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Limited Weight Impact After Switching From Boosted Protease Inhibitors to Dolutegravir in Persons With Human Immunodeficiency Virus With High Cardiovascular Risk: A Post Hoc Analysis of the 96-Week NEAT-022 Randomized Trial

Laura Waters, Lambert Assoumou, Ana González-Cordón, Stefano Rusconi, Pere Domingo, Mark Gompels, Stephane de Wit, François Raffi, Christoph Stephan, Mar Masiá, et al.

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Corresponding Author:	Esteban Martinez Hospital Clínic, University of Barcelona Barcelona, SPAIN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Hospital Clínic, University of Barcelona
Corresponding Author's Secondary Institution:	
First Author:	Laura Waters
First Author Secondary Information:	
Order of Authors:	Laura Waters
	Lambert Assoumou
	Ana Gonzalez-Cordon
	Stefano Rusconi
	Pere Domingo
	Mark Gompels
	Stephane de Wit
	François Raffi
	Christoph Stephan
	Mar Masia
	Jürgen Rockstroh
	Christine Katlama
	Georg Behrens
	Graeme Moyle
	Margaret Johnson
	Julie Fox
	Hans-Jürgen Stellbrink
	Giovanni Guaraldi
	Eric Florence
	Stefan Esser
	Jose M Gatell

	Anton Pozniak
	Esteban Martinez
Order of Authors Secondary Information:	
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Abstract:	Background : In the NEAT022 trial, virologically suppressed persons with HIV (PWH) at high cardiovascular risk switched from protease inhibitors to dolutegravir either immediately (DTG-IS) or after 48 weeks (DTG-DS), thus providing an ideal scenario of pure and replicated drug change in a homogeneous population free of the confounding “return-to-health” phenomenon characteristic of treatment-naïve individuals. Methods : Post-hoc analysis. Major endpoints were weight and body mass index (BMI) changes at 48 and 96 weeks. Factors associated with weight and BMI changes within the first 48 weeks of DTG exposure in each arm, the proportion of participants by category of percent weight change from baseline, and the proportions of BMI categories over time were also assessed. Results : Between May/2014 and November/2015, 204 (DTG-IS) and 208 (DTG-DS) participants were included. There was a significant weight increase (mean +810g DTG-IS arm and +979g DTG-DS arm) in the first 48 weeks post-switch, but weight remained stable from 48 to 96 weeks in the DTG-IS arm. Switching from boosted darunavir, white race, total-to-HDL cholesterol ratio <3.7, and normal/underweight BMI were independently associated with higher weight or BMI gains. The proportion of participants who gained or lost ≥5% weight increased similarly in both arms at 96 weeks and the proportions of BMI categories did not change over time. Conclusions : Switching from boosted protease inhibitors to dolutegravir in persons with HIV with high cardiovascular risk led to modest weight increases limited to the first 48 weeks that did not differ from those reported in the general population after 96 weeks.
Suggested Reviewers:	Jordan Lake jordan.e.lake@uth.tmc.edu Expert on metabolic issues and HIV
	Grace McComsey grace.mccomsey@uhhospitals.org Expert on metabolic issues and HIV
	Igho Ofotokun iofotok@emory.edu Expert on metabolic issues and HIV
	Peter Reiss p.reiss@amsterdamumc.nl Expert on metabolic issues and HIV
	Judith Currier jscurrier@mednet.ucla.edu Expert on metabolic issues and HIV
Opposed Reviewers:	

Limited and clinically non-significant weight impact after switching from boosted protease inhibitors to dolutegravir in people living with HIV with high cardiovascular risk: a post hoc analysis of the 96-week NEAT-022 randomized trial.

Authors: Laura Waters[1], Lambert Assoumou[2], Ana González-Cordón[3,4], Stefano Rusconi[5], Pere Domingo[4,6], Mark Gompels[7], Stephane de Wit[8], François Raffi[9], Christoph Stephan[10], Mar Masiá[4,11], Jürgen Rockstroh[12], Christine Katlama[13], Georg Behrens[14], Graeme Moyle[15], Margaret Johnson[16], Julie Fox[17], Hans-Jürgen Stellbrink[18], Giovanni Guaraldi[19], Eric Florence[20], Stefan Esser[21], José M. Gatell[22], Anton Pozniak[15], and Esteban Martínez[3,4] on behalf of the NEAT 022 Study Group*.

*Study Group team members are listed in the Acknowledgments

Centres: *[1]Mortimer Market Centre, Central & North West London NHS Foundation Trust, London, United Kingdom; [2]Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France; [3]Hospital Clínic-IDIBAPS, Universitat de Barcelona, Barcelona, Spain; [4]CIBER de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain; Dipartimento di Scienze Biomediche e Cliniche "Luigi Sacco^, Università degli Studi di Milano and Unità Operativa Malattie Infettive, Ospedale Civile di Legnano, ASST Ovest Milanese, Legnano (MI) Italy; [6]Hospital de Sant Pau, Barcelona, Spain; [7]North Bristol NHS Trust, Bristol, United Kingdom; [8]Centre Hospitalier Universitaire Saint-Pierre, B*russels, Belgium; *[9]Centre Hospitalier Universitaire, Nantes, France; [10]Universitätsklinikum, Goethe-University, Abteilung für Infektionskrankheiten, Frankfurt, Germany; [11]Hospital General Universitario de Elche, Elche, Spain; [12]Universitätsklinikum, Bonn, Germany; [13]Hôpital Universitaire Pitié Salpêtrière; [14]Medizinische Hochschule, Hannover, Germany; [15]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [16]Royal Free London NHS Foundation Trust, London, United Kingdom; [17]Guy's & St Thomas' NHS Foundation Trust/Kings College, London, United Kingdom; [18]ICH-Infektionsmedizinisches Centrum, Hamburg, Germany; [19]Università degli Studi di Modena e Reggio Emilia, Modena, Italy; [20]Universitair Ziekenhuis Antwerpen, Antwerp, Belgium; [21]Universitätsklinikum, Essen, Germany; [22]ViiV Healthcare, Barcelona, Spain.*

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Summary (40 words)**:**

Switching from boosted protease inhibitors to dolutegravir in persons with HIV with high cardiovascular risk led to modest weight increases limited to the first 48 weeks that did not differ from those reported in the general population after 96 weeks.

Contact information for corresponding author:

Dr. Esteban Martínez
Infectious Diseases Unit
Hospital Clinic
08036 Barcelona
Spain
Telephone: +34 93 227 55 74
Fax: +34 93 451 54 24
E-mail: estebanm@clinic.cat

Contact information for alternate corresponding author:

Dr. Laura Waters
Department of HIV & Sexual Health
Mortimer Market Centre
Central & North West London NHS Trust
London WC1E 6JB
United Kingdom
Telephone: +44 20 3317 5241
Fax: +44 20 7697 8307
E-mail: lwaters@nhs.net

Summary (251 words):

Background: In the NEAT022 trial, virologically suppressed persons with HIV (PWH) at high cardiovascular risk switched from protease inhibitors to dolutegravir either immediately (DTG-IS) or after 48 weeks (DTG-DS), thus providing an ideal scenario of pure and replicated drug change in a homogeneous population free of the confounding "return-to-health" phenomenon characteristic of treatment-naïve individuals.

Methods: Post-hoc analysis. Major endpoints were weight and body mass index (BMI) changes at 48 and 96 weeks. Factors associated with weight and BMI changes within the first 48 weeks of DTG exposure in each arm, the proportion of participants by category of percent weight change from baseline, and the proportions of BMI categories over time were also assessed.

Results: Between May/2014 and November/2015, 204 (DTG-IS) and 208 (DTG-DS) participants were included. There was a significant weight increase (mean +810g DTG-IS arm and +979g DTG-DS arm) in the first 48 weeks post-switch, but weight remained stable from 48 to 96 weeks in the DTG-IS arm. Switching from boosted darunavir, white race, total-to-HDL cholesterol ratio <3.7, and normal/underweight BMI were independently associated with higher weight or BMI gains. The proportion of participants who gained or lost ≥5% weight increased similarly in both arms at 96 weeks and the proportions of BMI categories did not change over time.

Conclusions: Switching from boosted protease inhibitors to dolutegravir in persons with HIV with high cardiovascular risk led to modest weight increases limited to the first 48 weeks that did not differ from those reported in the general population after 96 weeks.

Introduction

NEAT-022 is a randomized, non-inferiority, strategic trial comparing the efficacy, safety and impact on plasma lipids of switching the boosted protease inhibitor (PI/r) component to dolutegravir (DTG) vs. continuing PI/r in persons with HIV (PWH) suppressed on two nucleoside reverse transcriptase inhibitors plus a PI/r. Participants were considered at high risk for cardiovascular disease (CVD) risk as they were required being ≥50 years and/or having a Framingham 10-year risk score greater than 10% at 10 years. Eligible subjects were randomized to immediate or deferred (week 48) switch to DTG and followed up for 96 weeks. The primary results at 48 weeks (1) and the final results at 96 weeks (2) demonstrating non-inferior maintained virological suppression and significant lipid improvements on switch to DTG have been published.

Over recent years there have been several analyses of observational cohorts and randomized controlled trials showing differential impact in weight gain with different combinations of antiretroviral therapy (ART). Integrase inhibitors, particularly DTG and bictegravir, and tenofovir alafenamide (TAF) have been particularly associated with higher weight increases and women, black individuals and older people appear to be particularly at risk of excessive weight gain (3-5). Because both excessive and insufficient body mass index (BMI) are associated with negative outcomes in the general (6) and HIV-infected (7) populations, understanding the real impact of different antiretrovirals on weight and the risk factors and possible mechanisms for ART-related weight change is of crucial importance.

Many of the analyses demonstrating higher weight gains with integrase inhibitors have emerged from trials undertaken in treatment-naïve PWH in which the comparator arm usually contained efavirenz, a drug that may prevent weight gain, (4, 8, 9). In fact, efavirenz rapid metabolisers, who have lower plasma efavirenz levels, gained the same amount of weight than PLW treated dolutegravir plus the same nucleoside backbone in the ADVANCE

trial (10). Data from switching studies have been less clear because of differences in prior regimens or concomitant changes in nucleoside backbone drugs among other factors (11-15). More advanced HIV (e.g. high plasma HIV RNA levels or low CD4 cell counts) has been consistently associated with higher weight increases after ART initiation (3, 4). The “return-to-health” phenomenon, whereby weight increases after ART initiation, has been well characterized (16) and analysing the impact of ART switch in individuals who are virally suppressed may reduce the potential confounding of this phenomenon. We therefore analysed the impact of switching from the PI/r component to DTG in NEAT022 thus providing an ideal scenario of a randomized clinical trial, involving a pure drug change, that was replicated, free of the confounding “return-to-health” phenomenon characteristic of treatment-naïve individuals, and including a homogeneous population at high cardiovascular risk.

Methods

Participants

NEAT022 trial was conducted in 32 clinical sites in 6 European countries. Participants were recruited between May 2014 and November 2015. Eligible persons were HIV-positive adults older than 50 years, older than 18 years with a Framingham CVD risk score >10% at 10 years or both. They also had to be on a stable (at least 6 months) triple antiretroviral regimen consisting of a PI/r (ritonavir-boosted lopinavir, darunavir, atazanavir, saquinavir or fosamprenavir) plus two NRTI and with plasma HIV RNA <50 copies/mL for at least the previous 6 consecutive months. PLWH with prior evidence of primary viral resistance (if a resistance test was available) based on the presence of any major resistance-associated mutations to backbone NRTI were excluded, as were those with prior virological failure while on ART unless there was a documented lack of selection of resistance mutations.

Ethics

The trial was conducted in accordance to the Good Clinical Practice and ethical principles of the declaration of Helsinki. The protocol was reviewed and approved by the ethics committees of all participating sites. All participants provided written informed consent before undergoing study procedures. The study was registered on ClinicalTrials.gov NCT02098837 and EudraCT 2013-003704-39.

Randomization and masking

Eligible participants were randomly assigned 1:1 to either switch the PI/r component to DTG continuing the same background NRTI (immediate switch or IS), or to continue PI/r-based ART for 48 weeks (delayed switch or DS), at which point all participants remaining on a PI/r switched to DTG out to week 96 of follow-up. Participants were assigned to treatment

groups by computer-generated permuted blocks of four and stratified by country. The study design was open-label, but only the trial statistician had access to the entire randomization list during the trial.

Study procedures

Participants attended for study visits at screening, baseline, then 12-weekly for 96 weeks thereafter with an additional visit at week 4 or 52 in the IS or DS group, respectively. Each visit included general assessment of vital signs, adverse events and blood samples for routine safety, fasting lipid and immuno-virological measurements. Adherence was monitored by participant questioning regarding missed tablets at any moment during the trial or the week prior to each visit. PLWH and investigators were advised not to change administration of lipid-lowering agents during the study period unless strictly necessary. At each visit, participants were provided advice about smoking cessation, daily exercise, weight, diet and alcohol intake, and blood pressure control using a predefined written formulary. AIDS events and deaths, serious adverse events (SAEs), adverse events (AEs) grade 3 or above, AEs leading to modification of study drugs, all protocol discontinuations and all protocol defined episodes of virological failures required confirmation by an independent endpoint review committee, whose members were blinded to individual treatment regimens.

Endpoints

Briefly, the co-primary trial endpoints were maintenance of viral suppression and percentage change in total-cholesterol up to weeks 48 and 96. Main secondary end-points included safety & tolerability, change in lipid fractions and change in Framingham CVD risk score up to weeks 48 and 96.

The major endpoints of this post-hoc analysis were the changes in weight (Kg) and in BMI (kg/m^2) at week 48 and 96. Factors associated with the evolution of BMI and weight

within the first 48 weeks on DTG (immediate switch arm 0-48 weeks and deferred switch arm 48-96 weeks) were also assessed. We assessed the proportions of underweight (BMI<18.5 kg/m^2), normal (BMI 18.5-25 kg/m^2), overweight (BMI 25.01–30 kg/m^2) and obese (BMI >30 kg/m^2) participants over time. Finally, we analysed the magnitude of weight change by category over time defined by the proportion of participants experiencing at least 3% and 5% weight gain or loss as potential clinically meaningful cut-offs (17)

Statistical analyses

The study was powered for a non-inferiority efficacy endpoint. All randomized participants who received at one time the study treatment were included in the present analysis.

The changes in weight and BMI over time were compared within and between the groups using mixed models for repeated measures with random effects and spatial power covariance structure. The models included group, time and interaction between group and time. Time was chosen as continuous variable.

Univariable and multivariable analyses identified factors associated with the change in BMI and weight on DTG and considered: age, Framingham score (≤15% vs >15%), sex, race, HIV acquisition mode, CD4, hepatitis C antibody status, duration of viral suppression, time on cART, NRTI backbone, PI/r at baseline, eGFR and cardiovascular risk factors. Variables with univariable P<0.15 were retained for the multivariable analysis and multivariable analysis was adjusted for baseline BMI. As some parameters had missing values, we used multiple imputation approach to impute missing values. Continuous variables were modelled as categorical variables using terciles.

In order to explore whether a small difference in mean weight change could be masking more significant changes in a subgroup of individuals, we also analysed the evolution

to overweight and obesity, and the magnitude of weight change by category over time. The evolution of proportions by BMI categories and at least 5% weight change overtime were compared within and between the 2 groups using Generalised Estimation Equation (GEE) models with unstructured covariance matrix. The models included treatment group, time and interaction between treatment group and time. Time was chosen as categorical variable.

Variables were summarised as proportions for categorical variables, median and interquartile range (IQR) for continuous baseline variables, and mean and standard error (SE) for BMI and weight at each time point. All p-values are two-sided with a significance level of 5%. Analysis used SAS® statistical analysis software v9.4 and IBM SPSS statistics v24.

Results

Between May 2014 and November 2015, 455 participants were screened and 415 randomized: 205 to switch to a DTG-based regimen (DTG-IS arm) and 210 to continue their PI/r-based regimen (DTG-DS arm); 412 PLWH received at least one dose of study treatment (204 and 208 in the DTG-IS and DTG-DS arms, respectively). Study flowchart is shown in **Supplementary Figure 1**. Baseline characteristics were balanced between study groups including the duration of previous virological suppression, distribution of baseline PI/r, NRTI and the percentage of participants receiving lipid-lowering agents (**Table 1**). Of note the majority of participants were aged over 50 (88%), male (89%) and white (85%). For the DTG-DS group, characteristics at time of switch to DTG were roughly similar to study baseline. Baseline mean BMI was 26.2 kg/m^2 (SE 0.28) and 26.1 kg/m^2 (SE 0.28) in the DTG-IS and DTG-DS groups respectively. Baseline mean weight was 79.5 kg (SE 0.94) and 78.8 kg (SE 0.95) in the DTG-IS and DTG-DS groups respectively.

The evolution of weight and BMI over time in both arms, and the slopes of weight and BMI changes over 96 weeks are shown in **Figure 1**, **Supplementary Figure 2**, and **Supplimentary Tables 1** and **2**. The introduction of DTG increased weight and BMI particularly during the first 24-48 weeks and this finding was similarly reproduced in both arms. In the DTG-IS arm in which the exposure to DTG was longer, weight and BMI remained stable after the initial 48-week gains.

Table 2 shows the univariable and multivariable analysis of factors associated with the change in body weight and BMI at week 48. Switching from boosted darunavir (vs. other boosted PI), being white (vs. other races), having a total-to-HDL cholesterol ratio <3.7 (vs. ≥3.7), and having a normal or underweight BMI (vs. overweight or obese BMI) were independently associated with higher weight gains. Similar results were roughly reproduced when considering independent risk factors for higher BMI gains.

We analysed the magnitude of weight gain by category over time. The proportions of individuals experiencing 0 to 3%, >3% to 5%, and >5% weight gain or loss are illustrated in **Figure 2**. The proportion of participants who gained at least 5% weight increased significantly over time from 7.6% at W12 to 20.6% at W96 (P<0.001) in the immediate switch group and from 7.5% at W12 to 26.6% at W96 (P<0.001) in the deferred switch group, with a difference at W96 between the 2 groups of −6.0% (95% CI −14.6 to 2.6), which shows a non-significant difference between the treatment groups. Similarly, the proportions of participants who lost at least 5% weight also increased significantly in each arm with no significant differences at W96 between groups. Despite these significant changes in the extreme categories of at least 5% weight gain or loss, the proportions of individuals who were underweight, normal weight, overweight or obese did not change significantly over time in each arm and the differences between arms at 48 and 96 weeks were not statistically significant either (**Figure 3**).

Discussion

NEAT022 population comprised PWH virologically suppressed on a boosted PI-based triple regimen, mainly men, over 50 years, of white race, with relatively good CD4 cell counts, at high risk of CVD, and nearly 60% with a weight above normal. In this randomized clinical trial, switching from boosted PI to DTG led to significant decreases of plasma lipids and cardiovascular risk estimates over 96 weeks (1, 2).

The switching strategy was pure as the only antiretroviral change performed was the replacement of PI/r by DTG, while the nucleoside background remained unchanged. In the NEAT022 study, there were no PLWH on TAF because this drug was not available when the study began and the study did not allow for drug changes unless strictly necessary. Switching from PI/r to DTG led to significant, albeit numerically small, weight gains in the first 48 weeks after the switch. The pattern was consistently found in both IS and DS arms. Discontinuation of PI/r, introduction of DTG, or both could have been involved. Interestingly, in the IS group, which was exposed to DTG in the trial for 96 weeks, there were no further weight changes between 48 and 96 weeks, suggesting that the initial weight gain impact associated with the switching strategy may not necessarily be sustained over time. The amount of weight gain in the first 48 weeks of DTG exposure was 818 (DTG-IS arm) or 979 (DTG-DS arm) grams. Reported annual weight gain in European adult populations has been 300-500 grams (18), which helps to put into perspective the weight gain associated with switching from PI/r to DTG. After 96 weeks of DTG exposure, the weight change in the DTG-IS arm of the NEAT022 trial was within the range reported for European adults in the same period of time.

We identified several independent risk factors at baseline associated with a higher weight increase after the first 48 weeks of DTG exposure: switching from boosted darunavir (vs. other boosted PI), being white (vs. other races), having a total-to-HDL cholesterol ratio <3.7 (vs. ≥3.7), and having an underweight or normal (vs. overweight or obese) BMI. PWH

switching from boosted darunavir experienced a higher weight gain than PWH switching from other PIs. This might be relevant because darunavir is currently the most used PI worldwide, although cobicistat boosting is now more common than ritonavir boosting. In a Spanish multicentre randomized clinical trial comparing between ritonavir-boosted darunavir and boosted atazanavir plus tenofovir disoproxil fumarate/emtricitabine in antiretroviral-naive PWH, darunavir showed a better lipid profile (19) and less fat gain and less insulin resistance (20) than atazanavir at 96 weeks, although an U.S. trial with similar ART regimens and follow-up did not find such differences (21, 22). Another explanation may be plausible. Ritonavir-boosting may increase tenofovir exposure when concomitantly administered with tenofovir disoproxil fumarate (23), but the effect seems higher with darunavir (24) than with atazanavir (25). As tenofovir disoproxil fumarate suppresses weight gain (26), discontinuation of boosted darunavir might be associated with higher weight gain than discontinuation of boosted atazanavir.

In contrast to other studies, white race was associated with a higher weight gain although 85% of NEAT022 participants were of white race, making the study underpowered to examine an association between race and weight change. It is worth to remark that underweight PWH followed by normal weight PWH were the only BMI categories gaining weight above that expected in the general European adult population (18); overweight PWH gained less and obese PWH did not gain weight at all. Therefore, weight was gained inversely to baseline BMI status, and it did not specially impact on overweight or obese PWH. These findings suggest that the modest weight gain associated with switching from PI/r to DTG preferentially involved healthier people as reflected by their characteristics of normal (rather than elevated) total-to-HDL cholesterol ratio and underweight/normal (instead of overweight/obese) BMI among this population with high cardiovascular risk. It is reassuring that, among PLW with high cardiovascular risk, the modest and limited weight gain after switching from PI/r to DTG did not impact on those with a higher BMI or worse metabolic

status. In a pooled analysis of 12 prospective clinical trials wherein virologically suppressed PWH were randomized to switch or remain on a stable baseline regimen, moderate weight gains after antiretroviral switch were common and usually plateaued by 48 weeks (27), findings similar to those in NEAT022. In such pooled analysis, weight gain was correlated more strongly with baseline regimen, especially switch off drugs preventing weight gain such as tenofovir disoproxil fumarate or efavirenz, and with younger age and lower baseline BMI than with sex-, race-, or HIV-related factors.

There were significant changes (both, increases and losses) in proportions of persons in the extreme categories of percent weight change considered (>3% to 5%, and >5%) in both arms without significant differences at 96 weeks between arms, in accordance with the global changes in seen in weight and BMI. Exposure to DTG over 96 weeks did not increase further the proportions of persons who gained >3% to 5% or >5% of baseline weight relative to exposure to DTG over 48 weeks. The proportions of PWH according to BMI categories did not change significantly over time in each arm and the differences between arms at 48 and 96 weeks were not statistically significant either, further supporting the lack of clinically meaningful changes on BMI in the study population.

This study has limitations. The specific characteristics of the population and type of ART replaced by DTG should be considered with care before extrapolating these results to other populations or antiretroviral drugs switched. We did not collect information on food intake and physical exercise, but all participants received similar standardized lifestyle advices and the randomized nature of the study should not account for differences between arms. Finally, we did not undertake any anthropometric or body composition measurements to assess lean vs fat mass and subcutaneous vs visceral adiposity, which may all influence the clinical impact of weight gain *per se*.

In conclusion, switching from PI/r to DTG in PWH with high cardiovascular risk led to modest weight increases that were limited to the first 48 weeks, did not differ from what it would be expected in the general population at 96 weeks, and involved preferentially not overweight persons with a better metabolic status. These data do not suggest that the increase in weight associated with this switching strategy may be a clinically relevant problem. Further long follow-up studies are needed to see whether these findings are confirmed in other populations and with other antiretroviral drugs.

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Figures

Figure 1. Evolution of weight and body mass index (BMI), and change in weight and BMI according to modelled slopes.

- **Figure 1A:** Evolution of Weight, kg
- **Figure 1B:** Change in weight (kg) according to modelled slopes
- **Figure 1C:** Evolution of BMI. kg/m^2
- **Figure 1D:** Change in BMI according to modelled slopes

Figure 2: Evolution of the proportion of participants by category of percent weight change from baseline.

Figure 3: Proportion of participants in underweight, normal weight, overweight or obese body mass index (BMI) categories over time.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Conflicts of interest

L. Waters has received honoraria for lectures or advisory boards from Gilead, Janssen, MSD and ViiV.

S. Rusconi has received honoraria for lectures or advisory boards from Gilead, Janssen, MSD and ViiV.

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Lambert Assoumou and A. González-Cordón : none to declare.

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NEAT 022 study group investigators:

Belgium: Linos Vandekerckhove, Els Caluwé, Stephane De Wit, Coca Necsoi, Eric Florence, and Maartje Van Frankenhuijsen.

France: François Raffi, Clotilde Allavena, Véronique Reliquet, David Boutoille, Morane Cavellec, Elisabeth André-Garnier, Audrey Rodallec, Thierry Le Tourneau, Jérôme Connault, Jean-Michel Molina, Samuel Ferret, Miresta Previlon, Yazdan Yazdanpanah, Roland Landman, Véronique Joly, Adriana Pinto, Christine Katlama, Fabienne Caby, Nadine Ktorza and Luminita Schneider.

Germany: Christoph Stephan, Timo Wolf, Gundolf Schüttfort, Juergen Rockstroh, Jan-Christian Wasmuth, Carolynne Schwarze-Zander, Christoph Boesecke, Hans-Jurgen Stellbrink, Christian Hoffmann, Michael Sabranski, Stephan Esser, Robert Jablonka, Heidi Wiehler, Georg Behrens, Matthias Stoll, and Gerrit Ahrenstorf.

Italy: Giovanni Guaraldi, Giulia Nardini, Barbara Beghetto, Antonella D'Arminio Montforte, Teresa Bini, Viola Cogliandro, Massimo Di Pietro, Francesco Maria Fusco, Massimo Galli, Stefano Rusconi, Andrea Giacomelli, and Paola Meraviglia.

Spain: Esteban Martinez, Ana González-Cordón, José Maria Gatell, Berta Torres, Pere Domingo, Gracia Mateo, Mar Gutierrez, Joaquin Portilla, Esperanza Merino, Sergio Reus, Vicente Boix, Mar Masia, Félix Gutiérrez, Sergio Padilla, Bonaventura Clotet, Eugenia Negredo, Anna Bonjoch, José L. Casado, Sara Bañón-Escandell, Jose Saban, Africa Duque, Daniel Podzamczer, Maria Saumoy, Laura Acerete, Juan Gonzalez-Garcia, José Ignacio Bernardino, José Ramón Arribas, and Victor Hontañón.

United Kingdom: Graeme Moyle, Nicole Pagani, Margherita Bracchi, Jaime Vera, Amanda Clarke, Tanya Adams, Celia Richardson, Alan Winston, Borja Mora-Peris, Scott Mullaney, Laura Waters, Nahum de Esteban, Ana Milinkovic, Sarah Pett, Julie Fox, Juan Manuel Tiraboschi, Margaret Johnson, Mike Youle, Chloe Orkin, Simon Rackstraw, James Hand, Mark Gompels, Louise Jennings, Jane Nicholls and Sarah Johnston.

For further information on the protocol, please go to: https://www.neat-id.org/neat-022 and https://clinicaltrials.gov/ct2/show/NCT02098837

Contributions

LW and EM designed the study. LA undertook the statistical analyses. All authors were involved in the interpretation of data. LW and EM drafted the manuscript. All authors critically reviewed and subsequently approved the final version.

Table 1: Baseline characteristics

Figures presented as number (%) unless indicated otherwise	DTG-IS (n=205)	DTG-DS (n=210)	Total (n=415)
Age (years): median (IQR)	54 (51-58)	53 (51-57)	54 (51-58)
Age > 50 years	179 (87.3)	184 (87.6)	363 (87.5)
Framingham score at 10 years			
<10	50 (24.4)	59 (28.1)	109 (26.3)
10-15	62 (30.2)	53 (25.2)	115 (27.7)
15-20	41 (20.0)	48 (22.9)	89 (21.4)
>20	52 (25.4)	50 (23.8)	102 (24.6)
Male gender	181 (88.3)	189 (90.0)	370 (89.2)
White race	172 (83.9)	180 (85.7)	352 (84.8)
Mode of HIV-1 transmission			
Men who have sex with men	130 (63.4)	131 (62.4)	261 (62.9)
Heterosexual	43 (23.9)	48 (22.9)	97 (23.4)
Other	26 (12.7)	31 (14.8)	57 (13.7)
CD4+ count (cells per µL): median (IQR)	635 (495-819)	585 (471-830)	617 (477-820)
HIV RNA >50 copies per mL	7 (3.4)	1 (0.5)	8 (2)
Hepatitis C IgG antibodies detected	27 (13.4)	24 (11.6)	51 (12.5)
Time since undetectable viral load (< 50 copies per mL); years: median (IQR)	4.9 (2.5-9.1)	5.3 (2.3-8.5)	5 (2.4-8.8)
Backbone nucleos(t)ides			
Tenofovir disoproxil fumarate/emtricitabine	134 (65.4)	135 (64.3)	269 (64.8)
Abacavir/lamivudine	63 (30.7)	67 (31.9)	130 (31.3)
Other	8 (3.9)	8 (3.8)	16 (3.9)
PI/r at baseline			
Lopinavir	13 (6.4)	23 (11.0)	36 (8.7)
Darunavir	105 (51.5)	109 (51.9)	212 (51.2)
Atazanavir	77 (37.7)	72 (34.3)	151 (36.5)
Other	9 (4.4)	6 (2.9)	15 (3.7)
Current Smoker	78 (38.0)	79 (37.8)	157 (37.9)
Diabetes mellitus	11 (5.5)	13 (6.3)	24 (5.9)
Family history of cardiovascular disease	87 (43.3)	89 (43.4)	176 (43.3)
Receiving lipid lowering agents	63 (30.7)	60 (28.6)	123 (29.6)

High blood pressure	72 (35.3)	79 (37.6)	151 (36.5)
Daily exercise	64 (31.2)	59 (28.2)	123 (29.7)
Number of cardiovascular risk factors			
0	54 (26.3)	56 (26.7)	110 (26.5)
1	71 (34.6)	63 (30.0)	134 (32.3)
2	49 (23.9)	60 (28.6)	109 (26.3)
≥3	31 (15.1)	31 (14.8)	47 (11.3)
Fasting plasma lipids (mmol/L): median (IQR)			
Total cholesterol	5.2 (4.5-5.8)	5.1 (4.5-5.6)	5.1 (4.5-5.7)
Triglycerides	1.6 (1.2-2.3)	1.6 (1.2-2.2)	1.6 (1.2-2.2)
Non-HDL cholesterol	3.3 (2.9-4.0)	3.8 (3.1-4.4)	3.8 (3.2-4.5)
LDL-cholesterol	3.1 (2.5-3.7)	3.1 (2.5-3.6)	3.1 (2.5-3.6)
HDL-cholesterol	1.2 (1.0-1.5)	1.2 (1.0-1.5)	1.2 (1.0-1.5)
Total Cholesterol/HDL cholesterol ratio	4.2 (3.4-5.4)	4.1 (3.4-5.2)	4.1 (3.4-5.3)
eGFR (mL/minute): median (IQR)	90.8 (80.7-99.7)	91.4 (78.3-101.8)	91.1 (80-100.2)
Body mass index (BMI, Kg/m^2): median (IQR)	25.8 (23.7-28.1)	25.8 (23.5-28.2)	25.8 (23.5-28.2)
Underweight (<18 .5 kg/m^2)	2 (1.0)	5 (2.5)	6 (1.7)
Normal (18.5 – 25 kg/m^2)	74 (36.5)	84 (41.4)	158 (38.9)
Overweight (25.01 – 30 kg/m^2)	97 (47.8)	83 (40.9)	180 (44.3)
Obese (>30 kg/m^2)	30 (14.8)	31 (15.3)	61 (15.0)
Weight, Kg: median (IQR)	79.5 (72.1-86)	78.1 (69.5-87.8)	79.0 (71.0-87.0)

Data are n (%) or median (IQR: interquartile range).
DTG-IS: Dolutegravir Inmediate Switch; DTG-DS: Dolutegravir Deferred Switch

Table 2: Factors associated with the change in body mass index (BMI) and weight within the first 48 weeks on DTG (immediate switch arm 0-48 weeks and deferred switch arm 48-96 weeks)

A) Change in Weight

			Change from baseline in weight (Kg) at week 48			
			Univariable analysis		Multivariable analysis	
	Parameter	Baseline value Mean (sd)	Mean gain (95% CI)	P value	Mean gain (95% CI)	P value
PI at baseline	Darunavir	79.6 (13.9)	1.335 (0.815 ; 1.855)	0.0216	1.306 (0.716 ; 1.895)	0.0261
	Atazanavir	80.0 (13.4)	0.291 (-0.346 ; 0.929)		0.304 (-0.469 ; 1.077)	
	Other (lopinavir; saquinavir; fosamprenavir)	77.2 (13.8)	0.374 (-0.713 ; 1.462)		0.317 (-0.996 ; 1.629)	
Race	White	79.4 (13.8)	1.005 (0.616 ; 1.395)	0.1142	1.003 (0.494 ; 1.512)	0.0370
	Black	80.2 (13.3)	-0.033 (-1.264 ; 1.198)		-0.085 (-1.309 ; 1.139)	
	Other	79.8 (13.2)	-0.227 (-1.822 ; 1.368)		-0.351 (-2.418 ; 1.715)	
Triglycerides at baseline	<1.3 mmol/L	75.6 (13.4)	1.477 (0.853 ; 2.101)	0.0101	1.439 (0.642 ; 2.236)	0.1161
	1.3-1.9 mmol/L	79.6 (12.4)	0.975 (0.334 ; 1.616)		0.976 (0.278 ; 1.673)	
	>1.9 mmol/L	83.1 (14.2)	0.138 (-0.474 ; 0.75)		0.102 (-0.608 ; 0.813)	
TC/HDL ratio at baseline	<3.7	75.2 (12.3)	1.623 (1.007 ; 2.239)	0.0099	1.615 (0.795 ; 2.434)	0.0361
	3.7-4.8	80.3 (13.5)	0.371 (-0.262 ; 1.005)		0.345 (-0.374 ; 1.065)	
	>4.8	82.9 (14.2)	0.529 (-0.093 ; 1.152)		0.518 (-0.152 ; 1.188)	
Non-HDL-c at baseline	<3.4 mmol/L	78.7 (13.5)	1.255 (0.635 ; 1.874)	0.1132	1.232 (0.320 ; 2.143)	0.9517
	3.4-4.2 mmol/L	79.7 (13.8)	0.775 (0.137 ; 1.412)		0.774 (-0.055 ; 1.602)	
	>4.2 mmol/L	80.1 (13.9)	0.516 (-0.111 ; 1.143)		0.483 (-0.232 ; 1.197)	
BMI at baseline	Underweight (<18.5 kg/m2)	50.2 (5.2)	4.12 (1.081 ; 7.158)	0.0007	4.093 (2.771 ; 5.415)	0.0079
	Normal (18.5-25 Kg/m2)	69.3 (8.9)	1.619 (0.999 ; 2.239)		1.599 (0.962 ; 2.236)	
	Overweight (25.01-30 Kg/m2)	82.6 (7.9)	0.408 (-0.157 ; 0.974)		0.386 (-0.212 ; 0.985)	
	Obese (>30 Kg/m2)	97.2 (12.2)	-0.012 (-0.974 ; 0.949)		-0.015 (-0.813 ; 0.784)	

B) Change in BMI

			Change from baseline in BMI (Kg/m2) at week 48			
			Univariable analysis		Multivariable analysis	
	Parameter	Baseline value Mean (sd)	Mean (95% CI)	P value	Mean (95% CI)	P value
PI at baseline	Darunavir	26.4 (4.2)	0.462 (0.286 ; 0.638)	0.0154	0.453 (0.261 ; 0.646)	0.0158
	Atazanavir	26.4 (4.1)	0.098 (-0.118 ; 0.314)		0.102 (-0.152 ; 0.355)	
	Other (lopinavir; saquinavir; fosamprenavir)	25.4 (3.8)	0.106 (-0.267 ; 0.478)		0.079 (-0.344 ; 0.502)	
Race	White	26.1 (4.1)	0.341 (0.209 ; 0.473)	0.1424	0.339 (0.170 ; 0.509)	0.0420
	Black	27.4 (3.7)	0.014 (-0.403 ; 0.432)		-0.001 (-0.404 ; 0.402)	
	Other	26.7 (3.7)	-0.064 (-0.605 ; 0.477)		-0.124 (-0.824 ; 0.575)	
Triglycerides at baseline	<1.3 mmol/L	25.3 (3.9)	0.512 (0.301 ; 0.724)	0.0102	0.499 (0.239 ; 0.759)	0.1046
	1.3-1.9 mmol/L	26.3 (4.1)	0.317 (0.099 ; 0.535)		0.314 (0.082 ; 0.546)	
	>1.9 mmol/L	27.2 (4.1)	0.056 (-0.152 ; 0.263)		0.044 (-0.195 ; 0.283)	
TC/HDL ratio at baseline	<3.7	25.4 (4.1)	0.537 (0.327 ; 0.747)	0.0179	0.526 (0.250 ; 0.801)	0.0563
	3.7-4.8	26.2 (3.9)	0.141 (-0.074 ; 0.356)		0.137 (-0.107 ; 0.382)	
	>4.8	27.2 (4)	0.188 (-0.023 ; 0.399)		0.182 (-0.047 ; 0.411)	
BMI at baseline	Underweight (<18.5 kg/m2)	16.8 (0.8)	1.316 (0.284 ; 2.348)	0.0009	1.296 (0.802 ; 1.790)	0.0074
	Normal (18.5-25 Kg/m2)	22.8 (1.6)	0.556 (0.347 ; 0.764)		0.548 (0.335 ; 0.762)	
	Overweight (25.01-30 Kg/m2)	27 (1.3)	0.13 (-0.062 ; 0.322)		0.124 (-0.074 ; 0.322)	
	Obese (>30 Kg/m2)	33.2 (2.6)	0.018 (-0.305 ; 0.341)		0.018-(0.247 ; 0.283)	

Figure 1

Figure 1A: Evolution of Weight, kg

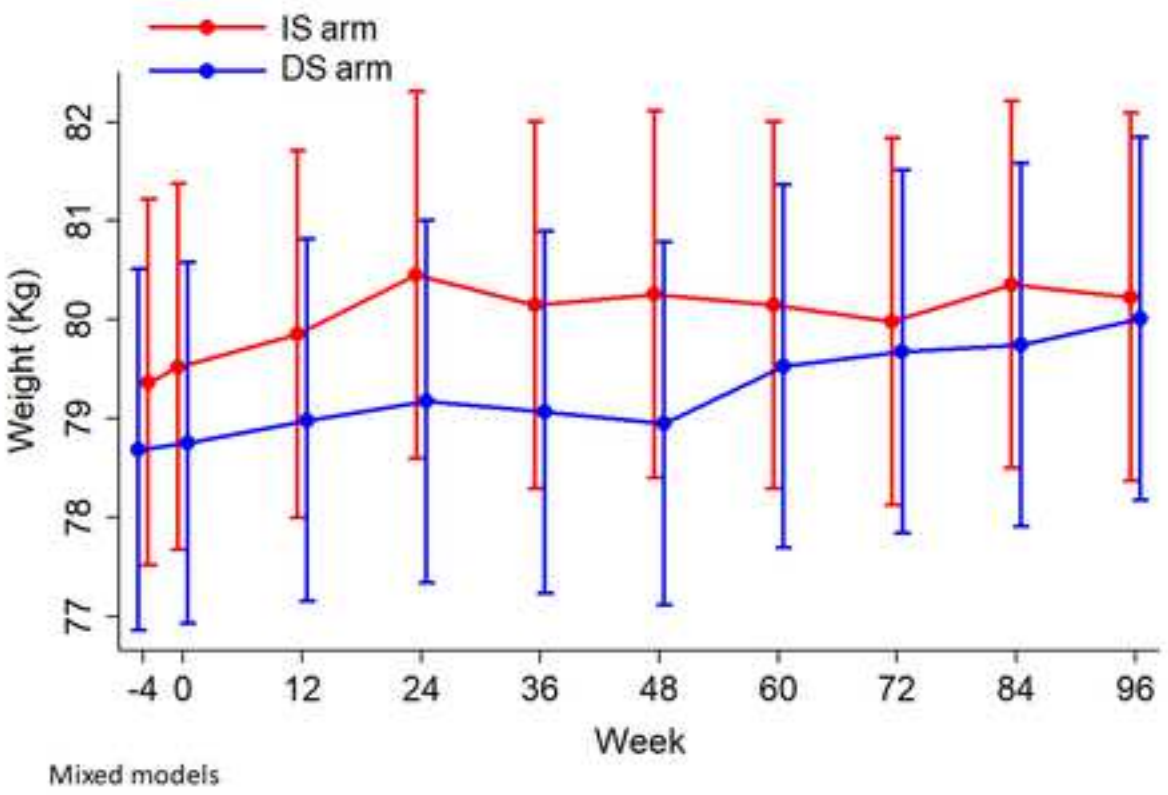
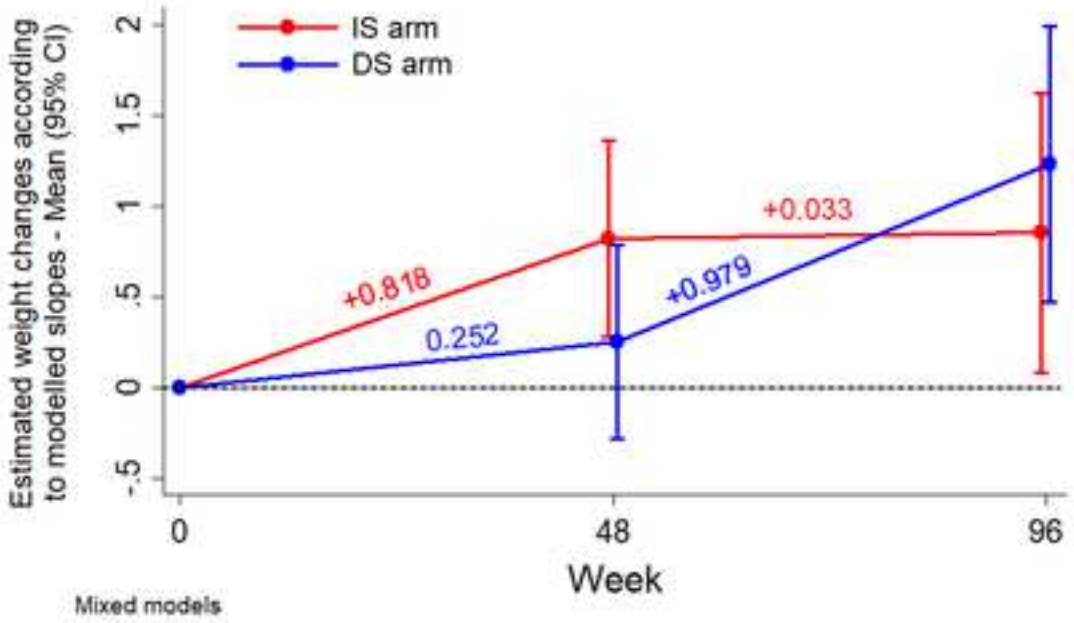


Figure 1

Figure 1B: Change in weight (kg) according to modelled slopes



Mixed models

	WEIGHT			
	0-48 week		48-96 week	
	Slope	P-value	Slope	P-value
DTG-I	0.818 (0.276)	0.003	0.033 (0.282)	0.907
DTG-D	0.252 (0.271)	0.353	0.979 (0.277)	<0.001
DTG-I vs DTG-D	0.008		0.002	

Figure 1

Figure 1C: Evolution of BMI. kg/m²

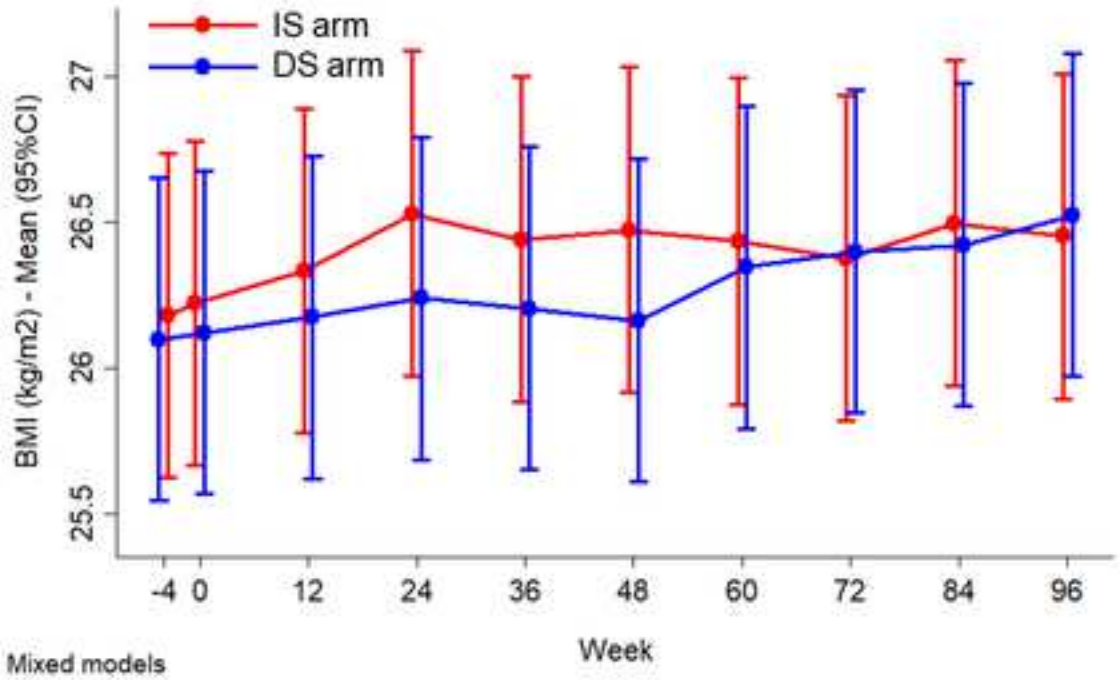
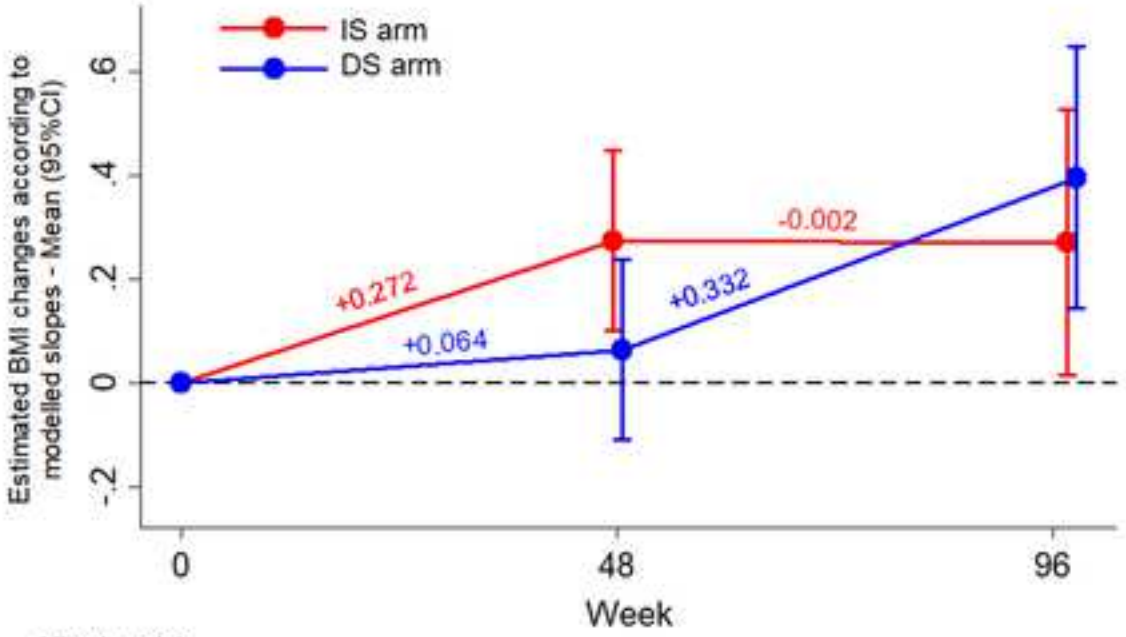


Figure 1

Figure 1D: Change in BMI according to modelled slopes



Mixed models

	0-48 week		48-96 week	
	Slope	P-value	Slope	P-value
DTG-I	0.272 (0.090)	0.003	-0.002 (0.095)	0.984
DTG-D	0.064 (0.088)	0.471	0.332 (0.094)	0.004
DTG-I vs DTG-D	0.008		0.002	

Figure 2

Figure 2: Evolution of the proportion of participants by category of percent weight change from baseline

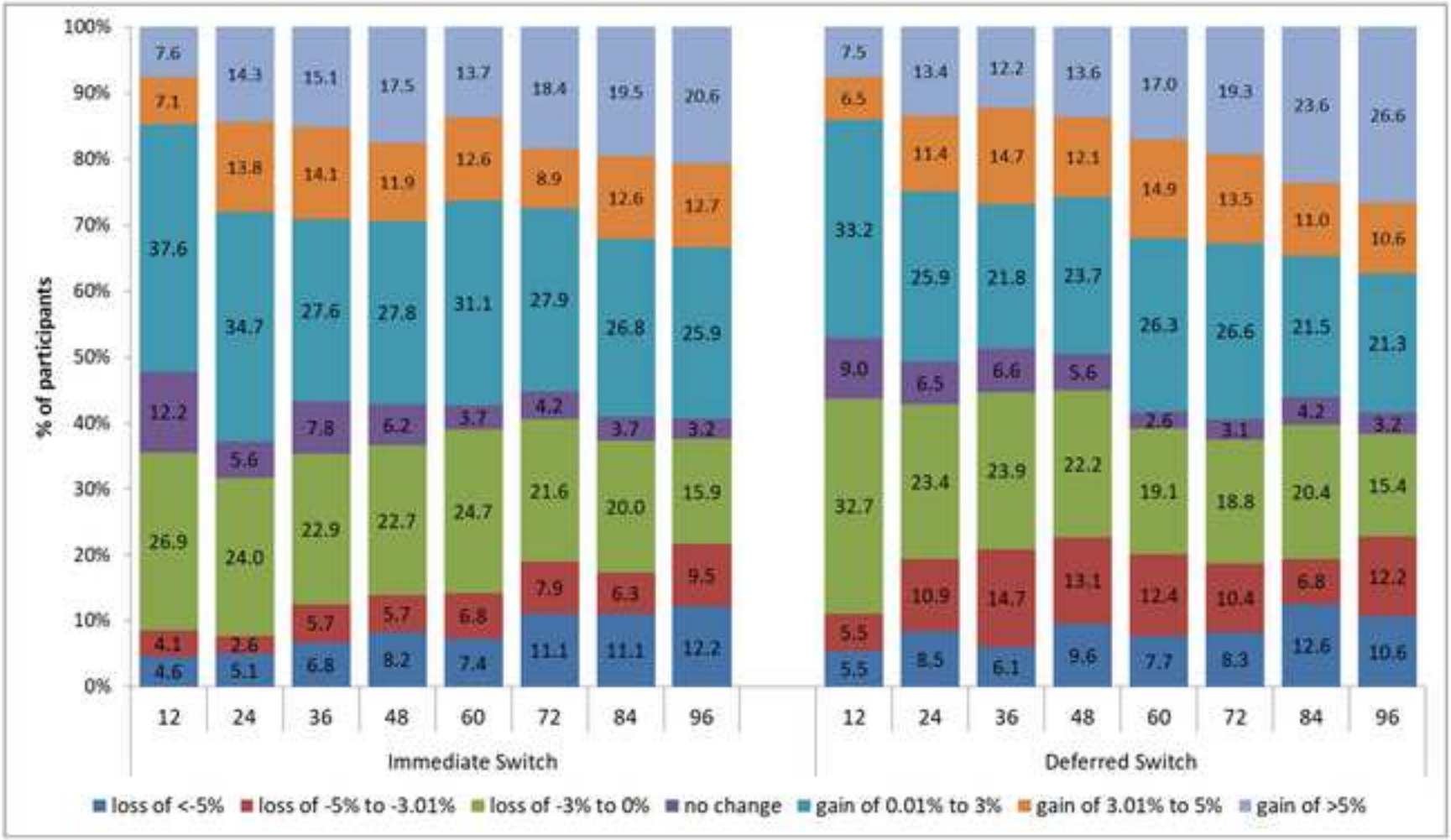
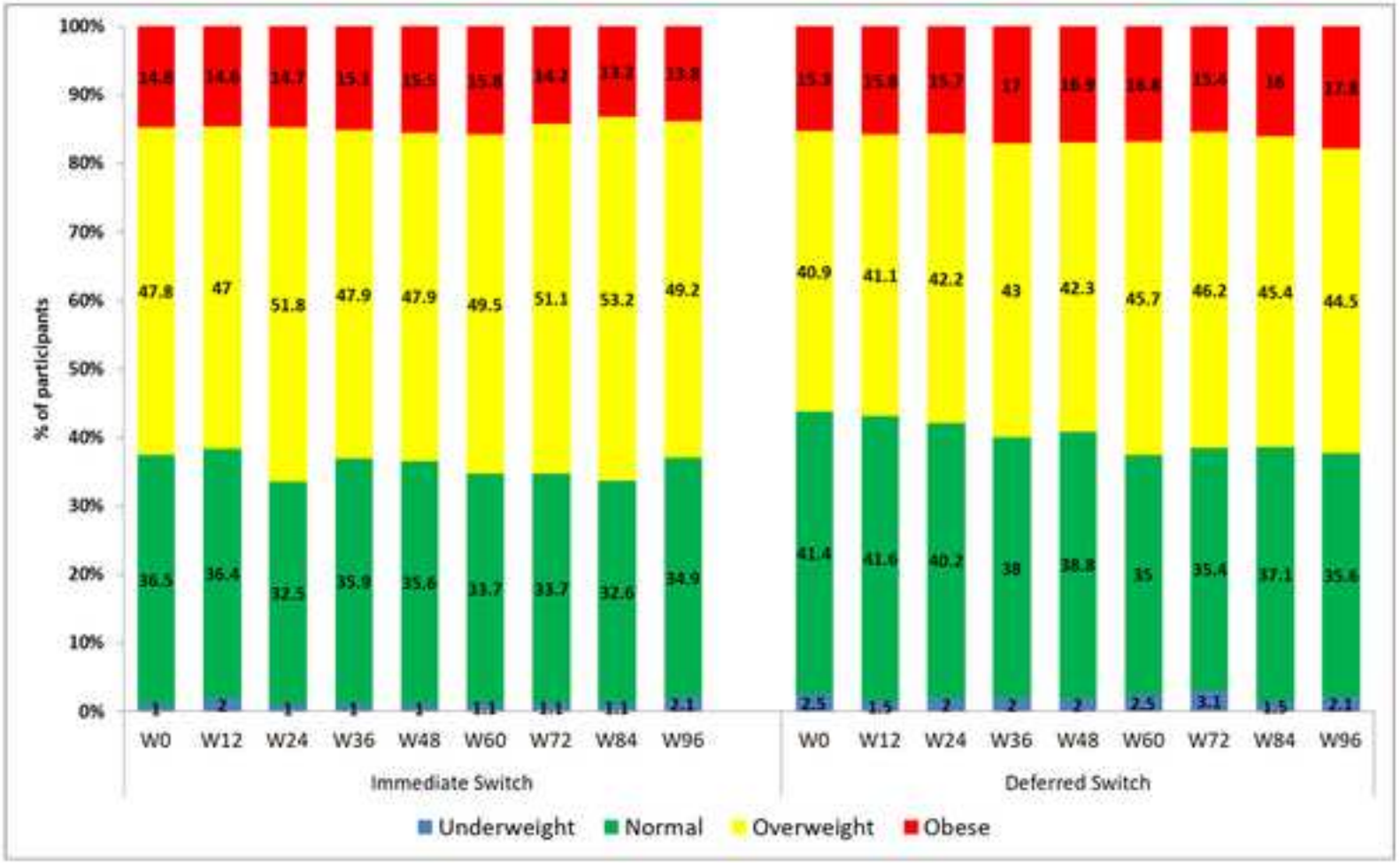
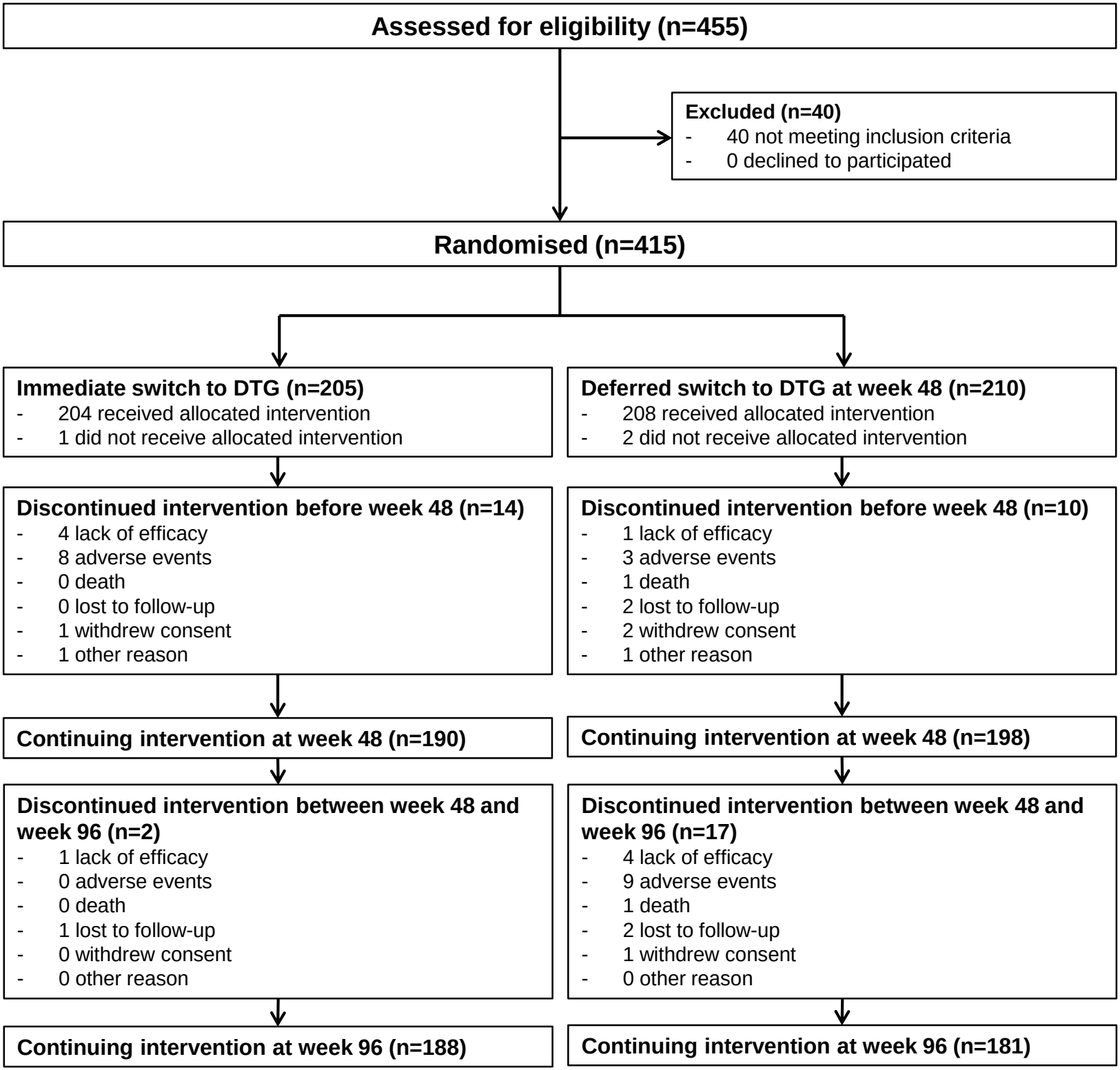


Figure 3

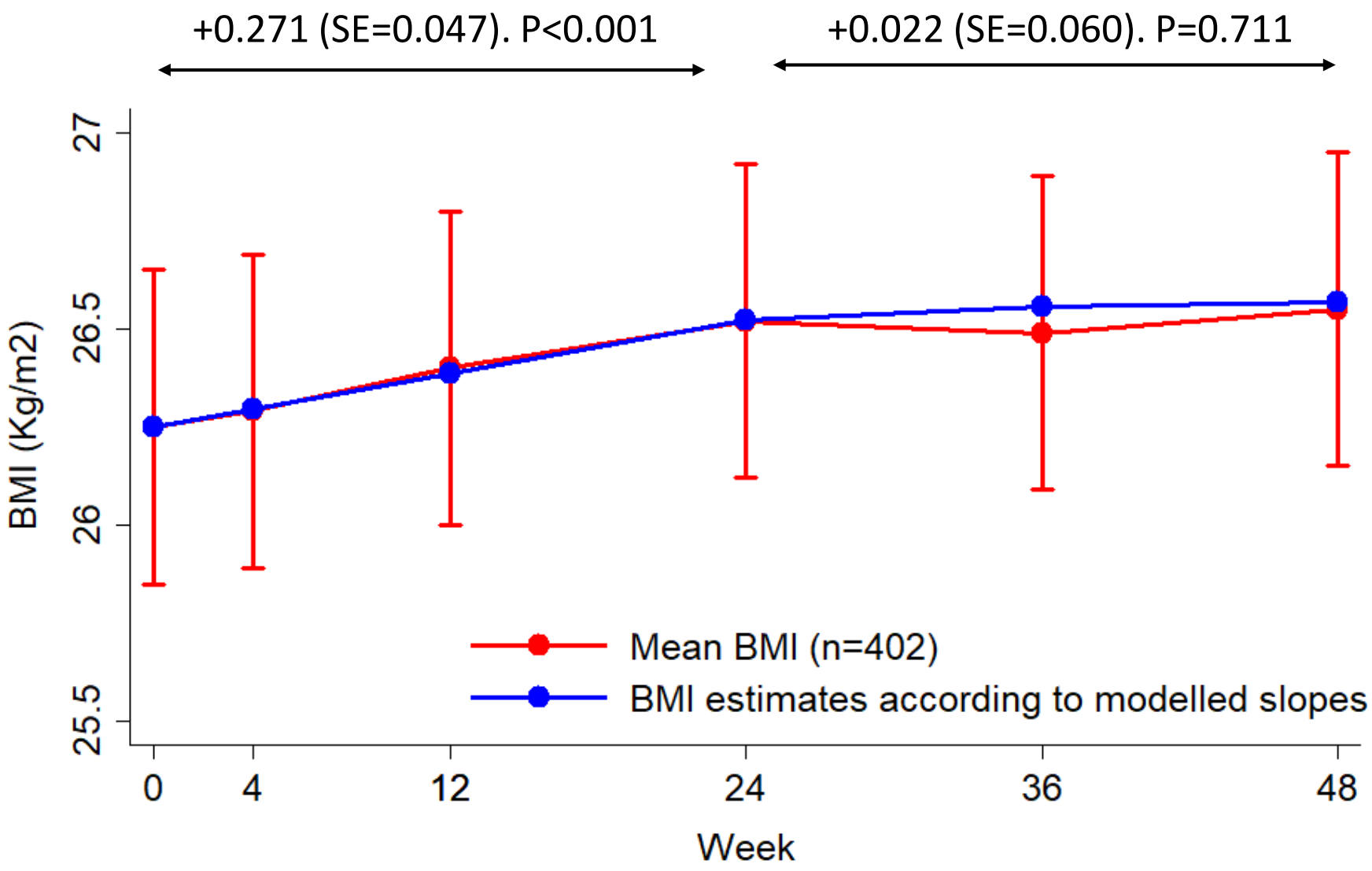
Figure 3: Proportion of participants in underweight, normal weight, overweight or obese categories body mass index (BMI) over time



Supplementary Figure 1: Study flowchart



Supplementary Figure 2: Evolution of BMI within the first 48-week on DTG (N=402)



Mixed models estimates

Supplementary Table 1: Evolution of WEIGHT (kg)

	DTG-I		DTG-D	
Week	Mean	SE	Mean	SE
-4	79.3694	0.9416	78.6891	0.9303
0	79.5261	0.9416	78.7568	0.9305
12	79.6561	0.9420	78.9840	0.9310
24	79.8563	0.9423	79.1780	0.9311
36	80.4565	0.9428	79.0674	0.9316
48	80.1464	0.9435	78.9531	0.9316
60	80.2572	0.9435	79.0011	0.9322
72	80.1513	0.9441	79.5335	0.9321
84	79.9876	0.9442	79.6811	0.9325
96	80.3557	0.9443	79.7485	0.9327

Mixed models were used to estimated the Mean (SE) of BMI at each time point

Supplementary Table 2: Evolution of BMI (kg/m^2)

	DTG-I		DTG-D	
Week	Mean	SE	Mean	SE
-4	26.182	0.283	26.100	0.281
0	26.224	0.283	26.124	0.281
12	26.334	0.284	26.176	0.281
24	26.531	0.284	26.241	0.281
36	26.442	0.284	26.206	0.281
48	26.474	0.284	26.166	0.281
60	26.436	0.284	26.348	0.281
72	26.379	0.284	26.401	0.282
84	26.498	0.284	26.423	0.282
96	26.454	0.285	26.525	0.282

Mixed models were used to estimated the Mean (SE) of BMI at each time point