)	0.17	0.1 (-0.22 to 0.42)	0.56
ART regimen type	NNRTI	95 (24)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	PI	41 (11)	-1.22 (-2.88 to 0.43)	0.15	0.08 (-0.26 to 0.41)	0.66	-0.09 (-0.62 to 0.44)	0.74
	DTG	58 (15)	0.34 (-1.6 to 2.29)	0.73	0.15 (-0.25 to 0.56)	0.47	-0.28 (-0.92 to 0.37)	0.41
	RAL	196 (50)	0.44 (-1.14 to 2.02)	0.59	0.22 (-0.13 to 0.56)	0.22	-0.17 (-0.7 to 0.36)	0.53
NRTI backbone	TDF+FTC	233 (60)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-
	ABC+3TC	157 (40)	-0.84 (-1.87 to 0.18)	0.11	-0.01 (-0.21 to 0.18)	0.88	0.08 (-0.24 to 0.4)	0.64
Year of ART initiation	2007-2010	49 (13)	0.18 (-1.79 to 2.15)	0.86	0.15 (-0.23 to 0.54)	0.45	-0.44 (-1.08 to 0.2)	0.18
	2011-2013	63 (16)	0.07 (-1.63 to 1.76)	0.94	0.23 (-0.17 to 0.63)	0.27	-0.49 (-1.08 to 0.1)	0.11
	2014-2016	195 (50)	0 [Reference]	-	0 [Reference]	-	0 [Reference]	-

No impact on weight gain rate if starting an INSTI

	2017-2020	83 (21)	0.37 (-0.73 to 1.47)	0.52	0.23 (0.01 to 0.46)	0.046	-0.26 (-0.64 to 0.12)	0.18

Associations between demographic/treatment characteristics and both average weight and BMI trajectories during the five years before and after ART initiation. Adjusted for age, CD4 and VL at switch and the other variables listed in the table. Estimates are expressed relative (Δ) to the average value at any given age (Figure 1). ABC=abacavir, ART=antiretroviral therapy, BMI=body mass index, CI=confidence interval, DTG=dolutegravir, FTC=emtricitabine, NNRTI=non-nucleoside reverse transcriptase inhibitors, PI=protease inhibitor, RAL=raltegravir, TDF=tenofovir disoproxil fumarate, 3TC=lamivudine


(a)
(b)
(c)
(d)
Weight at init (kg)
Pre−ART rate weight gain (kg/year)
Post−ART rate of weight gain (kg/year)
Post−ART change in rate of weight gain (kg/year)
SQRT CD4 at init
(e)
(f)
(g)
(h)
Weight at init (d−kg)
Pre−ART rate weight gain (d−kg/year)
Post−ART rate of weight gain (d−kg/year)
Post−ART change in rate of weight gain (d−kg/year)
Age at init (years)
(i)
(j)
(k)
(l)
VL at init (log10)

No impact on weight gain rate if starting an INSTI

Supplemental Digital Content 1

Table: Summary of cohort characteristics

	INSTI		Control		Total
	RAL	DTG	NNRTI	PI	
	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]
Sample	196 (50)	58 (15)	95 (24)	41 (11)	390 (100)
Male	170 (87)	52 (90)	90 (95)	34 (83)	346 (89)
Female*	26 (13)	6 (10)	5 (5)	7 (17)	44 (11)
Ethnicity	-	-	-	-	-
White	121 (62)	33 (57)	73 (77)	32 (78)	259 (66)
Black African	27 (14)	6 (10)	7 (7)	2 (5)	42 (11)
Other non-white†	48 (25)	19 (33)	15 (16)	7 (17)	89 (23)
CDC category at diagnosis	-	-	-	-	-
A	176 (90)	55 (95)	81 (85)	33 (81)	345 (89)
B	15 (8)	3 (5)	12 (13)	7 (17)	37 (10)
C	5 (3)	0 (0)	2 (2)	1 (2)	8 (2)
	[median, (IQR)]	[median, (IQR)]	[median, (IQR)]	[median, (IQR)]	[median, (IQR)]
Age at ART initiation (years)	40 (35-47)	37 (31-43)	40 (34-45)	40 (35-47)	40 (34-46)
HIV-1 diagnosis to ART initiation (years)	1.6 (0.2-4.7)	2.6 (0.3-3.9)	3.3 (1.4-5.2)	2.4 (0.3-4.7)	2.2 (0.3-4.7)
CD4+ T-cell count prior to ART initiation (cells/uL)‡	420 (328-595)	435 (322-535)	320 (245-410)	300 (240-430)	390 (290-528)
HIV-1 viral load prior to ART initiation (Log_{10} copies/ml)	4.4 (3.7-4.9)	4.5 (3.9-5.1)	4.6 (4.1-5.1)	4.9 (4.3-5.3)	4.5 (3.9-5.1)
Weight at ART initiation (kg)§	76 (68-85)	76 (68-83)	75 (69-81)	72 (65-77)	75 (68-83)
BMI at ART initiation (kg/m^2)	24.4 (22.3-27.2)	23.7 (22.1-26.6)	24.2 (22.8-26.3)	22.7 (21.5-24.6)	24.1 (22.2-26.8)

No impact on weight gain rate if starting an INSTI

NRTI backbones ¶	[n, %]	[n, %]	[n, %]	[n, %]	[n, %]
TDF+FTC	113 (58)	9 (16)	78 (82)	33 (81)	233 (60)
ABC+3TC	83 (42)	49 (85)	17 (18)	8 (20)	157 (40)
Year of ART initiation	-	-	-	-	-
2007-2010	0 (0)	0 (0)	36 (38)	13 (32)	49 (13)
2011-2013	6 (3)	0 (0)	37 (39)	20 (49)	63 (16)
2014-2016	131 (67)	35 (60)	22 (23)	7 (17)	195 (50)
2017-2020	59 (30)	23 (40)	0 (0)	1 (2)	83 (21)
Comorbidities #	-	-	-	-	-
Depression	42 (21)	9 (16)	19 (20)	13 (32)	83 (21)
Hypertension	20 (10)	1 (2)	6 (6)	5 (12)	32 (8)
NAFLD	16 (8)	3 (5)	13 (14)	5 (12)	37 (10)
T2DM	8 (4)	0 (0)	2 (2)	1 (2)	11 (3)
Renal impairment ‖	7 (4)	2 (3)	6 (6)	4 (10)	19 (5)
High cholesterol/lipids	6 (3)	2 (3)	9 (10)	7 (17)	24 (6)
IHD/CVD	3 (2)	1 (2)	1 (1)	0 (0)	5 (1)
Hypothyroidism	1 (1)	1 (2)	3 (3)	0 (0)	5 (1)
Menopause	3 (2)	0 (0)	1 (1)	1 (2)	5 (1)
OSA	0 (0)	0 (0)	1 (1)	1 (2)	2 (1)
AIDS-defining conditions	[n=5, 3%]	[n=1, 2%]	[n=2, 2%]	[n=1, 2%]	[n=9, 2%]
TB**	2 (40)	1 (100)	1 (50)	0 (0)	4 (45) ‖
PCP	2 (40)	0 (0)	0 (0)	0 (0)	2 (22)
Lymphoma	1 (20)	0 (0)	0 (0)	0 (0)	1 (11)
Isosporiasis	0 (0)	0 (0)	0 (0)	1 (100)	1 (11)

No impact on weight gain rate if starting an INSTI

Recurrent Pneumonia	0 (0)	0 (0)	1 (50)	0 (0)	1 (11)

*Includes 1 male-to-female transgender. †n=6 ethnicity not stated. ‡Last recorded ≤1 year prior to ART start. §Last recorded up to the day of ART start. ¶Individuals had to maintain the same NRTI backbone pre- and post-ART initiation. #Comorbidity data was collected from reported medical history in patient clinical records. ‖Includes chronic kidney disease of any cause and proximal renal tubulopathy. **One TB case occurred post-diagnosis with CDC category at diagnosis of A. ABC = abacavir, ART= Antiretroviral therapy, BMI=body mass index, CDC = Centre for Disease Control, CVD=cerebrovascular disease, DTG=dolutegravir, FTC = emtricitabine, IQR=interquartile range, IHD=ischaemic heart disease, INSTI = Integrase strand transfer inhibitor, NAFLD=non-alcoholic fatty liver disease, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, OSA=obstructive sleep apnoea, PCP = *Pneumocystis jirovecii* pneumonia, PI=Protease Inhibitor, RAL=raltegravir, TB = tuberculosis, TDF = tenofovir disoproxil fumarate, T2DM=type 2 diabetes mellitus, 3TC = lamivudine

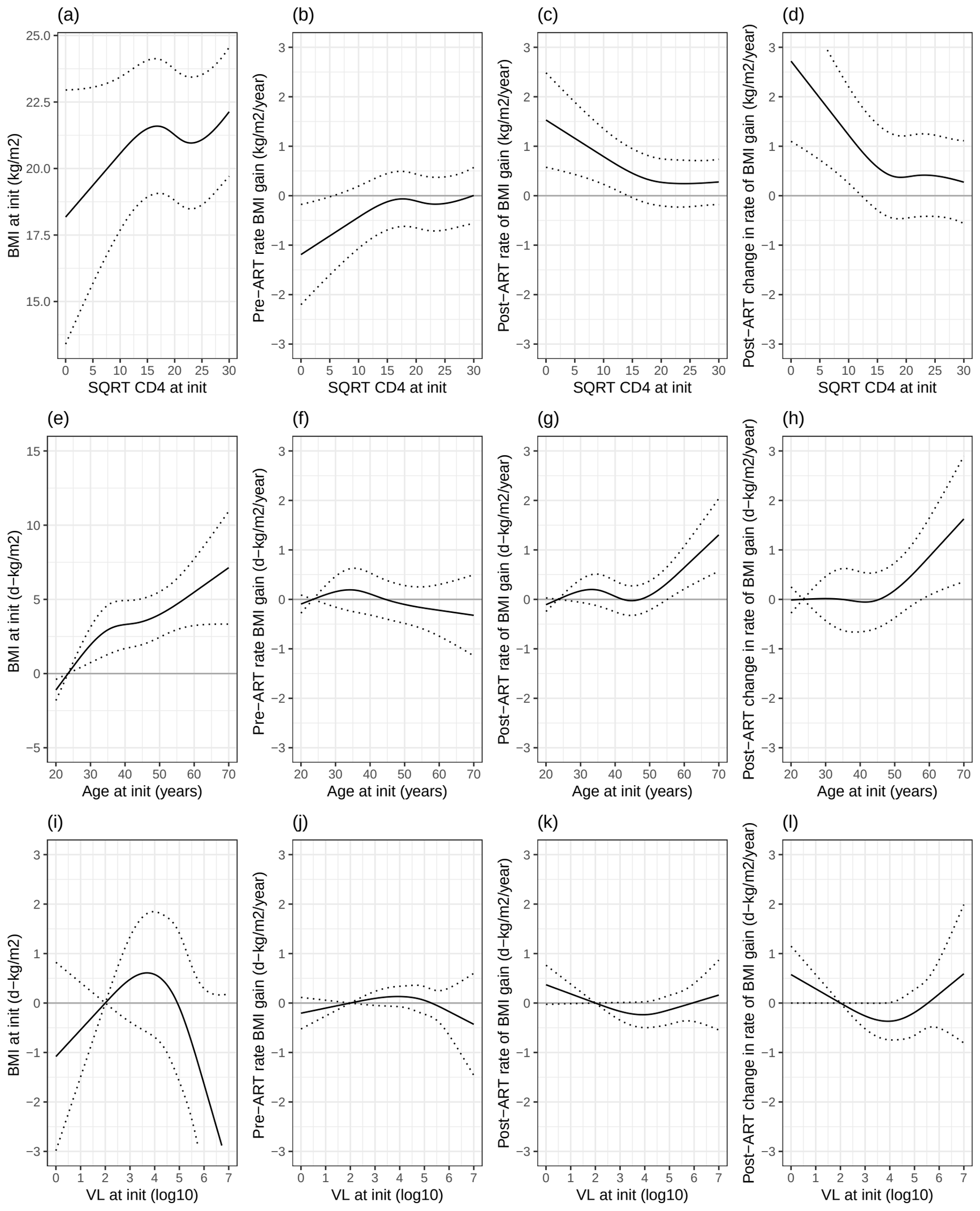
No impact on weight gain rate if starting an INSTI

Supplemental Digital Content 2

Table: Summary of unadjusted rate of weight change estimates, overall and by ART regimen.

		Weight at ART-initiation	*Pre-ART rate of weight gain*	*Post-ART rate of weight gain*	*Change in rate*
		[kg (95% CI)]	*[kg/year, (95% CI)]*	*[kg/year, (95% CI)]*	*[kg/year, (95% CI)]*
Total	-	77.3 (75.9 to 78.7)	0.44 (0.19 to 0.70)	0.88 (0.63 to 1.10)	0.44 (0.02 to 0.85)
By ART regimen type	NNRTI	75.5 (73.2 to 77.7)	-0.04 (-0.51 to 0.44)	0.79 (0.31 to 1.27)	0.83 (-0.01 to 1.66)
	PI	73.9 (70.1 to 77.7)	0.36 (-0.19 to 0.91)	0.74 (0.23 to 1.24)	0.38 (-0.54 to 1.30)
	DTG	77.1 (74.0 to 80.1)	0.65 (-0.03 to 1.3)	0.68 (0.07 to 1.30)	0.03 (-0.98 to 1.00)
	RAL	78.9 (76.7 to 81.0)	0.69 (0.32 to 1.1)	1.11 (0.74 to 1.50)	0.43 (-0.18 to 1.00)

ART=antiretroviral therapy, CI=confidence interval, DTG=dolutegravir, NNRTI: non-nucleoside reverse transcriptase inhibitor, PI=protease inhibitor, RAL=raltegravir


(a)
BMI at init (kg/m2)
SQRT CD4 at init
(b)
Pre−ART rate BMI gain (kg/m2/year)
SQRT CD4 at init
(c)
Post−ART rate of BMI gain (kg/m2/year)
SQRT CD4 at init
(d)
Post−ART change in rate of BMI gain (kg/m2/year)
SQRT CD4 at init
(e)
BMI at init (d−kg/m2)
Age at init (years)
(f)
Pre−ART rate BMI gain (d−kg/m2/year)
Age at init (years)
(g)
Post−ART rate of BMI gain (d−kg/m2/year)
Age at init (years)
(h)
Post−ART change in rate of BMI gain (d−kg/m2/year)
Age at init (years)
(i)
BMI at init (d−kg/m2)
VL at init (log10)
(j)
Pre−ART rate BMI gain (d−kg/m2/year)
VL at init (log10)
(k)
Post−ART rate of BMI gain (d−kg/m2/year)
VL at init (log10)
(l)
Post−ART change in rate of BMI gain (d−kg/m2/year)
VL at init (log10)