Association between contemporary antiretrovirals and increase in body mass index: results from the prospective RESPOND Cohort Study

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Research in context

Evidence before this study

We used Pubmed to search for observational and randomised studies on weight gain amongst people living with HIV who were receiving contemporary antiretrovirals (ARVs), focussing on integrase inhibitors and tenofovir alafenamide (TAF). Search terms used were “tenofovir alafenamide”; “TAF”; “dolutegravir”; “DTG”, “raltegravir”, “RAL”, “integrase inhibitors”, “INSTIs” AND (“weight” OR “BMI”). Searches were limited to publication before 01 March 2020. Abstracts from proceedings at conferences over the last 3 years and additional articles suggested by Study Group members were also included.

Evidence collated suggested that there is an association between use of TAF, DTG and weight gain. However, studies have generally been small, national and assessed regimens in which TAF and DTG were used concomitantly rather than assessing the individual effects of these ARVs. Further, comparator regimens have often contained ARVs with known impact on BMI.

Added value of this study

We investigated factors associated with weight gain amongst people living with HIV in the RESPOND cohort. RESPOND is a large multinational heterogeneous cohort with data from real life settings and with focus on newer drugs. This allowed enough power in the study to detect associations between use of specific ARVs and BMI increase compared to lamivudine (3TC) (a weight neutral control ARV), rather than regimens and BMI increase. We were further able to assess these associations in several sensitivity analyses including in those who were ART-naïve, in those with a high pre-ART CD4 count and in those with high pre-ARV BMI. Previous explanations for associations seen include the comparator drug being a weight suppressive drug. However, by comparing to a weight neutral drug, 3TC, those explanations do not hold.

Implications of all the available evidence

In line with smaller, generally national studies, we found use of DTG, RAL and TAF were associated with a clinically meaningful >7% BMI increase when comparing pre-ARV BMI to current BMI. By comparing to a weight neutral drug, 3TC, previous explanations for these associations do not hold.

People living with HIV and clinicians prescribing ARVs should be aware of these associations before making the decision to start either DTG or TAF. Further research on the consequences of ARV-related weight gain is planned.

Abstract

Background

Weight gain has been related to use of tenofovir alafenamide (TAF), rilpivirine, protease-inhibitors and integrase inhibitors (INSTIs), including dolutegravir (DTG) but independent effects of individual antiretroviral drugs (ARVs) on weight gain are not fully understood. We investigated associations between pre-specified clinically significant increase (>7%) in body mass index (BMI) and contemporary ARV use.

Methods

For all ARVs received at/after RESPOND entry, changes from pre-ARV BMI levels (baseline) were considered at each BMI measured whilst receiving the ARV. Logistic regression was used to identify individual ARVs that were associated with first occurrence of >7% BMI increase from pre-ARV BMI. Analyses were adjusted for time on ARVs, pre-ARV BMI, demographics, geographical region, CD4 count, viral load, smoking status, and AIDS at baseline.

Results

14703 people were included, of whom 7863 (54%) had >7% BMI increase. At baseline, 20% were ART-naïve, 39% on INSTIs, 74% male and 75% of white ethnicity. Compared to lamivudine (3TC), use of DTG (Odds ratio (OR): 1.27 [confidence interval (CI): 1.17, 1.38]), raltegravir (RAL) (1.37 [1.20, 1.56]) and TAF (1.38 [1.22, 1.35]) were significantly associated with >7% BMI increase, as was low pre-ARV BMI (2.10 [1.91, 2.31] underweight vs. healthy weight) and black ethnicity (1.61 [1.47, 1.76] vs. white ethnicity). Higher CD4 count was associated with a reduced risk of BMI increase (0.97 [0.96, 0.98] per 100 cells higher).

ORs for DTG and TAF remained independently associated with >7% BMI increase when received individually (DTG without TAF: 1.21 [1.19, 1.32], TAF without DTG: (1.21 [1.19, 1.32]) vs. 3TC) but were higher when used concomitantly (DTG: 1.79 [1.52, 2.11], TAF: 1.70 [1.44, 2.01] vs. 3TC).

Interpretation

Compared to 3TC use of DTG, RAL and TAF, and black ethnicity were associated with significant BMI increase independent of pre-ARV BMI, CD4 count and time on ARVs. Clinicians and PLWH should be aware of the associations seen between DTG, TAF, RAL and weight gain, particularly given the potential consequences of weight gain, such as insulin resistance, dyslipidaemia and hypertension.

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Association between newer antiretrovirals and increase in body mass index in RESPOND

Introduction

Weight gain in people living with HIV (PLWH) has been associated with exposure to integrase strand transfer inhibitors (INSTIs), particularly dolutegravir (DTG), in both observational studies (1-7), and in randomised controlled trials (8-13). There is evidence to suggest that amongst those receiving INSTIs, weight gain is more prevalent in women (2, 4, 6, 7) and amongst those of black ethnicity (6, 7, 14). There is also emerging evidence suggesting that the nucleoside-analogue reverse transcriptase inhibitor (NRTI) tenofovir alafenamide (TAF) may have an additional effect on weight gain, particularly when co-administered with DTG (8, 15-20)).

Weight gain, particularly in PLWH starting antiretroviral treatment (ART), can reflect a general improvement in overall health with reduced catabolic and inflammatory activity and improved appetite also known as 'return to health'. However, recent results suggest the impact of antiretroviral therapy (ART) on body weight differs according to the specific regimen used; the ADVANCE trial showed that PLWH on TAF plus DTG had greater increase in trunk or limb fat mass compared to those receiving other regimens (9) and metabolic syndromes were also more prevalent in those receiving DTG plus TAF. However, there was no evidence of incidental diabetes amongst those receiving DTG in the NAMSAL trial (12).

Given DTG and TAF are recommended antiretrovirals (ARVs) in first-line regimens (21-23), it is particularly important to disentangle the effects of these individual ARVs on weight gain. This is difficult as both ARVs can be prescribed concomitantly and hence it is unclear which ARV, if any, has the largest effect on weight gain. Further, the observational studies that have investigated this question have to date been small, with short follow-up, a low number of people on INSTIs and the comparator commonly an ARV with known negative impact on weight such as efavirenz (EFV) (1-7). Weight gain has generally been assessed from a pre-regimen or current value and hence it has not been possible to identify associations between individual ARVs and weight gain.

Whilst a standardised definition of weight gain does not exist in the HIV field, a >7% increase is standardised in research looking at for example, impact of anti-psychotics on weight gain (24-26). Using this standardised definition of >7% increase in BMI, we investigated factors associated with weight gain amongst people in the RESPOND cohort, focussing particularly on contemporary ARVs such as DTG and TAF.

Methods

Study design and participants

The International Cohort Consortium of Infectious Diseases (RESPOND) is a prospective, multi-cohort collaboration, including data from 17 well-established cohorts and over 29,000 PLWH. PLWH under

prospective follow up from 2012 and older than 18 years were eligible for inclusion. Each cohort contributed a pre-defined minimum number of participants related to the size of the specific cohort (with a minimum of 1000 participants). Participants were required to have a CD4 count and HIV viral load (VL) measurement in the 12 months prior to or within 3 months after baseline. A comprehensive description of RESPOND has been previously published (27).
Cohorts were included in these analyses if height and weight had been recorded for >80% of their RESPOND enrolled participants, resulting in inclusion of 9/17 cohorts. For all those included in the analyses, baseline was defined as the date of the last BMI measurement recorded within 12 months prior to the earliest ARV start date of the regimen being received at RESPOND entry (27). A dataset was created with multiple rows for each person, such that firstly each BMI measurement recorded after baseline on that drug formed a separate row and secondly each ARV being received at each BMI measurement also formed a separate row. Hence each row of data contained unique information on a specific ARV drug and on-ARV BMI. All rows of data also had information on the BMI date and measurement before start of the ARV drug (within 12 months) and data on the covariates described below. This allowed us to determine change in BMI from pre-ARV BMI (pre-individual antiretroviral BMI) to on-ARV BMI for all individual drugs being received using all relevant BMI measurements (Appendix, Page 1, Table A1). Total exposure time of each ARV was calculated at each BMI measurement and included in the model as a potential confounder.

Outcomes and statistical analysis
In the primary analysis, weight gain was defined as a >7% increase from pre-ARV BMI to on-ARV BMI (24-26). Logistic regression, using generalised estimating equations to account for within-person and current BMI measure clustering and weighted according to number of drugs being received was used to identify individual ARVs (categorised according to whether or not the ARV was being received at the time of the BMI measurement) that were associated with first occurrence of >7% BMI increase. Lamivudine (3TC) was chosen as the reference ARV against which other ARVs were compared, as it was commonly received and has not previously been associated with weight changes. Whilst 3TC is commonly prescribed with abacavir (ABC) as part of a single tablet regimen, in RESPOND, 39% of regimens including 3TC *did not* include ABC and further, sensitivity analyses were performed in which all use of 3TC with ABC was removed (and hence the comparator for drugs was 3TC only when received without ABC) (Appendix, Page 2.

We only considered rows of data for which the on-ARV BMI date was before December 2018 (administrative censoring date). Analyses were adjusted for the following potential confounders: total exposure time to ARV at time of current BMI measure, pre-ARV BMI, demographics, geographical region, baseline CD4 count, baseline viral load, baseline smoking status, non-cancer AIDS events and AIDS-related cancers at baseline. Pre-specified interactions were assessed between DTG/TAF and CD4 count, ethnicity and pre-ARV BMI.

Given the focus on DTG and TAF, analyses were also stratified according to whether people were receiving DTG with TAF, DTG without TAF and TAF without DTG. In sensitivity analyses, only the first BMI in each 6-month period was taken into consideration. Separate analyses were conducted for people who were ART-naïve at baseline (treatment changes amongst this subset were still included). These analyses were adjusted for the same factors as the primary analysis with the exception that CD4 count was fitted as pre-ART CD4 count rather than CD4 count at baseline. Amongst this group of ART-naïve people, analyses were also restricted to those with pre-ART CD4 counts >350 cells/mm^3. This was under the assumption that these individuals were relatively healthy individuals and hence weight gain was not to the same extent reflecting a 'return to health' effect as could be the case in those with severe immunodeficiency. Of note, in these analyses we have assumed 'return to health' as being classified as normal weight in the general HIV-negative population. To assess factors associated with a potential return to health, further analyses were restricted to those with a pre-ARV BMI <23 (chosen as the threshold as a 7% increase for those with BMI>23 would result in them being in the 'overweight' category)
Finally, for each individual, the maximum percentage change in BMI (from pre-ARV BMI to on-ARV BMI) was calculated. The 95^{th} percentile of this change was used to define the top 5% of weight gainers, i.e. those with a BMI increase of >30%; factors associated with this outcome were investigated.

All analyses were performed using SAS version 9.4 (Statistical Analysis Software, Cary, NC, USA).

Role of the funding source
As per RESPOND governance (https://chip.dk/Portals/0/files/RESPOND/Study%20documents/RESPOND%20governance%20and%20procedures_v6_2020SEP30.pdf?ver=2020-10-20-163958-080), funders of the study were also academic collaborators, and employees/associates could be included as co-authors if they met the ICJME criteria. However, neither funding bodies, nor employees/associates hereof, were in a position to in any way veto study design, data collection, data analysis, data interpretation, and/or writing of the manuscript.
Ethics approval for RESPOND is the responsibility of each participating site/cohort. This includes ensuring that all necessary documents and approvals by Ethics Committee (IRB or IC) are obtained according to local/national regulations before initiating study-related activities and in case of any future amendments to the study protocol. Participants consent to share data with RESPOND according to local requirements. Enrolled participants are pseudonymized by assigning a unique identifier by the participating cohort before data transfer. According to their national or local requirements, all cohorts in RESPOND have the approval to share data with RESPOND. Data are stored on secure servers at the RESPOND coordinating centre located within the Danish Capital Region of Copenhagen, in accordance with current legislation and under approval by The Danish Data Protection Agency (approval no. 2012-58-0004, j.nr.: RH-2018-15, 26/1/2018), currently under the EU's General Data Protection Regulation (EU) 2016/679.

Results

Of the 19,176 people from cohorts with routine height and weight measurements, 14,703 (76.7%) were eligible for these analyses and contributed at least one row of data (Appendix, Figure A1,). Compared to those excluded (N= 4473), people included in the analyses were more likely to be from Western Europe (60.0% vs. 39.7%, p<0.0001) and a higher proportion were receiving an INSTI-based regimen at baseline compared to those excluded (39.2% vs. 28.4%, p<0.0001).

Of the 14,703 participants, 7868 (53.5%) experienced a >7% BMI increase on at least one occasion at median 18.4 (interquartile range: 7.8, 40.4) months after start of ARV.

Table 1 shows characteristics at baseline for those included in these analyses. At baseline, those with a BMI increase of >7% were more likely to be female (59.3% vs. 40.8%), of black ethnicity (64.1% vs. 35.9%) and had lower CD4 counts (median 398: 244, 600] vs. 493 [331, 700] cells/mm^3). Table 2 shows average one-year BMI change and maximum BMI change from pre-ARV BMI.

Factors associated with a 7% increase in BMI are shown in Table 3. In multivariable analyses, lower pre-ARV BMI (odds ratio [OR]: 2.10 [95% confidence interval (CI): 1.91, 2.31] for BMI <18.5 vs. BMI between 18.5 - 24.9), shorter duration on ARV (1.64 (1.50, 1.79) comparing 3-6 months to greater than 3 years),being of black ethnicity (1.61 (1.47, 1.76) vs. white ethnicity) and use of DTG (1.27 [1.17, 1.38]), etravirine (ETR) (1.31 [1.08, 1.59]), raltegravir (RAL) (1.37 (1.20, 1.56)) and TAF (1.38 (1.22, 1.55)) compared to 3TC were associated with an increased risk of >7% BMI increase. Use of several ARVs including tenofovir disoproxil (TDF) and ABC were significantly associated with a reduced risk of BMI increase relative to 3TC. People living in Western Europe and those with higher CD4 counts (0.97 [0.96, 0.98] per 100 cell increase) at baseline were less likely to have a BMI increase of >7%. The association between female sex and >7% BMI increase was not statistically significant (1.06 (0.99, 1.14)). We found no evidence that the effect of DTG or TAF on weight gained differed according to CD4 count, ethnicity or pre-ARV BMI (p-values for interaction 0.54, 0.19, 0.72, respectively). Analyses were repeated using time-updated variables for age, CD4 count, viral load and smoking status; results remained similar to above (data not shown).

A summary of the crude percentages of weight change over time for the ARVs found to be significantly associated with BMI increase (along with the reference ARV, 3TC) are shown in Figure 1. In this descriptive analysis, there is a steady increase in those with >7% increase in weight over time, up until around 2 years since start of the ARV. After this point, the percentage of people with >7% BMI increase is lower than the previous period for all ARVs considered. At 3 months since start of the ARV, 9% of those receiving 3TC had experienced >7% BMI increase, compared to 16% of those on RAL, 13% of those on DTG and 10% of those on TAF. After 3 months, those on 3TC, DTG and TAF appeared to have similar patterns of weight gain, i.e. around 17% with >7% BMI increase at one year after starting the ARV, whilst those on RAL appeared to be more likely to experience >7% weight gain at all time points.

The multivariable model used for the primary analysis was stratified according to whether or not DTG and TAF were used together (amongst those receiving DTG or TAF, 57% used DTG without TAF, 23% used DTG and TAF together and 20% used TAF without DTG). The OR for DTG compared to 3TC was lower but still significant when DTG was used without TAF (DTG OR: 1.21 [1.19, 1.32]) than it was for when DTG was used with TAF (DTG OR 1.79 [1.52, 2.11]. Similarly, the OR for TAF compared to 3TC was lower when used without DTG (TAF OR: 1.33 [1.15, 1.53]) than it was when used with DTG (TAF OR: 1.70 [1.44, 2.01]). In instances in which DTG was not used with TAF, TDF was used concomitantly with DTG in 25% of regimens. After removing those using DTG with TAF or TDF, DTG was still significantly associated with an increased risk of >7% BMI increase (1.24 (1.13, 1.37)). Results from sensitivity analyses in which only the first BMI within a 6-month period was included remained similar to the primary analyses (data not shown).

In analyses restricted to ART-naïve people (N=2990), 49% (N=1492) experienced a >7% BMI increase on at least one occasion. Factors associated with BMI increase remained broadly similar to those seen in the primary analysis. In adjusted analyses, whilst RAL was not significantly associated with BMI increase amongst ART-naïve people (1.07 (0.79, 1.43) vs. 3TC), DTG and TAF both remained significant (OR for DTG: 1.39 (1.22, 1.59), TAF: 1.32 (1.07, 1.63) vs. 3TC). Higher pre-ART CD4 count was associated with a reduced risk of BMI increase (0.96 (0.94, 0.97) per 50 cell/mm^3 increase).

The association between pre-ART CD4 count and >7% BMI increase was investigated further. Amongst ART-naïve people with CD4 counts $\leq$100 (n=297), 101-250 (n=588), 251-350 (n=601) and >350 (n=1476) cells/mm^3, the percentage of people with a >7% BMI increase was 77%, 59%, 45% and 42% respectively. Adjusted analyses restricted to naïve people with pre-ART CD4 counts >350 cells/mm^3 showed a significant association between DTG and >7% BMI increase (1.29 (1.08, 1.54)), and a similar OR for TAF ((1.25 (0.93, 1.70)) compared to 3TC.
Analyses restricted to naive people with BMI>20 (N=2580) also showed a significant association between use of DTG (1.44 (1.23, 1.68) vs. 3TC), TAF (1.38 (1.09, 1.74) vs. 3TC) and >7% BMI increase. In order to investigate factors associated with a potential return to health upon ART initiation, analyses were restricted to naïve people with pre-ARV BMI of <23 (N=1584, of whom 718 (45.3%) had a >7% BMI increase on at least one occasion). Whilst power was limited, in adjusted analyses, compared to 3TC, use of DTG (1.48 [1.20, 1.83]) and TAF (1.64 [1.16, 2.32]) remained associated with a >7% BMI increase, with higher ORs than those seen in the main analysis.

The 95th centile of the maximum BMI increase per person was 30%. Of the 749 people who experienced >30% BMI increase, 166 (22.2%) had a pre-ARV BMI of <18.5 (underweight). Of these, the corresponding BMI to the 30% increase was between 18.5-24.9 (healthy weight) for 50.6%, between 25 and 29.9 (overweight) for 38.6% and 30 or over (obese) for 9.6% of people.

Univariate and multivariable associations between factors of interest and a >30% increase in BMI are shown in Table 4. Longer duration of receiving ARVs and lower pre-ARV BMI were associated with an increased risk of >30% increase in BMI. Compared to 3TC, both DTG and TAF remained independently associated with >30% increase in BMI (DTG: 2.10 (1.62, 2.72), TAF: 2.16 (1.40, 3.33)). Females, those of black ethnicity, those with lower CD4 counts and those of heterosexual risk group, or history of injecting drug use risk group were also at an increased risk of BMI >30% increase. Multivariable odds ratios for DTG and TAF from all the above analyses are shown in Figure 2.

Discussion

In the large heterogeneous RESPOND cohort consortium, use of DTG, RAL and TAF (compared to 3TC), were independently associated with a BMI increase of >7% from pre-ARV BMI to on-ARV BMI. In analyses restricted to use of DTG without TAF, and TAF without DTG, both ARVs remained significantly associated with BMI increase of >7%. Similar results were seen amongst those who were treatment naïve at the baseline, those with high CD4 counts prior to starting treatment, those with low pre-ARV BMIs and when the outcome was extreme weight gain defined as BMI increase of >30% from pre-ARV BMI. In line with a recent study by Sax et al, cobicistat-boosted elvitegravir, and cobicistat as a booster were not associated with >7% BMI increase (28). There was an association seen between ETR and >7% BMI increase, but given the small sample size/wide confidence interval, this result should be interpreted with caution (Appendix, page 4).

Our results are from a large international cohort and are in line with smaller, generally national previous studies which also show an association between DTG and weight gain, albeit with definitions of weight gain that differ between studies (1-4, 6-8, 10-13, 20). However, whilst other studies have alluded to weight gain being considerably higher amongst those receiving TAF with/without DTG (8, 18, 29) we have been able to show that use of both DTG and TAF are independently associated with BMI increase compared to 3TC. Further, as expected given the independent additive effects of DTG and TAF, the magnitude of the association is greater for both ARVs when taken together than when either ARV is taken alone. We have further shown that the reason for the lower, albeit significant magnitude of effect seen amongst those using DTG without TAF is not explained by DTG being used with TDF instead (shown to suppress the accumulation of weight (30)). In analyses in which DTG was not used with either TAF or TDF, an association between DTG and BMI increase was still evident.

In the primary analysis, BMI increase of >7% was most likely to occur in the first three years of receiving a specific ARV (although may have continued to increase beyond 7% thereafter) and amongst people with low pre-ARV BMI. People with low-CD4 counts prior to starting treatment were also more likely to have a BMI increase compared to those with CD4 counts >350, as seen in other studies (3, 5, 9) This suggests that for a subset of people, a BMI increase may well reflect a 'return to health' or return to social norm effect rather than a negative effect of weight gain. However, 'return

to health' is unlikely to be the full explanation for the associations seen, indicated by the fact that only use of certain ARVs were independently associated with this BMI increase.

Amongst those with higher CD4 counts at start of treatment, the association between TAF and BMI increase did not reach significance, potentially due to a lack of power; only 10% of those in the primary analysis were included in this sub-analysis. We did however continue to detect a significant association between use of DTG and BMI increase. Though we were underpowered to further restrict this group to those with low viral loads, the associations seen do underline that BMI increase amongst those receiving DTG and potentially TAF is not limited to those who are returning to healthy weight.

Compared to 3TC, several ARVs had a decreased risk of BMI increase. These included older drugs such as didanosine and zidovudine which are no longer commonly used (evident by the larger confidence intervals seen), as well as ABC which has been associated with nausea and loss of appetite though other mechanisms may also be at play, and TDF which has known suppressive weight effects (30). INSTIs are thought to cause less adverse effects and a better gastrointestinal tolerance with contemporary ARVs such as TAF and DTG has been suggested as a possible mechanism of weight increase, but in the ADVANCE study a better 96 week gastrointestinal tolerability did not explain the association (9). The finding of a stronger impact in black women might further suggest effects related to differences in pharmacogenetics and changes in several metabolic pathways may also contribute to the observed weight changes with TAF (9). Surprisingly, FTC also had a decreased risk of BMI increase compared to 3TC. It is possible that this was a consequence of unmeasured confounding, or the effect of FTC was modified by other drugs in the regimen (e.g. DTG was more commonly prescribed with 3TC [19%] than with FTC [8%]).

As seen in other studies (6, 7, 14), we found black ethnicity to be significantly associated with BMI increase. DTG has been found to be associated with weight gain in trials conducted in sub-Saharan Africa (9, 12) which consist of a predominately black population. Whilst we did not find a significant interaction between ethnicity and DTG or TAF, it is likely that we did not have enough power to detect such an interaction – only 10% RESPOND participants were of black ethnicity. Female sex has been well documented to increase the risk of weight gain amongst those receiving INSTIs (2, 4, 6, 7). Whilst it is possible that we had inadequate power to detect significance between sex and BMI increases (only a quarter of those included were female and even fewer were both female and of black African origin), we are not able to say definitively why we did not find a strong effect between sex and weight gain as seen in some other studies.

A higher risk of >30% BMI increase was associated with receiving ARVs for at least 3 years versus shorter durations, in contrast to the primary analysis. This is not surprising as to have a BMI increase of >30% is likely to take considerable time. This also suggests that the magnitude of BMI gain continues to increase beyond the 7% increase outcome in the primary analysis and even after 3

years of receiving the ARV. This result is in agreement with the absence of reaching a *plateau* in weight increase in the ADVANCE study for up to 144 weeks, particularly in women (9).

In addition to our primary outcome in which follow up ended if a >7% BMI increase occurred, we conducted a more descriptive analysis to further investigate the nature of the temporal BMI changes which suggested that the chances of experiencing >7% BMI increase rose steadily in the first 2 years since start of 3TC, TAF, DTG and RAL. After this point, a lower percentage of people on these ARVs experienced such increase. BMI increases were more evident in the first three months since start of DTG compared to those receiving 3TC but appeared similar thereafter. A higher percentage of people receiving RAL experienced a BMI increase of >7% at all time points compared to those receiving 3TC. Of note, these analyses were descriptive and not adjusted for potential confounding factors and in particular pre-ARV BMI which is strongly associated with the outcome. To further assess these associations, a trajectories analysis with spline points would be required. Whilst such an analysis is beyond the scope of this manuscript, the descriptive analysis we have performed does give a valuable insight to the nature of the association between time on ARV and BMI increase, in addition to that already seen in the primary analysis. Our choice of a dichotomised endpoint further has the advantage of ease of comparison with other studies, is easily interpretable for individual ARVs and is a standardised definition of weight gain in other fields.

Limitations of this study are in line with those inherent with observational studies. Despite adjusting for a wide range of baseline characteristics, residual confounding cannot be ruled out. Factors known to influence weight such as genetics, diet and exercise, menopausal status and other indicators of weight such as non-ART medication are not routinely collected in RESPOND. Weight gain is also part of the ageing process and whilst we did not see this in our analysis, we may have had inadequate power to assess the impact of ageing due to the relatively young median age (45 years) We have not been able to assess the effect of Bictegravir as the dataset was censored in 2018. There is also the possibility that the associations seen may potentially be a consequence of confounding by indication; DTG is recommended as part of first-line regimens and INSTIs in general may be more likely to be prescribed to those with low CD4 counts. We were not able to directly interpret ‘time on ARV’ for each ARV due to the structure of the dataset, but all models were adjusted for this variable. Further, we performed descriptive analyses in which weight changes according to time since start of ARV were shown for specific ARVs. Finally, we have assumed that combined use of ARVs was not associated with modifying the effect seen of the ARV under question; we appreciate that this assumption may not hold in all cases (page 1, appendix).

However, there are also several strengths of this study. We were able to assess associations of individual drugs and weight gain by focussing on specific pre-ARV BMIs rather than BMIs prior to a

regimen of interest. For DTG and TAF, we were able to show independent associations between each ARV and BMI increase. RESPOND is a large heterogeneous cohort with focus on newer drugs, allowing enough power to detect associations between specific ARVs and BMI increase for these drugs compared to a weight neutral ARV. Data provided to RESPOND is from real-life settings, allowing generalisability across regions.

Conclusion

In conclusion, we identified a significant and consistent association between exposure to DTG, TAF, RAL and BMI increase. TAF is increasingly favoured over TDF due to a presumed lower likelihood of adverse events and is now often prescribed with DTG. We have shown that both TAF and DTG are independently associated with BMI increase (and the magnitude of the association is greater for both ARVs when used concomitantly). This is true for several sub-populations including those with low pre-ARV BMIs, those ART-naïve and those with high CD4 counts. Weight gain is associated with potential consequences such as insulin resistance, dyslipidaemia and hypertension. These in turn can result in an increased risk of cardiovascular disease. Further analyses to look at these outcomes in relation to weight gain are planned. When making the decision to start new ARVs, clinicians and PLWH should be aware of the potential weight gain associated with DTG and TAF particularly in the first three years, and also of the more extreme weight gain seen in a subset of people beyond three years. The accumulation of weight gain over time and the impact on weight once DTG and TAF are discontinued needs to be investigated further.

Table 1: Characteristics at baseline[1] of the 14703 people included in the analyses

Variable		>7% weight increase N (%)	
		No	Yes
People included		6835 (46.5%)	7868 (53.5%)
RESPOND cohort entry date	Median (IQR)	2013 (2012, 2015)	2012 (2012, 2015)
Age (years)	Median (IQR)	45 (37, 53)	42 (35, 49)
Sex N (%)	Male	5305 (48.5%)	5643 (51.5%)
	Female	1530 (40.8%)	2225 (59.3%)
Ethnicity N (%)	White	5293 (48.2%)	5691 (51.8%)
	Black	508 (35.9%)	906 (64.1%)
	Other	207 (41.2%)	295 (58.8%)
	Unknown/missing[2]	827 (45.9%)	976 (54.1%)
Risk group N (%)	MSM	3318 (49.7%)	3357 (50.3%)
	IDU	883 (44.5%)	1100 (55.5%)
	Heterosexual	2150 (42.6%)	2893 (57.4%)
	Other	215 (46.1%)	251 (53.9%)
	Unknown/missing	269 (50.2%)	267 (49.8%)
CD4 count (cells/mm^3)	Median (IQR)	493 (331, 700)	398 (244, 600)
Viral load (copies/mL)	Median (IQR)	49 (20, 16487)	313 (39, 50043)
Smoking status N (%)	Never	2537 (49.8%)	2557 (50.2%)
	Current	2440 (46.3%)	2829 (53.7%)
	Previous	717 (51.0%)	689 (49.0%)
	Unknown	1141 (38.9%)	1793 (61.1%)
Region[3]	W Europe	3793 (43.0%)	5029 (57.0%)
	S Europe	1263 (55.1%)	1028 (44.9%)
	N Europe/Australia	919 (46.8%)	1045 (53.2%)
	E and EC Europe	860 (52.9%)	766 (47.1%)
ART naïve at RESPOND cohort entry	No	5317 (45.4%)	6396 (54.6%)
	Yes	1518 (50.8%)	1472 (49.2%)
BMI prior to first ARV included in the analysis	Median (IQR)	23.9 (21.8, 26.4)	23.0 (20.8, 25.4)
'3rd' drug in ART regimen	NNRTI	1838 (47.5%)	2032 (52.5%)
	PI	1325 (42.6%)	1783 (57.4%)
	INSTI	2809 (48.7%)	2960 (51.3%)
	Other[4]	863 (44.1%)	1093 (55.9%)

AIDS-defining malignancies	No	6578 (46.5%)	7570 (53.5%)
	Yes	257 (46.3%)	298 (53.7%)
AIDS non-malignancies	No	5712 (47.8%)	6240 (52.2%)
	Yes	1123 (40.8%)	1628 (59.2%)

[1]Baseline defined as last BMI measurement within 12 months before start of first ARV being received at RESPOND entry or after RESPOND entry if not on ART at RESPOND entry

[2]Several cohorts in RESPOND are prohibited by national law to collect information on ethnicity

[3]W Europe=Western Europe (Austria, Belgium, France, Germany, Luxembourg, Switzerland); S Europe =Southern Europe (Argentina, Greece, Israel, Italy, Portugal, Spain); N Europe/Aust= Northern Europe and Australia (Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom, Australia); E and EC Europe= Eastern and East Central Europe (Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine. The nine cohorts included in the analysis were: Austrian HIV Cohort Study (AHIVCOS), The Australian HIV Observational Database (AHOD), AIDS Therapy Evaluation in the Netherlands Cohort (ATHENA), EuroSIDA Cohort, Italian Cohort Naive Antiretrovirals (ICONA), Nice HIV Cohort, Swiss HIV Cohort Study (SHCS), San Raffaele Scientific Institute, CHU Saint-Pierre.

Further details on RESPOND can be found here: (27)

[4] 46% of those on 'other' regimens did not have an NRTI in their regimen.

NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; INSTI: Integrase Strand Transfer inhibitors; MSM: Men having sex with men; IDU: Injecting drug users

Table 2: Median Pre-ARV BMI, change in BMI after one year from ARV start date, and change in BMI after three years from ARV start date

ARV	N ever received ARV	Pre-ARV BMI	Median (inter-quartile range) percentage change from pre-ARV BMI to BMI one year after ARV start[1] (%)	Median (inter-quartile range) percentage change from pre-ARV BMI to BMI 3 years after ARV start[1] (%)
NRTIs				
3TC	5234	23.2 (21.0, 25.9)	1.6 (-1.7, 5.8)%	2.5 (-2.1, 8.2)%
ABC	4377	23.3 (21.2, 25.9)	1.4 (-1.8, 5.0)%	1.6 (-2.7, 7.0)%
DDI	410	22.8 (20.8, 25.1)	0.0 (-3.0, 4.1)%	1.1 (-2.9, 6.0)%
FTC	8164	23.5 (21.3, 26.2)	1.4 (-2.0, 5.4)%	2.0 (-2.0, 7.0)%
TAF	3955	24.2 (21.7, 27.2)	2.2 (-0.9, 5.8)%	*Sample size <10*
TDF	7642	23.5 (21.3, 26.0)	1.2 (-2.3, 5.3)%	1.8 (-2.4, 7.1)%
ZDV	1185	23.1 (21.0, 25.6)	0.0 (-2.5, 4.8)%	1.9 (-1.7, 6.6)%
PIs				
ATV	2283	23.5 (21.2, 26.2)	1.9 (-1.4, 5.6)%	1.9 (-1.4, 5.6)%
DRV	3043	23.5 (21.2, 26.4)	1.7 (-1.8, 5.8)%	2.3 (-2.3, 7.0)%
FPV	325	23.6 (21.0, 26.0)	2.7 (-1.1, 7.0)%	1.6 (-2.5, 8.3)%
LPV	1560	23.1 (21.0, 25.5)	1.0 (-2.7, 5.4)%	1.4 (-3.3, 7.6)%
RTV (any)	4516	23.3 (21.1, 26.1)	1.8 (-1.7, 6.1)%	2.5 (-1.7, 7.7)%
NRTIs				
EFV	2418	23.5 (21.6, 25.9)	0.0 (-2.7, 4.1)%	1.4 (-2.7, 5.8)%
ETR	518	23.7 (21.2, 26.5)	1.4 (-1.7, 6.0)%	2.5 (-2.1, 7.6)%
NVP	1334	23.4 (21.4, 26.2)	0.9 (-1.8, 4.3)%	2.2 (-2.0, 6.5)%
RPV	2041	24.0 (21.8, 26.8)	1.5 (-1.8, 4.5)%	1.8 (-2.1, 6.7)%
INSTIs				
DTG	4418	23.7 (21.5, 26.6)	1.9 (-1.5, 6.0)%	2.4 (-1.9, 7.5)%
EVG/c	1604	24.0 (21.6. 26.8)	1.4 (-1.6, 5.0)%	2.8 (-0.8, 8.0)%
RAL	1473	23.8 (21.2, 26.7)	1.8 (-1.7, 6.3)%	2.1 (-2.2, 7.5)%
Other				
COBI	2055	24.0 (21.6, 26.8)	1.4 (-1.9, 5.0)%	2.9 (-0.4, 8.0)%

3TC: lamivudine, ABC: abacavir, DDI: didanosine, FTC: emtricitabine, TAF: tenofovir alafenamide, TDF: tenofovir disoproxil fumerate, ZDV: zidovudine, ATV: atazanavir, DRV: darunavir, FPV: fosamprenavir, LPV: lopinavir, RTV: ritonavir (any dose), EFV: efavirenz, ETV: etravirine, NVP: nevirapine, RPV: rilpivirine, DTG: dolutegravir, EVG/c: cobicistat boosted elvitegravir , RAL: raltegravir, COBI: cobicistat

[1] For people who did experience >7% BMI increase, the one year/three year change in may have occurred after date of >7% BMI increase. Number under follow up differs from that in the 'N ever received column'; unless stated otherwise, all ARVs included in the table had at least 100 events

Table 3: Association between variables of interest and a 7% increase in BMI from pre-drug BMI

N=14703: 7868 (53.5%) experienced >7% BMI increase

Variable		Univariate analyses		Multivariable analyses	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Time on ARV	0 to 3 months	0.62 (0.52, 0.74)	<0.0001	0.97 (0.88, 1.06)	<0.0001
	3 to 6 months	1.88 (1.73, 2.04)		1.64 (1.50, 1.79)	
	6 to 12 months	1.84 (1.72, 1.98)		1.66 (1.54, 1.79)	
	1 to 2 years	1.57 (1.46, 1.67)		1.45 (1.35, 1.56)	
	2 to 3 years	1.29 (1.19, 1.39)		1.23 (1.13, 1.33)	
	>3 years	1 (ref)		1 (ref)	
Pre-ARV BMI	Underweight (<18.5)	2.25 (2.06, 2.47)	<0.0001	2.10 (1.91, 2.31)	<0.0001
	Healthy (18.5 - 24.9)	1 (ref)		1 (ref)	
	Overweight (25 – 29.9)	0.73 (0.69, 0.78)		0.73 (0.69, 0.78)	
	Obese (≥30)	0.61 (0.55, 0.69)		0.58 (0.52, 0.65)	
ARV	3TC	1 (ref)	<0.0001	1 (ref)	<0.0001
	ABC	0.88 (0.84, 0.93)		0.94 (0.89, 0.99)	
	DDI	0.83 (0.67, 1.02)		0.71 (0.58, 0.89)	
	FTC	0.87 (0.82, 0.93)		0.92 (0.87, 0.99)	
	TAF	1.29 (1.15, 1.44)		1.38 (1.22, 1.55)	
	TDF	0.82 (0.78, 0.87)		0.86 (0.81, 0.91)	
	ZDV	0.96 (0.87, 1.06)		0.89 (0.81, 0.99)	
	ATV	0.98 (0.90, 1.06)		1.00 (0.92, 1.09)	
	DRV	1.03 (0.94, 1.12)		1.05 (0.96, 1.15)	
	FPV	1.11 (0.93, 1.33)		1.12 (0.93, 1.35)	
	LPV	0.92 (0.84, 1.01)		0.84 (0.77, 0.93)	
	RTV (any)	1.00 (0.93, 1.06)		1.02 (0.95, 1.08)	
	EFV	0.69 (0.64, 0.75)		0.74 (0.68, 0.80)	
	ETR	1.23 (1.02, 1.49)		1.31 (1.08, 1.59)	
	NVP	0.81 (0.73, 0.90)		0.92 (0.82, 1.02)	

	RPV	0.92 (0.81, 1.04)		1.01 (0.89, 1.15)	
	DTG	1.18 (1.09, 1.28)		1.27 (1.17, 1.38)	
	EVG/c	1.00 (0.88, 1.14)		1.01 (0.88, 1.15)	
	RAL	1.30 (1.14, 1.48)		1.37 (1.20, 1.56)	
	COBI	1.06 (0.94, 1.20)		1.04 (0.91, 1.18)	
	Other/Unknown	0.81 (0.65, 1.02)		0.67 (0.53, 0.85)	
Age at baseline	Per 10 year increase	0.86 (0.84, 0.88)	<0.0001	0.92 (0.89, 0.94)	<0.0001
Sex	Male	1 (ref)	<0.0001	1 (ref)	0.085
	Female	1.28 (1.21, 1.35)		1.06 (0.99, 1.14)	
Ethnicity	White	1 (ref)	<0.0001	1 (ref)	<0.0001
	Black	1.53 (1.41, 1.65)		1.61 (1.47, 1.76)	
	Other	1.16 (1.02, 1.32)		1.04 (0.91, 1.19)	
	Unknown/missing	0.98 (0.91, 1.06)		0.91 (0.83, 0.99)	
Risk	MSM	1 (ref)	<0.0001	1 (ref)	0.0015
	IDU	1.29 (1.19, 1.39)		1.12 (1.03, 1.23)	
	Heterosexual	1.20 (1.14, 1.27)		1.10 (1.02, 1.18)	
	Other	1.03 (0.89, 1.18)		1.02 (0.88, 1.18)	
	Unknown/missing	1.44 (1.23, 1.65)		1.31 (1.14, 1.52)	
Region	Western Europe	1 (ref)	<0.0001	1 (ref)	<0.0001
	S Europe	1.43 (1.33, 1.54)		1.54 (1.43, 1.67)	
	N Europe/Australia	1.14 (1.06, 1.23)		1.43 (1.32, 1.56)	
	E and EC Europe	1.40 (1.29, 1.53)		1.47 (1.34, 1.62)	
CD4 count at baseline	Per 100 cells higher	0.97 (0.97, 0.98)	<0.0001	0.97 (0.96, 0.98)	<0.0001
Viral load at baseline	Per 1 log higher	1.08 (1.06, 1.10)	<0.0001	1.05 (1.03, 1.07)	<0.0001
Smoking status at baseline	Never	1 (ref)	<0.0001	1 (ref)	0.071
	Current	1.06 (1.00, 1.13)		1.05 (0.98, 1.12)	
	Previous	0.87 (0.80. 0.96)		0.98 (0.89, 1.08)	
	Unknown	1.07 (1.00, 1.14)		1.09 (1.01, 1.17)	
AIDS defining malignancies	No	1 (ref)	0.59	1 (ref)	

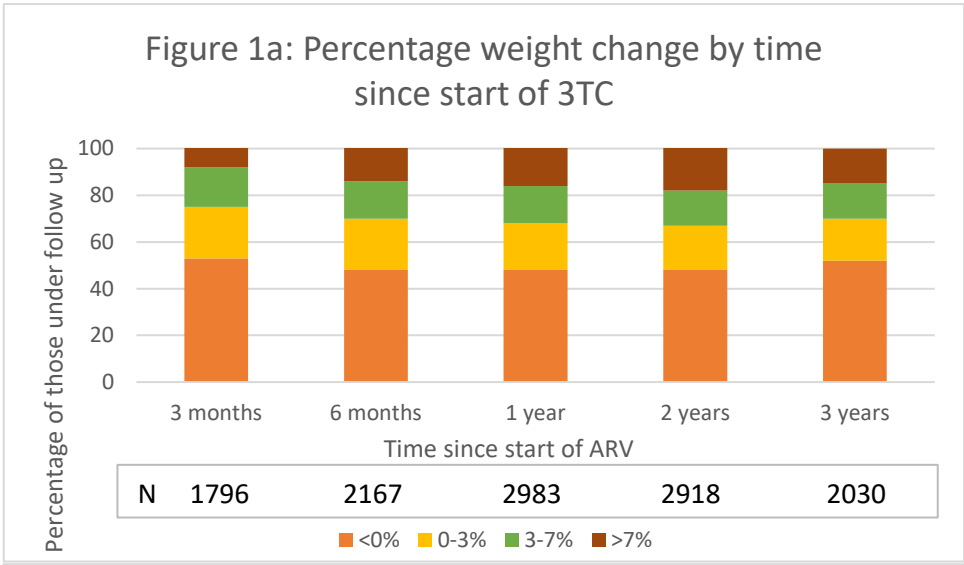
	Yes	1.04 (0.91, 1.18)		1.15 (1.01, 1.32)	0.044
Non-cancer AIDS events	No	1 (ref)	0.00010	1 (ref)	
	Yes	1.12 (1.06, 1.19)		1.13 (1.06, 1.21)	0.00030

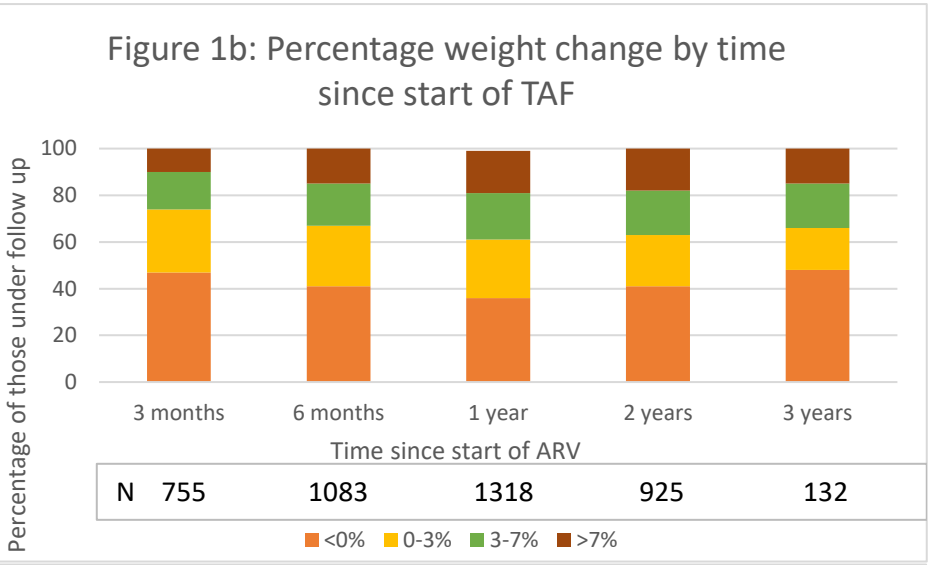
3TC: lamivudine, ABC: abacavir, , DDI: didanosine, FTC: emtricitabine, , TAF: tenofovir alafenamide, TDF: tenofovir disoproxil fumerate, ZDV: zidovudine, ATV: atazanavir, DRV: darunavir, FPV: fosamprenavir, LPV: lopinavir, RTV: ritonavir (any dose), EFV: efavirenz, ETV: etravirine, NVP: nevirapine, RPV: rilpivirine, DTG: dolutegravir, EVG/c: cobicistat boosted elvitegravir, RAL: raltegravir, COBI: cobicistat,

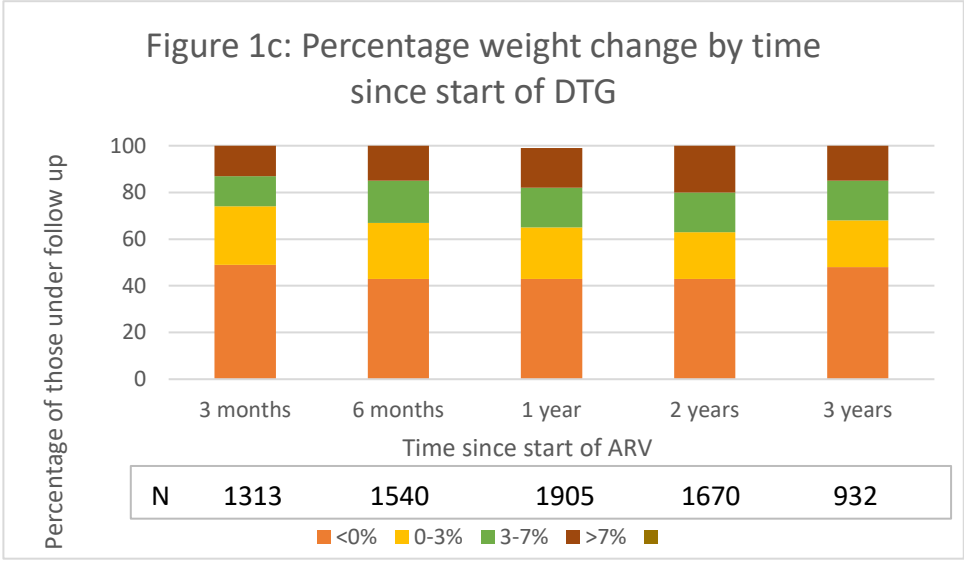
Odds ratios reported for only those ARVs for which a minimum of 100 events occurred (ORs for D4T stavudine, SQV saquinavir, APV amprenavir and MVC: Maraviroc not shown)

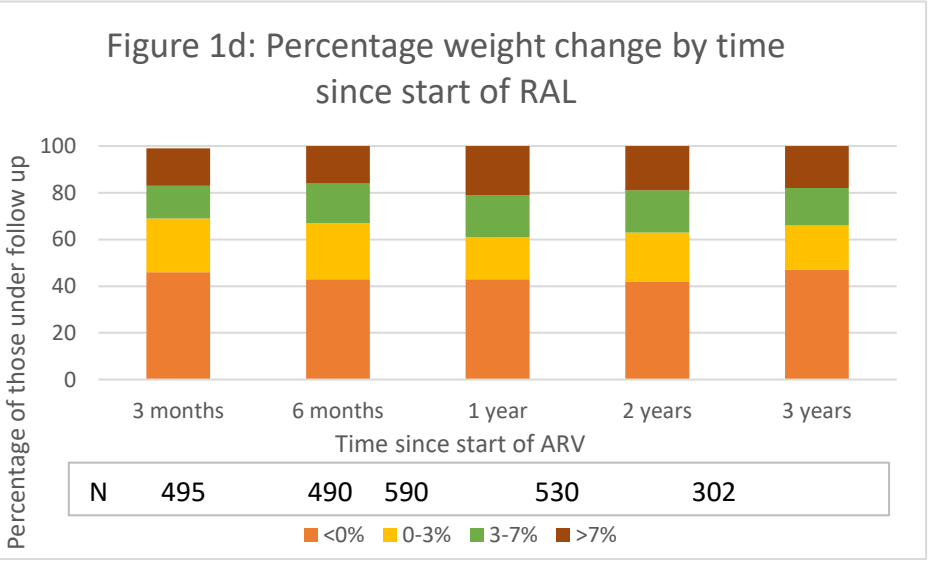
Note: In initial analyses, regression models were also adjusted for hepatitis B and C status, diabetes, dyslipidaemia, hypertension, end stage liver and renal disease, chronic kidney disease, CVD and cancers at baseline, i.e. at the first pre-ARV BMI measurement available. However, given that the first pre-ARV BMI was recorded at a relatively early date where event reporting was not required on the same level as prospectively collected data, a large proportion of people had missing values for these variables. Further, associations between these variables and the outcome were non-significant in multivariable analyses and hence it was decided not to include these variables in the primary model.

Figure 1: Percentage increase in BMI stratified by time since start of 3TC, TAF, DTG and RAL









N refers to number of people with a BMI measurement at the time since start of the ARV

Table 4: Association between variables of interest and a 30% increase in BMI from pre-drug BMI

N=14703: 749 (5.1%) experienced >30% BMI increase

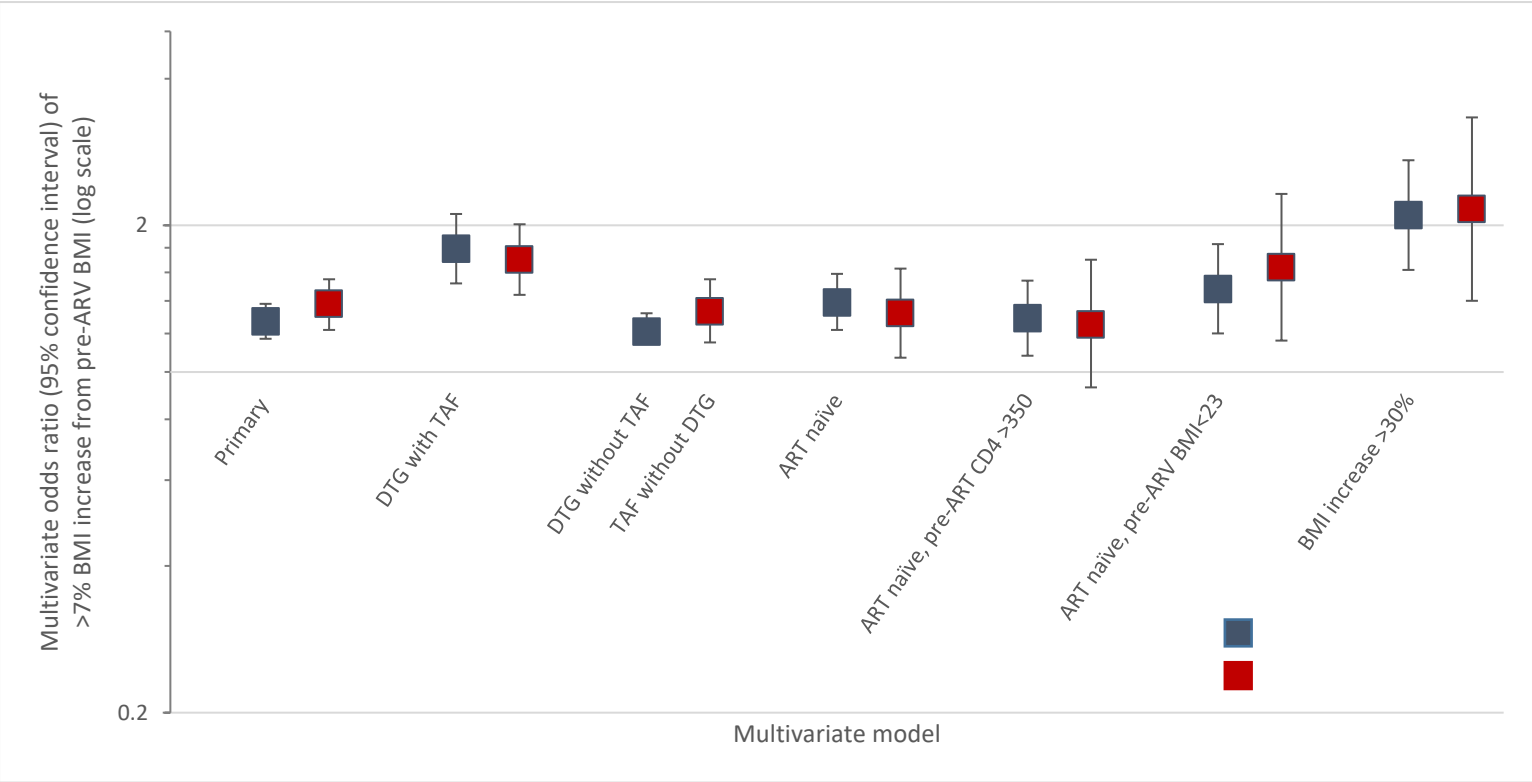
Variable		Univariate analyses		Multivariable analyses	
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Time on ARV	< 3 months	0.29 (0.12, 0.67)	<0.0001	0.22 (0.13, 0.38)	<0.0001
	3 to 6 months	0.34 (0.21, 0.56)		0.26 (0.16, 0.44)	
	6 to 12 months	0.38 (0.26, 0.55)		0.32 (0.22, 0.47)	
	1 to 2 years	0.66 (0.53, 0.85)		0.61 (0.48, 0.77)	
	2 to 3 years	0.61 (0.48, 0.79)		0.58 (0.44, 0.75)	
	>3 years	1 (ref)		1 (ref)	
Pre-ARV BMI	Per 1 unit increase	0.78 (0.75, 0.81)	<0.0001	0.79 (0.76, 0.82)	<0.0001
ARV	3TC	1 (ref)		1 (ref)	<0.0001
	ABC	0.86 (0.75, 0.99)		1.01 (0.88, 1.16)	
	FTC	0.90 (0.75, 1.09)		1.22 (1.00, 1.49)	
	TAF	0.69 (0.46, 1.02)		2.16 (1.40, 3.33)	
	TDF	0.88 (0.73, 1.06)		1.06 (0.87, 1.28)	
	ZDV	0.55 (0.36, 0.85)		0.49 (0.31, 0.76)	
	ATV	0.83 (0.63, 1.09)		0.96 (0.72, 1.27)	
	DRV	0.84 (0.64, 1.11)		1.17 (0.88, 1.54)	
	FPV	0.69 (0.36, 1.35)		0.79 (0.41, 1.52)	
	LPV	1.12 (0.84, 1.48)		0.95 (0.71, 1.27)	
	RTV	0.98 (0.66, 1.46)		1.01 (0.82, 1.24)	
	EFV	0.69 (0.53, 0.90)		0.82 (0.63, 1.08)	
	ETR	0.88 (0.48, 1.60)		1.30 (0.72, 2.37)	
	NVP	0.59 (0.42, 0.83)		0.64 (0.45, 0.90)	
	RPV	0.67 (0.45, 1.00)		1.35 (0.89, 2.03)	

	DTG	0.96 (0.75, 1.23)		2.10[1] (1.62, 2.72)	
	EVG/c	0.37 (0.18, 0.75)		0.91 (0.44, 1.85)	
	RAL	0.98 (0.66, 1.46)		1.52 (1.02, 2.28)	
	COBI	0.39 (0.21, 0.75)		0.94 (0.49, 1.79)	
	Other	0.68 (0.46, 1.02)		0.73 (0.49, 1.10)	
Age at baseline	Per 10 year increase	0.79 (0.72, 0.86)	<0.0001	0.96 (0.87, 1.05)	0.36
Sex	Male	1 (ref)	<0.0001	1 (ref)	0.0034
	Female	2.13 (1.81, 2.51)		1.37 (1.11, 1.69)	
Ethnicity	White	1 (ref)	0.00030	1 (ref)	<0.0001
	Black	1.76 (1.40, 2.20)		2.17 (1.67, 2.82)	
	Other	1.05 (0.70, 1.59)		0.78 (0.51, 1.21)	
	Unknown/missing	0.85 (0.66, 1.10)		0.83 (0.60, 1.14)	
Risk	MSM	1 (ref)	<0.0001	1 (ref)	0.016
	IDU	2.45 (1.93, 3.10)		1.62 (1.23, 2.13)	
	Heterosexual	1.93 (1.58, 2.34)		1.33 (1.03, 1.73)	
	Other	2.15 (1.45, 3.19)		1.57 (1.03, 2.28)	
	Unknown/missing	2.00 (1.25, 3.22)		1.49 (0.90, 2.47)	
Region	Western Europe	1 (ref)	<0.0001	1 (ref)	<0.0001
	S Europe	1.58 (1.21, 2.05)		2.10 (1.60, 2.77)	
	N Europe/Australia	0.87 (0.66, 1.13)		1.38 (1.00, 1.89)	
	E and EC Europe	1.98 (1.52, 2.58)		2.53 (1.87, 3.41)	
CD4 at baseline	Per 50 cells higher	0.92 (0.90, 0.94)	<0.0001	0.96 (0.94, 0.98)	0.00010
Viral load at baseline	Per 1 log higher	1.20 (1.14, 1.26)	<0.0001	1.15 (1.08, 1.22)	<0.0001
Smoking status at baseline	Never	1 (ref)	0.020	1 (ref)	0.61
	Current	1.10 (0.89, 1.35)		0.94 (0.75, 1.18)	
	Previous	0.87 (0.62, 1.23)		0.99 (0.69, 1.42)	
	Unknown	1.33 (1.07, 1.64)		1.09 (0.87, 1.38)	
AIDS defining malignancies	No	1 (ref)		1 (ref)	0.22

	Yes	0.59 (0.37, 0.94)	0.0044	0.77 (0.48, 1.23)	
Non-cancer AIDS events	No	1 (ref)	<0.0001	1 (ref)	0.0012
	Yes	1.59 (1.33, 1.89)		1.38 (1.15, 1.65)	

[1] Change from univariate estimates after adjusting for time on drug

Figure 2: Association between DTG, TAF (versus 3TC) and >7% BMI increase according to various multivariable models



Primary model adjusted for time on ARV, pre-ARV BMI, demographics, geographical region, baseline CD4 count, viral load, smoking status and AIDS events

DTG with TAF – As primary, but restricted to records in which DTG and TAF were received concomitantly
DTG without TAF – As primary, but restricted to records in which DTG was taken without TAF
TAF without DTG – As primary, but restricted to records in which TAF was taken without DTG
ART naïve – Restricted to ART naïve people at RESPOND entry, adjusted for same confounders as primary model with CD4 at baselinereplaced by CD4 count prior to ART initiation
ART naïve, pre ART CD4 > 350 – As above, restricted to those with pre-ART CD4 counts >350 ('healthy' individuals)
ART naïve, pre ARV BMI <23 – As ART naïve, restricted to those with pre-ARV BMI <23

BMI increase >30% - Alternative outcome to BMI increase >7%

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Author's contributions

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LBM and AM have accessed and verified the data

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Data sharing agreement

The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts (please see https://chip.dk/Research/Studies/RESPOND/Study-documents) should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk). The secretariat will direct the proposal to the relevant Scientific Interest Group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review.

Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be evaluated. Upon completion of the review, feedback will be provided to the proposer(s). In some circumstances, a revision of the concept may be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (up to 3 persons who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center. All persons involved in the process of reviewing these research concepts are bound by confidentiality.

All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definition can be found in the latest version of "Standard Operating Procedure for data transfer in RESPOND, EuroSIDA, MISTRAL, and CARE," of the publicly available at https://chip.dk/Research/Studies/RESPOND/Study-documents.

For any inquiries regarding data-sharing, please contact the RESPOND secretariat (respond.rigshospitalet@regionh.dk) and Dorthe Raben, Director of Research Coordination (Dorthe.raben@regionh.dk)'