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REVIEW ARTICLE

Antiretrovirals and Weight Change: Weighing the Evidence

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Body weight is influenced by an interplay of individual and environmental factors. In people with HIV (PWH), weight is also influenced by disease status with loss accompanying disease progression that is reversed with effective antiretroviral therapy (ART). Weight changes in comparative ART trials differ by regimen, with greater gains observed with the integrase strand transfer inhibitors (INSTIs) dolutegravir and bictegravir, particularly when co-administered with tenofovir alafenamide fumarate (TAF), compared to regimens that include agents such as tenofovir disoproxil fumarate (TDF) that attenuate weight gain. We review weight changes in major randomized trials of pre-exposure prophylaxis (PrEP) and initial and switch HIV therapy, highlighting the challenges to assessing the role of ART in weight change. This examination forms the basis for a model that questions assumptions regarding an association between INSTI and TAF and excessive weight gain and calls for more careful consideration of these data when making HIV treatment decisions.

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INTRODUCTION

HIV treatment is increasingly potent, effective, convenient, safe, and well-tolerated, especially regimens that include the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) and bictegravir (BIC). Both INSTIs have a high barrier to viral resistance, few drug interactions, and are taken once daily, often as a single tablet co-formulated with other antiretroviral(s). US Food and Drug Administration (FDA) approval of tenofovir alafenamide fumarate (TAF), a nucleotide reverse transcriptase inhibitor (NRTI) with a reduced risk of renal and bone effects compared to tenofovir disoproxil fumarate (TDF), further enhanced antiretroviral safety, as did the use of the two-drug regimen DTG plus lamivudine (3TC).[1-6] US and European HIV treatment guidelines include TAF plus either of these INSTIs along with 3TC or emtricitabine (FTC), or DTG plus 3TC, among the recommended regimens for initial treatment.[1, 2, 7, 8] The World Health Organization (WHO) HIV management guidelines also recommend DTG as a preferred initial therapy with TDF plus either 3TC or FTC.[2] Given cost considerations, TAF is reserved for those with osteoporosis or impaired renal function. As such, DTG and TDF are among the most commonly used antiretrovirals, worldwide.

However, there are concerns that INSTIs, particularly when co-administered with TAF, may promote excessive weight gain.[1, 9-14] Initially described in observational cohorts, larger increases in weight with INSTIs, both with and without concomitant TAF, compared to non-INSTI regimens, have been reported in randomized clinical trials enrolling individuals naïve to HIV therapy as well as those switching antiretrovirals.[14-17] These findings have led some clinicians and people with HIV (PWH) to avoid newer INSTIs and TAF due to concerns they will cause excessive weight gain.[18]

In this paper, we have assembled as an expert panel to review weight changes in general global populations and PWH, as well as weight data from select major randomized trials that enrolled people without HIV (pre-exposure prophylaxis (PrEP)) and antiretroviral trials in PWH, including initial HIV therapy and switch studies in those with virologic suppression. This expert review concludes with a synthesis of the reviewed data and a proposed model by which to consider factors related and unrelated to treatment that influence weight changes in PWH and suggestions for potential future investigations.

Trends in Weight in the General Population

There has been a substantial increase in weight among diverse populations across the world.[19] In an analysis of body mass index (BMI) data collected from >19 million adults living in 186 countries, age-standardized mean BMI significantly increased between 1974 and 2014 from 21.7

kg/m^2 to 24.2 kg/m^2 for men and 22.1 kg/m^2 to 24.4 kg/m^2 in women, with rises seen in all regions. During this period, global obesity prevalence tripled in men and doubled in women.[20] In the US, > 42% of Americans were obese in 2017-2018, and 10% were severely obese, up from 31% and 5% respectively a decade earlier.[21] Between 2011 and 2018, the mean weight of 13,802 randomly selected Americans aged 36-79 years participating in the National Health and Nutrition Examination Survey (NHANES) increased by 4.2 kg and during this period 36% gained >10% body weight.[22] Younger participants, women, and Non-Hispanic Blacks, particularly Black women, gained the most weight.

Drivers of global obesity include changes in the food environment, with increased consumption of energy-rich foods and drinks, as well as a decrease in physical activity.[23] Social determinants of health, including food insecurity and access to affordable and nutritious foods rather than ultra-processed, calorie-dense products, also have been demonstrated to contribute to elevated rates of overweight status and obesity - structural factors often prevalent in communities most affected by HIV.[23-25]

Trials of Antiretrovirals as Pre-Exposure Prophylaxis in People Without HIV Infection

Studies of PrEP provide opportunities to assess the weight changing properties of antiretrovirals not confounded by HIV-related factors that may influence weight (Figure 2A), and as all PrEP trials to date have included TDF, TAF, or both, allow comparison of these agents free from the return to health effect associated with antiretroviral initiation and the influence of other agents (with the exception of 3TC or FTC).

In the placebo-controlled iPrEx trial of TDF/FTC that enrolled 2,499 men who have sex with men (MSM) and transgender women (TGW)[26, 27] median weight increased in the placebo arm by almost 1.0 kg by week 72 and 1.5 kg by week 96: consistent with the 0.5 to 1.0 kg expected annual weight gain in a general population.[19-22] In contrast, in the TDF/FTC arm there was no significant change in weight during the first year; those with detectable plasma tenofovir levels gained a median of 0.6 kg by week 72.

In the double-blind, randomized DISCOVER PrEP trial comparing TDF/FTC with TAF/FTC in MSM and TGW (N=5,387), TDF/FTC arm participants experienced a median gain of 0.6 kg by week 96, similar to the weight change observed with TDF/FTC in iPrEx.[17] In contrast, the TAF/FTC arm experienced a median increase in weight of 1.7 kg at week 96, consistent with the iPrEx placebo arm and the gain expected over this period in the general adult population, suggesting TAF had a neutral effect on weight.

In the placebo-controlled HIV Prevention Trials Network (HPTN) 077 trial (n=146 with paired weight data), weight change at 41 weeks in those randomized to intramuscular (IM) cabotegravir (CAB) was a median of 1.1 kg - nearly identical to the 1.0 kg gain in those to assigned placebo.[28] In the HPTN 083 trial of IM CAB versus TDF/FTC in MSM and TGW, those randomized to CAB experienced weight gain of 1.5 kg by week 40, similar to that seen in HPTN 077; however,

TDF/FTC participants lost a median of 0.5 kg.[29] HPTN 084 used an identical design to compare IM CAB and TDF/FTC in cis-women, and both study arms gained weight over time, with greater gains seen in those randomized to CAB.[30] The disparate median weight change among those assigned TDF/FTC in HPTN 083 and 084 may be explained by sex-depended differences but it is also notable that adherence to TDF in HPTN 084 was low. Only 36% of the dried blood samples from women on TDF had levels indicating 4 or more doses per week; 38% of samples were below quantification.[30]

A meta-analysis of seven HIV PrEP trials, including iPrEx and HPTN 084, found that those taking TDF were more likely to experience weight loss compared with control participants.[31] TDF was associated with a 44% greater odds of experiencing a 5% or greater weight loss compared to controls (placebo or CAB).

Trials of Antiretrovirals for Initial Treatment of HIV

Weight gain in PWH initiating antiretrovirals has been associated with advanced disease including low CD4+ cell counts (i.e., <200/mm^3), high plasma HIV RNA levels (i.e., >100,000 copies/mL), and opportunistic conditions.[15, 32]

In an analysis of weight change among 5,680 treatment-naïve participants enrolled in eight antiretroviral comparative trials conducted between 2003 and 2015, an association between greater weight gain at 96 weeks and initiation of BIC, DTG or TAF versus older antiretrovirals was demonstrated.[15]

Similarly, the ADVANCE trial, a randomized, open-label, controlled study of three first-line HIV therapies that enrolled 1,053 adult PWH in South Africa reported greater mean increases in weight in participants randomized to DTG, TAF and FTC compared to DTG with TDF and FTC, which in turn was higher than those receiving EFV with TDF and FTC. [33] The magnitude of the weight gain was greater for women.[33, 34] By 144 weeks, women assigned to DTG plus TAF/FTC gained a mean of 12.3 kg, compared to 7.4 kg for women taking DTG plus TDF/FTC and 5.5 kg for those on EFV/TDF/FTC.[33] Among men, the same stepwise differential change in weight was observed across the study arms but with smaller mean absolute increases in weight. Treatment-emergent metabolic syndrome was significantly more likely in those treated with DTG + TAF/FTC, developing in 8.4% compared to 5.9% treated with DTG + TDF/FTC and 3.9% on EFV/TDF/FTC.[34] Incident metabolic syndrome was higher for women than men. In body composition analyses, increases in both fat and lean tissue were observed, with women gaining more fat than men.

Single nucleotide polymorphisms at the CYP2B6 gene known to effect EFV metabolism were examined in 171 ADVANCE participants randomized to EFV/TDF/FTC who were categorized as slow, intermediate, or extensive EFV metabolizers.[36] Over 48 weeks, weight increases were lowest among the slow and intermediate EFV metabolizers, but in the extensive metabolizers, who comprised 30% of the sample, weight increased to a similar degree as in men and women

randomized to DTG plus TDF/FTC. Therefore, participants expected to have higher EFV plasma levels had less weight gain than those predicted to have lower levels, pointing to a potential exposure-dependent weight attenuating effect of EFV

Other trials of initial HIV treatment support the effect of TDF on attenuation of weight gain. In the GEMINI trials, 1,433 treatment-naive participants were randomized to DTG plus TDF/FTC or DTG plus 3TC and although all received DTG, the mean weight change from baseline to week 96 was lower at 2.1 kg in those receiving TDF compared to 3.1 kg gained during this period in those in the DTG plus 3TC group (p value not reported).[37]

The DRIVE-AHEAD trial randomized treatment-naïve participants to the non-nucleoside reverse transcriptase inhibitor doravirine (DOR) combined with 3TC/TDF or EFV/TDF/FTC (n=364 and n=364, respectively).[38, 39] Over 96 weeks, the average weight gain was 1.2 kg for the DOR/TDF/3TC arm and 1.0 kg for the EFV/TDF/FTC arm (p=NS). The weight gain in both study arms was relatively low compared to increases expected based on general population weight data,[19-22] as well as those observed in clinical trials in which the study medications excluded TDF and/or EFV, and may reflect attenuation of weight gain in both arms by TDF. Furthermore, the EFV metabolism status of the participants is unknown and may have differed from ADVANCE, where there were weight changes differences among the two TDF arms. Overall, the finding from this and the DOR/ISL versus BIC/TAF/FTC suggest that DOR and BIC have similar effects on weigh. A prospective head-to head, 96-week comparison of DOR/3TC/TDF versus DTG + TAF/FTC in treatment-naïve individuals is on-going and will include a comparison of weight changes as well as renal and bone outcomes (NCT05924438).

A randomized double blind, placebo controlled trial that did not include TDF or EFV compared DOR plus the investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI) islatravir (ISL) to BIC/FTC/TAF in 507 treatment-naive participants.[40] The change in weight between the two arms at 48 weeks was similar (+3.45 kg with DOR/ISL and +3.32 kg with BIC/FTC/TAF). These data support a similar return to expected weight when regimens do not include a weight attenuating antiretroviral.

Trials of Switching Antiretrovirals for Treatment of HIV

Studies of weight change in virologically suppressed PWH who switch ART are not confounded by the reversal of weight loss related to untreated HIV. However, interpretation of these studies is complex and must consider both the pre- and post-switch regimen effects on weight.

Weight change during 12 randomized, controlled ART switch trials that enrolled 7,316 individuals was examined in those who maintained their pre-study regimen versus 4,166 randomized to switch ART.[16] Switching from TDF to TAF and from EFV to either RPV or EVG/c was independently associated with weight increases of $\geq$10% over 96 weeks. In contrast, weight change was not significantly different between those switching from a boosted PI to either EVG/c or BIC versus those remaining on the boosted PI.

The reversibility of changes in weight following switch was also demonstrated in a follow-up study of participants in the ADVANCE trial who transitioned from study medication to DTG/TDF/3TC, the new standard initial regimen in South Africa.[41] Among women who were originally randomized to DTG plus TAF/FTC, the switch to the TDF-based regimen led to a significant median 1.6 kg decline in weight; for men originally assigned to DTG plus TAF/FTC, there was a non-significant median 0.2 kg weight drop . In contrast, those initially receiving EFV/TDF/FTC experienced a median 2.9 kg weight increase after switching to DTG plus TDF/3TC, 2.3 kg for men and 2.9 kg for women (the change was only significant for men).

The SALSA trial (n=493) enrolled mostly cis-gender male PWH virologically suppressed on regimens containing three active antiretrovirals (at entry 44% on TDF, 50% on NNRTI (mostly EFV), 40% on INSTI (almost half DTG), and 10% on PI) randomized to continue their regimen or switch to DTG/3TC.[42, 43] By week 48, there was a significantly greater weight increase with switching to DTG/3TC compared to continuing the pre-study regimen (2.1 kg versus 0.6 kg at week 48).[43] This differential change in weight was driven by those switching from a TDF-based regimen to DTG/3TC, who experienced a mean increase of 2.4 kg versus 0.1 kg in those remaining on a TDF-based regimen (difference = 2.4 kg 95% CI: 1.2, 3.6). For the 174 participants entering the trial on a TAF-based regimen, there was no significant difference in weight change at week 48 in those who switched compared to those maintained on their pre-study regimen (1.4 kg versus 1.6 kg, respectively; difference 0.2: 95% CI: -1.2, 1.5), underscoring the differential change in weight that occurs when switching from TDF compared to TAF, and the reversibility of the effect of TDF on weight when discontinued.

The TANGO trial randomized virologically suppressed participants on TAF-containing 3 active drug regimens (N=741) to switch to DTG/3TC or continue their baseline regimen (at entry 80% on INSTI (84% of these on DTG)).[44-46] Over 144 weeks, the mean adjusted weight increased similarly in both study arms: 2.2 kg in those switching to DTG/3TC and 1.7 kg in those maintaining their TAF-containing regimen.[44] SOLAR, another trial of switching from TAF while maintaining an INSTI in the regimen, enrolled 672 PWH with suppressed viremia on BIC/FTC/TAF who were randomized to continue that regimen or switch to IM CAB and RPV.[47] At month 12, the median change in weight was -0.40 kg in the CAB plus RPV group and +0.05 kg in the BIC/FTC/TAF group, a non-significant difference. Both trials demonstrated a lack of impact on weight from the removal of TAF.

Lastly, the DEFINE trial examined the effects of switching from an INSTI to darunavir (DRV) plus cobicistat (c) while maintaining TAF in 103 participants who had experienced at least a 10% increase in weight within the prior 36 months while receiving TAF/FTC and an INSTI (~90% were on BIC or DTG).[48] At 24 weeks there was no significant difference in weight change between the two groups (+0.63 kg with DRV/c/TAF/FTC and -0.24 kg with continued INSTI + TAF/FTC (p=0.24)). Similarly, study MK-8591A-018 randomized 643 virologically suppressed participants on BIC/FTC/TAF to maintain this regimen or switch to ISL/DOR.[49] At 48 weeks of study, the mean increase from baseline in weight was small and not significantly

different between the two study arms (+0.55 kg BIC/FTC/TAF versus +0.23 kg DOR/ISL; p=0.4). Changes in weight in ART switch trials with 48 week data at are found in Figure 2B.

The neutrality of newer INSTIs on weight is further supported by a recent ACTG randomized, double-blind, placebo-controlled trial that explored the addition of DTG with and without the CCR5 antagonist maraviroc to background ART with the aim of improving neurocognitive impairment.[50] Over 96 weeks, BMI increased 0.32 kg/m^2 among the 191 participants, with no significant differences between those adding DTG versus those adding placebo. The lack of a weight-promoting effect of DTG-based ART is also supported by an analysis of 23,131 Kenyan PWH who switched from either NVP or EFV to DTG, where the rate of weight gained per year increased post-switch only in those switching from EFV but not from NVP.[51]

Evaluating the Available Evidence to Inform Practice

The clinical trials described above provide strong evidence for the weight neutrality of DTG, BIC and TAF and the weight attenuating effects of TDF, in particular when combined with EFV, and underpin an alternative model of the effect of antiretrovirals on weight gain in PWH as illustrated in Figure 1. The changes in weight in trials of TAF and CAB as PrEP that are consistent with those in PrEP trial placebo recipients and in comparable general populations, argue against an inherent weight-promoting effect of these two agents. This is underscored by studies that remove TAF (i.e., TANGO and SALSA),[37-43] with minimal impact on weight. That BIC also does not promote excess weight gain is supported by the absence of a difference in weight change during initial HIV therapy with BIC/FTC/TAF compared to DOR/ISL and in studies of switching from BIC, such as SOLAR and MK-8591A-018, where changes in weight with continued BIC/FTC/TAF were not significantly different from those with regimen switch, and were similar to expected weight gain.[47, 49] Adding DTG to a stable regimen, as was done in the ACTG neurocognitive impairment trial,[50] did not lead to greater weight gain than observed in those who added placebo, a finding that also argues against DTG-induced weight gain.

The finding in the ADVANCE trial of substantially greater increases in weight among those randomized to DTG plus TAF/FTC, especially among women, is likely explained by the inclusion of weight attenuating agents in the other two study arms – TDF in both arms, TDF and EFV in one. It is notable that the mean BMI of women in the DTG plus TAF/FTC arm at 96 weeks was 28.6 kg/m^2, a substantial increase from their baseline BMI of 25.6 kg/m^2. The 96 week BMI is similar to the mean reported BMI of women in South Africa, 29.6 kg/m^2, where the trial was conducted, although higher than the reported BMI among women in Zimbabwe, where almost a third of the overall participant pool resided.[20] This suggests that the weight gain some of these women experienced, if not necessarily a return to health phenomenon, may be a return toward a societal norm and prior weight set point.

Given the strong association between TDF and weight attenuation as well as the drop in weight that ADVANCE participants experienced when switching from TAF to TDF, clinicians may be

tempted to switch to a TDF-containing regimen. However, the benefits of any resulting weight reduction must be balanced against the known bone and renal adverse effects of TDF, albeit these TDF-related effects are more frequent when the regimen also includes a pharmacological booster, which raise circulating tenofovir levels. Future research is needed to assess the trade-offs between potential benefits of weight attenuation with TDF and its adverse effects.[52]

There are limited data to support antiretroviral switches for weight loss and treatment guidelines recommend against modification solely due to increases in weight.[1] As demonstrated in the SALSA, TANGO, and SOLAR trials, removing TAF from a regimen while maintaining an INSTI did not result in weight change.[42-47] A strategy of switching from a TAF-containing regimen that includes BIC, DTG, or RAL to DOR + TAF/FTC or DOR + TDF/FTC versus continued therapy with the original INSTI + TAF combination in those with a BMI of 30 kg/m^2 or more is being tested in an ACTG study (NCT04636437).

The consequences of obesity and weight gain in PWH have been reviewed [53-55] and there are reports of an association between weight gained during antiretroviral therapy with INSTI and/or TAF (including as PrEP) and increases in blood pressure and diabetes mellitus incidence.[56-59] As in the general population, strategies are needed to mitigate these consequences. Adoption of diets that emphasize plant-based foods and limit the intake of carbohydrates and saturated fats such as the Mediterranean diet are associated with declines in weight and improvement in lipid and glycemic parameters.[60, 61] Exercise complements diet and provides added benefits in terms of cardiovascular health, muscle strengthening, cancer risk reduction, and the prevention of frailty.[63] Lifestyle measures that are evidence-based, accessible, and affordable should be recommended to all with excessive weight gain. In some individuals medical therapy for obesity can be also considered.[64]

In all cases of excessive weight gain, clinicians must consider contributing factors, including use of antidepressants and antipsychotics, smoking cessation, changes in illicit substance or marijuana use, stress and mood disorders, and endocrine disorders, among others. The timing of weight gain after an initiation or switch in antiretroviral regimen can also be informative, as the weight gain typically occurs shortly after start of the new regimen, with leveling of the rate of weight gain within the first year.

CONCLUSIONS

The gain in weight seen in those treated with DTG, BIC, and/or TAF in clinical trials, observational studies, and clinical practice have led to a perception that these agents cause an excessive increase in weight. These observations have led some clinicians to consider alternative antiretrovirals as initial therapy or a switch regimen as a strategy to avoid or reverse excess weight gain. However, a comprehensive examination of major clinical trials suggest TDF-based regimens, in particular when given with EFV, attenuate weight gain, while DTG, BIC, and TAF

can be considered neutral and not a cause of excessive weight gain. Given the efficacy and safety advantages of DTG, BIC, and TAF-based regimens, it is imperative that their associations with unexpected, undesired, or unhealthy increases in weight be rigorously evaluated before being accepted as causal.

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JK has served as a consultant to Gilead, Merck, Theratechnologies and Janssen Pharmaceuticals, and has received research support from Gilead Sciences and Merck.

GM has served as an advisor to Novartis and Ipsen Pharmaceuticals and a speaker for Gilead Sciences, GlaxoSmithKline, Merck, Sharp, Dohm UK, and ViiV Healthcare.

PS has served as a Scientific Advisory Board member/Consultant for Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, Merck & Co, and Janssen Pharmaceuticals, He has received research support from Gilead Sciences, GlaxoSmithKline/ViiV Healthcare

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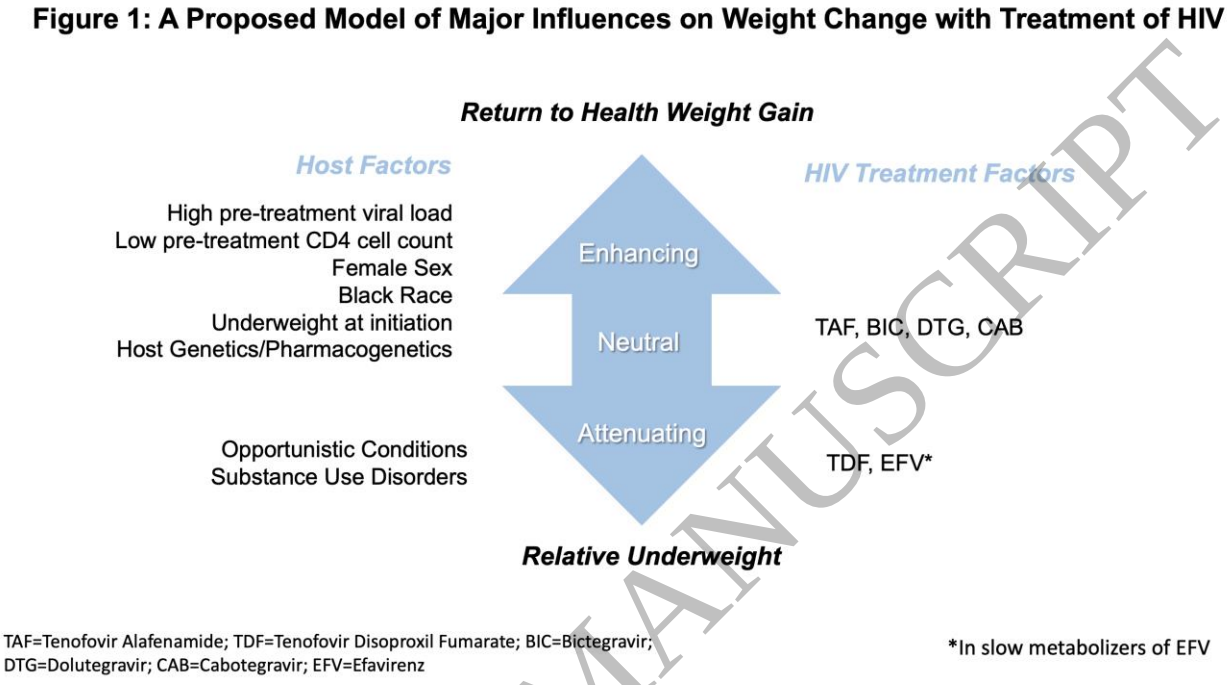
FIGURE LEGENDS:

Figure 1. A proposed model of major influences on weight change with treatment of HIV.



TAF = Tenofovir Alafenamide; TDF = Tenofovir Disoproxil Fumarate; BIC = Bictegravir; DTG = Dolutegravir; CAB = Cabotegravir; EFV = Efavirenz.

Figure 2. Changes in weight in major trials of PrEP (A) and ART Switch (B)