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MAJOR ARTICLE

Incidence of hypertension and blood pressure changes in persons with HIV at high risk for cardiovascular disease switching from boosted protease inhibitors to dolutegravir: a post-hoc analysis of the 96-week randomised NEAT-022 trial

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Background: Integrase inhibitors have been recently linked to a higher risk for hypertension. In NEAT022 randomized trial, virologically suppressed persons with HIV (PWH) with high cardiovascular risk switched from protease inhibitors to dolutegravir either immediately (DTG-I) or after 48 weeks (DTG-D).

Methods: Primary endpoint was incident hypertension at 48 weeks. Secondary endpoints were changes in systolic (SBP) and diastolic (DBP) blood pressure; adverse events and discontinuations associated with high blood pressure; and factors associated with incident hypertension.

Results: At baseline, 191 (46.4%) participants had hypertension and 24 persons without hypertension were receiving antihypertensive medications for other reasons. In the 197 PWH (n=98, DTG-I arm; n=99, DTG-D arm) without hypertension or antihypertensive agents at baseline, incidence rates per 100 person-years were 40.3 and 36.3 (DTG-I) and 34.7 and 52.0 (DTG-D) at 48 (P=0. 5755) and 96 (P=0. 2347) weeks. SBP or DBP changes did not differed between arms. DBP (mean, 95% confidence interval) significantly increased in both DTG-I (+2.78 mmHg (1.07-4.50), P=0.0016] and DTG-D [+2.29 mmHg (0.35-4.23), P=0.0211] arms in the first 48 weeks of exposure to dolutegravir. Four (3 under dolutegravir, 1 under protease inhibitors) participants discontinued study drugs due to adverse events associated with high blood pressure. Classical factors, but not treatment arm, were independently associated with incident hypertension.

Conclusions: PWH at high risk for cardiovascular disease showed high rates of hypertension at baseline and after 96 weeks. Switching to dolutegravir did not negatively impact on the incidence of hypertension or blood pressure changes relative to continuing protease inhibitors.

Keywords: Blood pressure, hypertension, switch, dolutegravir

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INTRODUCTION

Risks for cardiovascular disease (CVD) in general and hypertension in particular in people with HIV (PWH) increase over time in excess to those in the general population (1). Classical cardiovascular risk factors (2) and low CD4 cell nadir have been associated with a higher risk of hypertension in PWH (3, 4). Initiation of antiretroviral therapy usually increases blood pressure in antiretroviral-naive PWH although its clinical impact appears to be low (5). Integrase

inhibitors have been recently associated with an incidence of hypertension higher than non-nucleoside reverse transcriptase inhibitors and similar to protease inhibitors in the RESPOND cohort (6). Other smaller cohort studies have suggested that initiating or switching to integrase inhibitors as a class or more specifically dolutegravir is associated with increases in both weight gain and blood pressure, or with a higher risk of hypertension than taking antiretroviral drugs from other classes (7-11). Previously, lopinavir/ritonavir (12) and non-nucleoside reverse transcriptase inhibitors (13, 14) had been associated in other cohorts, although large cohorts such as D:A:D did not find any independent association between exposure to individual antiretroviral drugs and risk of hypertension (15). Inherent limitations accross cohort studies may include residual confounding, channeling bias, lack of standardisation of blood pressure measurements, and different historical settings.

NEAT–022 is a strategic trial comparing the efficacy, safety, and impact on plasma lipids of switching the boosted protease inhibitor (PI/r) component to dolutegravir (DTG) versus continuing PI/r in PWH at high risk for CVD suppressed on two nucleoside reverse transcriptase inhibitors (NRTIs) plus one PI/r. Primary 48-week (16) and final 96-week (17) results demonstrated noninferior virological suppression and significant lipid and CVD risk reductions on switching to DTG relative to continuing PI/r. In order to gain a more clear understanding on whether specific integrase inhibitors may impact on blood pressure, we analysed the effects of switching from PI/r to dolutegravir in the NEAT022 study thus providing an ideal scenario of a randomized clinical trial, involving a pure drug change, that was replicated, free of the confounding increasing blood pressure effects observed in treatment-naïve PWH initiating ART, and including a homogeneous population at high risk for CVD. Because of the beneficial effects of the switching strategy on plasma lipids and CVD risk, we hypothesized that switching from protease inhibitors to dolutegravir would not negatively impact on blood pressure relative to continuing protease inhibitors.

METHODS

Participants

NEAT022 trial was conducted in 32 clinical sites across 6 European countries. Participants were recruited between May 2014 and November 2015. Eligible persons were PWH ≥50 years and/or ≥18 years with a Framingham CVD risk score >10% at 10 years receiving two NRTI plus one PI/r and having plasma HIV RNA <50 copies/mL for at least the previous 6 months. The protocol was approved by the ethics committees of all participating sites. All participants provided written informed consent. The study is registered on ClinicalTrials.gov NCT02098837 and EudraCT 2013-003704-39.

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Randomization and masking

Eligible participants were randomly assigned 1:1 in an open-label fashion to either switch the PI/r anchor to DTG (immediate switch or DTG-I) or to continue PI/r-based ART for 48 weeks (delayed switch or DTG-D) at which point all participants remaining on a PI/r switched to DTG out to week 96 (**Supplementary figure 1**). Participants were assigned to treatment groups by computer-generated permuted blocks of four and stratified by country.

Study procedures

Blood pressure was monitored following a standardized procedure at screening, baseline, and weeks 4 (DTG-I group only), 12, 24, 36, 48, 52 (DTG-D group only), 60, 72, 84, and 96. Blood pressure was measured according to European guidelines by trained nurses at each participating centre using validated semi-automatic or automatic oscillometric sphygmomanometers (18).

General assessment of vital signs, adverse events, and blood samples for routine safety, fasting lipid and immuno-virological measurements were also included at each visit. Participants also received advice on smoking cessation, daily exercise, weight, diet and alcohol intake, and blood pressure control. AIDS events and deaths, serious adverse events, adverse events grade 3 or above, adverse events leading study drug discontinuation, all protocol discontinuations and all protocol defined episodes of virological failures required confirmation by an independent endpoint review committee blinded to treatment regimens.

Endpoints

The primary endpoint was the incidence of a new diagnosis of hypertension at 48 weeks. For the purpose of this analysis, persons with hypertension or antihypertensive drugs at baseline were excluded. The thresholds of blood pressure used to define hypertension were ≥130 mmHg for systolic blood pressure (SBP) or ≥85 mmHg for diastolic blood pressure (DBP) which have been used in guidelines to define "high-normal blood pressure" (19, 20) or "stage 1 hypertension" (21). Hypertension at baseline was considered if: 1) hypertension had been diagnosed prior to screening and baseline; or 2) SBP ≥130 mmHg at screening and baseline and/or DBP ≥85 mmHg at screening and baseline in participants without a prior diagnosis of hypertension. From week 4 to week 96, hypertension was defined as any of the following possibilities: 1) SBP ≥130 mmHg and/or DBP ≥85 mmHg at a given visit plus SBP ≥130 mmHg and/or DBP ≥85 mmHg at the subsequent visit (with the first visit considered as the date of diagnosis); 2) one single SBP ≥130 mmHg and/or DBP ≥85 mmHg at a given visit with use of antihypertensive medications within six months (with the visit in which the blood pressure was above the thresholds considered as the date of diagnosis); or 3) initiation of antihypertensive medications without a recorded high blood pressure between 2 consecutive visits (with the visit following the date of antihypertensive initiation considered as the date of diagnosis). Any drug potentially accepted for treatment of hypertension was considered as an antihypertensive medication (22).

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Among secondary end-points, we considered: incidence of a new diagnosis of hypertension at 96 weeks; proportion of participants with hypertension and factors associated with hypertension at baseline; changes from baseline in SBP and DBP per arm at 48 and 96 weeks; number of participants with hypertension reported among adverse events and number of study drug discontinuations due to this reason; baseline factors (including treatment arm) associated with hypertension at 48 and 96 weeks; and relationship between weight and blood pressure.

Statistical analyses

The primary and all secondary end points were analysed on a modified intention-to-treat (mITT) basis. The mITT population consisted of all randomized participants who received study treatment at least once. Baseline characteristics were summarized overall and by treatment arm using median and interquartile range for continuous variables and number and percentage for categorical variables. The nonparametric Man-Whitney test was used to compare continuous variables and the chi-square or Fisher exact tests for categorical variables.

The incidence rates of hypertension were estimated by the total number of persons diagnosed with hypertension divided by the total number of person-years. Incidence rate ratios (IRR) and the associated 95% CI were calculated using a Poisson regression model to compare the incidence between the two-treatment arms (DTG-I and DTG-D). Assuming a 35% incidence rate of hypertension in the DTG-D at 48 weeks, sample sizes of 3946, 1006, 494, 304, or 200 participants respectively would be needed to detect differences of 5%, 10%, 15%, 20%, or 25% in incidence rates between the two treatment groups at week 48 with 80% power and 5% type I error.

Logistic regression models or Poisson regression analyses were used to identify factors associated with hypertension at baseline or with the incidence of hypertension at weeks 48 and 96, respectively. Variables with univariate p-value <0.20 were retained for the multivariable analysis. A backward elimination technique (alpha=0.05) was used.

The changes in the proportion of persons with hypertension from baseline to week 48, from week 48 to week 96, and from baseline to week 96 were compared within and between the two treatment arms (DTG-I and DTG-D) using a generalized estimating equation (GEE), with independent covariance structure, a binomial distribution, and a log link to estimate the relative risk.

To account for dilution bias due to regression to the mean in assessing the impact of study treatment on blood pressure changes, changes in SBP and DBP from baseline to week 48, week 48 to week 96, and baseline to week 96 were compared within and between the 2 treatment arms (DTG-I and DTG-D) using linear mixed models for repeated measures with random intercept and unstructured covariance matrix, adjusted for groups defined by baseline SBP and DBP. Models included treatment groups, time, groups defined by baseline SBP and DBP, interaction between treatment groups and time, and interaction between groups defined by baseline SBP and

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DBP and time. Time was considered a categorical variable. Regression-to-the-mean in blood pressure changes was estimated with the MacMahon method (23). Therefore, participants were classified into strata of 10 mm Hg baseline blood pressure. Baseline SBP levels were categorized as follows: <120, 120-129, and ≥130 mm Hg. Baseline DBP levels were categorized as follows: <70, 70-79, and ≥80 mm Hg. Mean blood pressure values at baseline and during follow-up were calculated overall and for groups defined by baseline SBP and DBP. For participants starting antihypertensive agents, a last observation carried forward approach was used and the blood pressure result leading to the start of antihypertensive treatment was used in the analysis for the rest of the trial.

Nonparametric Spearman correlation test was used to assess the association between body weight and SBP and DBP at baseline, and between change from baseline in body weight and change from baseline in SBP and DBP at week 48 and 96. Changes in cardiovascular risk scores from baseline to week 48 or week 96 were estimated with linear mixed models for repeated measures. SAS® statistical analysis v9.4 and IBM SPSS statistics v24 software were used.

RESULTS

Between May 2014 and November 2015, 455 PLW were screened, 415 randomized [205 switched from PI/r to DTG at baseline (DTG-I arm) and 210 switched from PI/r to DTG at week 48 (DTG-D arm)], and 412 (204 DTG-I, 208 DTG-D) PWH received at least one dose of study treatment. Study flowchart is shown in **Supplementary Figure 2**. Most persons were over 50 years (88%), male (89%) and white (85%) (**Table 1A**). At baseline, 191 (46.4%) participants had hypertension and 91 (22.1%) were taking antihypertensive drugs; 24 persons without hypertension at baseline were receiving antihypertensive medications for indications other than hypertension including ischemic heart disease, arrhythmias, heart failure, or proteinuria. Threfore, there were 197 PWH (n=98, DTG-I arm; n=99, DTG-D arm) without hypertension or antihypertensive agents at baseline. Baseline characteristics in people without hypertension or antihypertensive agents at baseline (**Table 1B**) were well balanced between arms. A 10-year Framinghan CVD risk score >15% [OR 2,996 (95%CI 1,961-4,577), P<0.0001], obesity [OR 2,203 (95%CI 1,184-4,099), P=0.013], and antihypertensive agents for indications other than hypertension [OR 4,080 (95%CI 2,378-7,000), P<0.0001] were independently associated with hypertension at baseline (**Table 2**).

In the population included for the primary outcome (n=197), there were 56 persons with incident hypertension (incidence rate 37,4 per 100 person-years) between baseline and 48 weeks, 45 persons (incidence rate 43,9 per 100 person-years) between 48 and 96 weeks, and 101 persons (incidence rate 40,1 per 100 person-years) between baseline and 96 weeks. Between baseline and 48 weeks, there were 29 persons in the DTG-I arm (incidence rate 40,3 per 100 person-years) and 27 persons in the DTG-D (incidence rate 34.7 per 100 person-years) arm fulfilling criteria

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for incident hypertension [incidence rate ratio 0.86 (95% CI 0.51-1.45), P=0.5755]. Between 48 and 96 weeks, there were 19 persons in the DTG-I arm (incidence rate 36.3 per 100 person-years) and 26 persons in the DTG-D (incidence rate 52.0 per 100 person-years) arm developing hypertension [incidence rate ratio 1.43 (95% CI 0.76-2.74), P=0.2347]. Between baseline and 96 weeks, there were 48 persons in the DTG-I arm (incidence rate 38.6 per 100 person-years) and 53 persons in the DTG-D (incidence rate 41.5 per 100 person-years) arm developing hypertension [incidence rate ratio 1.07 (95% CI 0.73-1.59), P=0.7196].

In the overall population (n=412), there were non-significant increasing trends in proportion of participants with hypertension from baseline to week 48, from week 48 to week 96, and from baseline to week 96 (**Figure 1**).

In the population without hypertension or antihypertensives at baseline (n=197), there were no significant differences in SBP changes between arms from baseline to week 48, from week 48 to week 96, or from baseline to week 96 accounting for the impact of regression to the mean (**Figure 2A**). In the DTG-D, SBP significantly increased from week 48 to week 96 [mean +3.04 mmHg (95% confidence interval 0.07-6.02), P=0.0452]. In both arms, SBP significantly increased from baseline to week 96: DTG-I [mean +4.46 mmHg (95% confidence interval 1.64-7.27), P=0.0021]; DTG-D [mean +3.68 mmHg (95% confidence interval 0.88-6.48), P=0.0102].

There were no significant differences in DBP changes between arms from baseline to week 48, from week 48 to week 96, or from baseline to week 96 accounting for the impact of regression to the mean (**Figure 2B**). In the DTG-I arm, DBP significantly increased from baseline to week 48 [mean +2.78 mmHg (95% confidence interval 1.07-4.50), P=0.0016]. In the DTG-D arm, DBP also increased from week 48 to week 96 [mean +2.29 mmHg (95% confidence interval 0.35-4.23), P=0.0211]. In both arms, DBP significantly increased from baseline to week 96: DTG-I [mean +3.28 mmHg (95% confidence interval 1.36-5.19), P=0.0009]; DTG-D [mean +3.71 mmHg (95% confidence interval 1.78-5.64), P=0.0002].

Among the 412 PWH who received at least one dose of study treatment, adverse events associated with high blood pressure or hypertension were reported in 19 participants. In the DTG-I arm, there were 11 participants who had these adverse events reported at 0, 2, 12, 18, 24, 26, 35, 52, 60, 61, and 86 weeks (in all cases, under DTG exposure). In the DTG-D arm, there were 8 participants, of whom 5 had these adverse events reported when they were exposed to PI/r (11, 12, 36, 36, and 47 weeks), and 3 when exposed to DTG (56, 63, and 76 weeks). These adverse events were graded as mild in seven cases (3 DTG-I arm; 4 DTG-D arm), moderate in eleven cases (8 DTG-I arm; 3 DTG-D arm), and severe in one case (DTG-I arm). Investigators reported these effects as "possible related" in one participant of the DTG-D arm and "unlikely related" or "unrelated" in the rest. Four (3 under DTG exposure and 1 under PI/r exposure) participants discontinued study drugs due to adverse events associated with high blood pressure or hypertension. The week at discontinuation and the additional adverse effects reported were: 2

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(anxiety, confusion, hangover feeling, insomnia, nightmares, and shaking) and 16 (headache) weeks in the DTG-I arm, and 38 (headache, nausea, and vomiting) and 55 (paresthesia, anxiety, asthenia, headache, and sleep disorder) weeks in the DTG-D arm.

Being between 50-60 years [IRR 3,594 (95%CI 1,105-11,689), P=0.0335] or >60 years [IRR 6,131 (95%CI 1,740-21,600), P=0.0048]; male [IRR 5,405 (95%CI 1,634-17,857), P=0.0057]; black race [IRR 2,844 (95%CI 1,238-6,529), P=0.0137]; and lack of daily exercise [IRR 3,594 (95%CI 1,105-11,689), P=0.0089] were baseline factors independently associated with a higher risk of hypertension at week 48 (**Table 3A**). A 10-year Framinghan CVD risk score >15% [IRR 2,125 (95%CI 1,352-3,340), P=0.0011], female [IRR 0,4656 (95%CI 0,2348-0,9235), P=0.0287], current smokers [IRR 0,55 (95%CI 0,3523-0,8587), P=0.0085], and daily exercise [IRR 0,448 (95%CI 0,280-0,717), P=0.0008] were baseline factors independently associated with hypertension at week 96 (**Table 3B**). Treatment arm, either DTG-I or DTG-D, was not an independent risk factor for incidental hypertension at weeks 48 or 96.

There were weak correlations between weight or BMI and blood pressure at baseline in the whole population (n=412) (**Figure 3A**), and even weaker between changes in weight or BMI and changes in blood pressure at weeks 48 (**Figure 3B**) and 96 (**Figure 3C**) in the population without hypertension or antihypertensive agents at baseline (n=197). Changes in CV risk were in general favourable for the switch strategy (**Supplemmentary Table 1**).

DISCUSSION

In this population with HIV at high risk for CVD switching from PIr to DTG, nearly one out of two participants had hypertension at baseline. The incidence of *de novo* hypertension over time was five times higher than that reported in the general adult population in Europe (24) or in the USA (25), and at least double than that reported in the general adult population with HIV (6, 26). We are not aware of any published randomized clinical trial assessing the impact of antiretroviral therapy on blood pressure or hypertension. In the NEAT022 study, we did not find any difference in the incidence rates of hypertension between arms at weeks 48 and 96 among PWH without hypertension and antihypertensive agents at baseline.

Both SBP and DBP increased by approximately +4 mmHg over 96 weeks in both arms. In participants with the lowest baseline values, SBP and DBP increased while in those with the highest baseline values decreased suggesting a regression-towards-the-mean effect (27). Interestingly, DBP significantly increased by a mean of +2-4 mmHg in both DTG-I and DTG-D arms in the first 48 weeks after switching from PI/r to DTG (**Table 3B**), therefore suggesting a potential relationship with the withdrawal of PI/r and/or the introduction of DTG; in any case, the range of blood pressure increases was less than the 10 mmHg cutoff considered as a clinically relevant change (28).

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Classical cardiovascular risk factors (2), but not treatment arm or HIV-related factors, were independently associated with incidental hypertension at weeks 48 or 96. Surprisingly current smoking was associated with a lower risk of incidental hypertension at 96 weeks; smoking causes acute blood pressure elevation, although some studies have found similar or lower BPs in smokers compared with nonsmokers (29, 30). There were weak correlations between weight or BMI and blood pressure at baseline, and between changes in weight or BMI and changes in blood pressure at weeks 48 and 96. We have previously reported modest weight gain in NEAT022 study limited to the first 48 weeks post-switch (31). Some clinicians have raised concerns that weight gain might eventually increase blood pressure (7) and cardiovascular disease (32) in PWH at high risk for CVD, but we did not confirm these concerns in this NEAT022 post-hoc analysis.

Our study has limitations. The study population had a high risk for cardiovascular disease and other specific characteristics that may not apply to other PWH. There were few women or black people, factors that have been shown to be more associated with weight gain. In clinical practice worldwide, switch to DTG has more commonly occurred from a non-nucleoside reverse transcriptase inhibitor, primarily efavirenz, than from PI/r; data suggest that efavirenz (but not PI/r) suppresses weight and thus the switch from efavirenz to DTG leads to pronounced weight gain and a potential impact on hypertension for some PWH. Tenofovir alafenamide (TAF), a popular drug nowadays that shows synergism with integrase inhibitors in promoting weight gain, was not used in NEAT022. We did not evaluate potential hypertension risk factors such as non-antiretroviral pro-hypertensive medications, anxiety, diet, physical inactivity, and family history of hypertension, although the randomized design may have tempered potential differences in these characteristics between the two arms.. Because of the confounding effects of prior hypertension and antihypertensive agents, the population of NEAT022 was reduced in half for the purpose of this analysis, therefore diminishing the power of the study. The main strength was that data generated from a randomized clinical trial in which standardized blood pressure measurements had been planned.

In summary, the population with HIV of the NEAT022 study at high risk for CVD showed a high prevalence of hypertension at baseline and a remarkably high incidence of hypertension during 96 weeks of follow-up. Therefore, prevention and treatment of hypertension should be a priority in clinical care of aging PWH (33). Switching to dolutegravir did not negatively impact on the incidence of hypertension relative to continue protease inhibitors. Despite the reduction in sample size, we can conclude that a difference of at least 25% in the incidence of hypertension between arms at 48 weeks could be excluded. However, smaller differences in the risk of hypertension might exist and should be assessed in larger trials or meta-analyses.

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NOTES

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

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Contributions

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

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Conflicts of interest

A. Gonzalez-Cordon has received honoraria for lectures (Gilead, Janssen, MSD and ViiV), advisory boards (ViiV) or travel grants (Gilead, MSD and ViiV) and her institution has received research grants from Gilead, Janssen, MSD and ViiV.

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J. Fox has received honoraria for lectures, advisory boards or travel grants and consulting fees from Gilead, Janssen, MSD and ViiV.

H. J. Stellbrink has received honoraria for lectures (Gilead, ViiV, MSD), advisory boards (Gilead, ViiV, MSD) or travel grants (Gilead) and his institution has received research grants (Gilead, ViiV, MSD, Janssen, GSK, Heidelberg) from Gilead, GSK, Heildelberg Immunotherapeutics, Janssen, MSD and ViiV, and reports consulting fees from Gilead, ViiV, Janssen & Cilag, and MSD; payment for expert testimony from Gilead; receipt of equipment from Gilead.

G. Guaraldi has received honoraria for lectures, advisory boards or travel grants and his institution has received research grants from Gilead, MSD and ViiV.

E. Florence has received honoraria for lectures (Gilead and ViiV), advisory boards or travel grants from Gilead, Janssen, MSD and ViiV.

S. Esser has received honoraria for lectures, advisory boards or travel grants and grants or contracts paid to institution from Gilead, MSD and ViiV and Janssen.

J. M. Gatell is a full-time employee of and owns stock in ViiV as Senior Global Medical Director since 1 May 2018.

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A. Pozniak has received honoraria for lectures or advisory boards and consulting fees and his institution has received research grants from Gilead, Janssen, MSD and ViiV.

E. Martínez has received honoraria for lectures (Gilead, ViiV, MSD) or advisory boards and his institution has received research grants (MSD, ViiV) and consulting fees from Gilead, Janssen, MSD, Theratechnologies, and ViiV.

A. Sempere, L. Assoumou, S. de Wit, and M. Johnson: none to declare.

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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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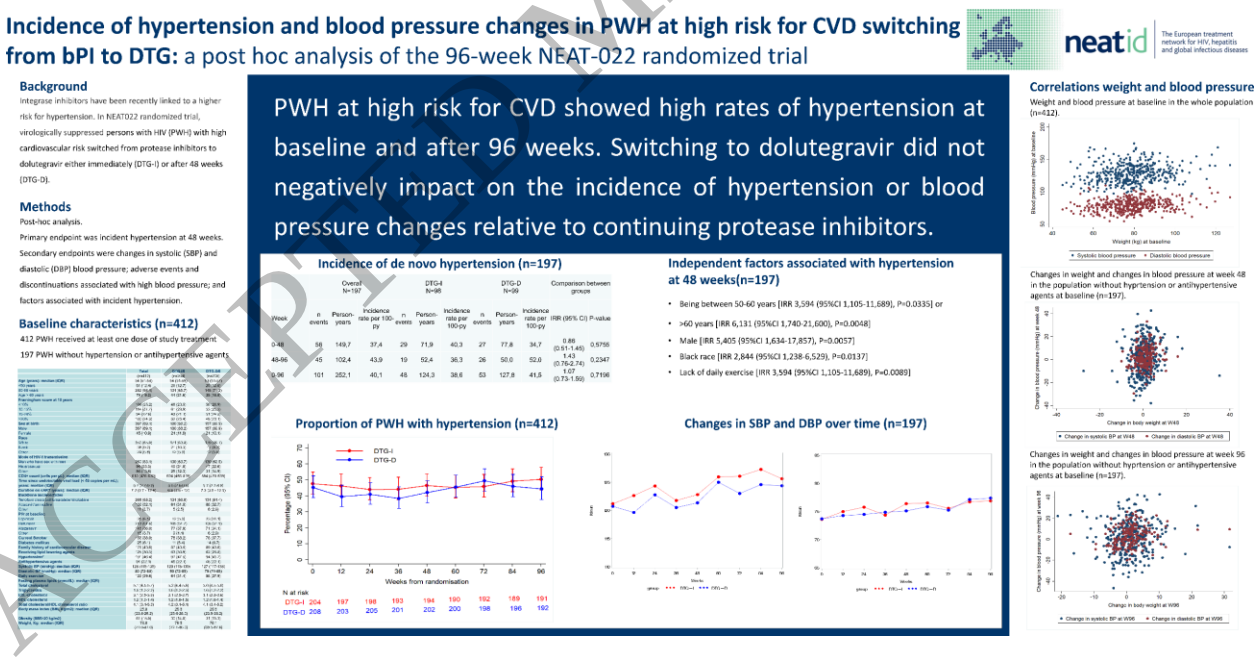
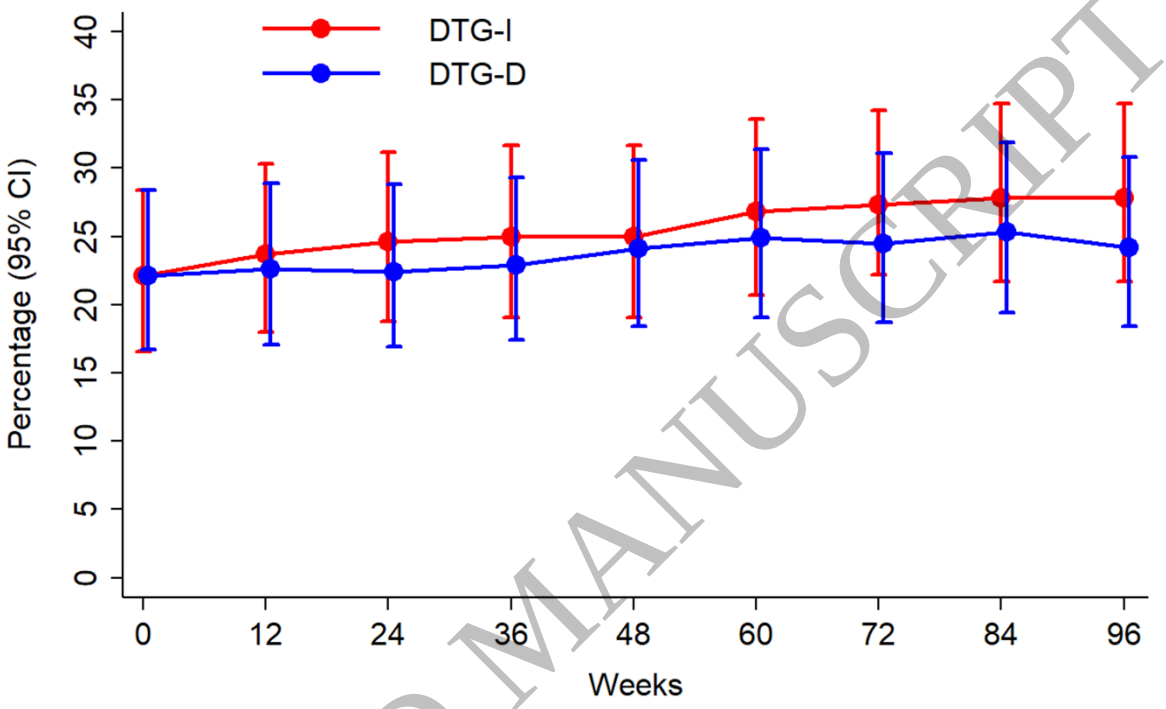


Graphical Abstract

FIGURE LEGENDS

Figure 1. Proportion of participants with hypertension over time in the whole population (n=412).



	Immediate Switch change within group		Deferred Switch change within group		P-value for comparison between groups	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Change from baseline to week 48	1.13 (0.98-1.31)	0.0823	1.09 (0.98-1.21)	0.0979	1.04 (0.87-1.24)	0.6735
Change from week 48 to week 96	1.11 (1.02-1.21)	0.0148	1.00 (0.92-1.10)	0.9239	1.11 (0.98-1.25)	0.1025
Change from baseline to week 96	1.26 (1.07-1.48)	0.0048	1.1 (0.97-1.24)	0.1522	1.15 (0.94-1.41)	0.1777

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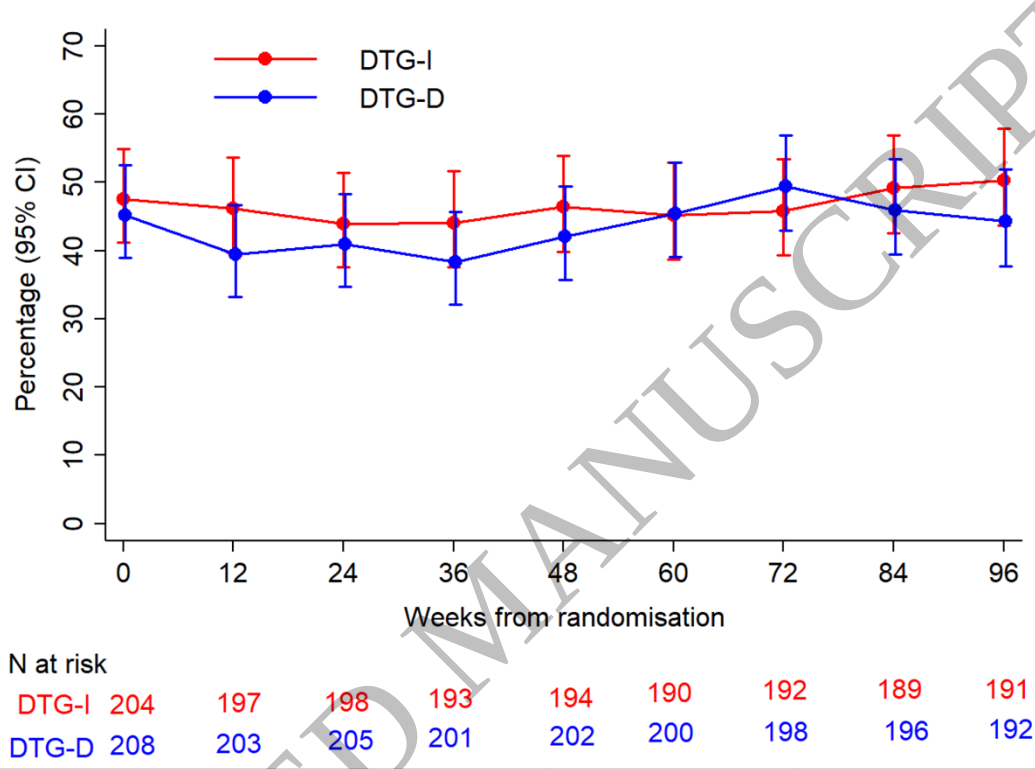
Figure 2A. Change from baseline in systolic blood pressure in the population without hypertension or antihypertensives (n=197) accounting for the impact of regression to the mean.

Figure 2B. Change from baseline in diastolic blood pressure in the population without hypertension or antihypertensives (n=197) accounting for the impact of regression to the mean.



	Immediate Switch change within group		Deferred Switch change within group		P-value for comparison between groups	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Change from baseline to week 48	0.98 (0.85-1.13)	0.7358	0.93 (0.79-1.1)	0.4006	1.05 (0.84-1.31)	0.6765
Change from week 48 to week 96	1.08 (0.93-1.27)	0.314	1.05 (0.88-1.26)	0.5839	1.03 (0.81-1.31)	0.8101
Change from baseline to week 96	1.06 (0.91-1.23)	0.4747	0.98 (0.82-1.18)	0.8255	1.08 (0.85-1.37)	0.5311

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Figure 3A. Correlation between weight and blood pressure at baseline in the whole population (n=412).

Figure 3B. Correlation between changes in weight and changes in blood pressure at week 48 in the population without hyprtension or antihypertensive agents at baseline (n=197).

Figure 3C. Correlation between changes in weight and changes in blood pressure at week 96 in the population without hyprtension or antihypertensive agents at baseline (n=197).

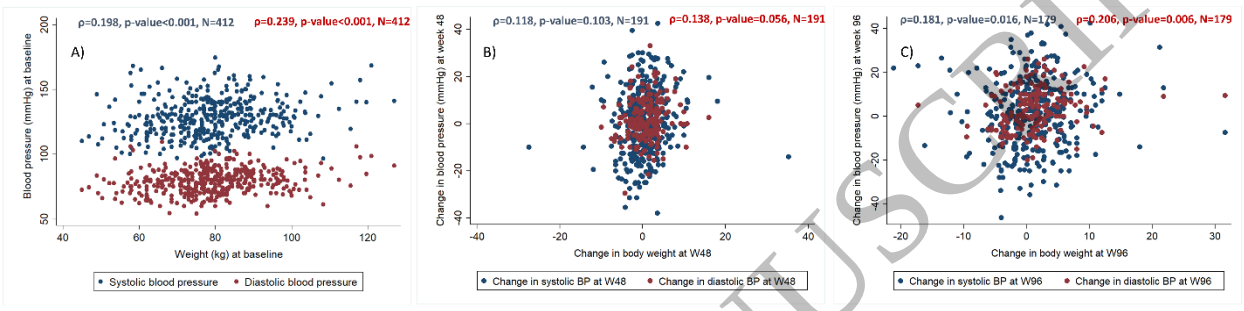

Table 1A. Baseline characteristics (whole population, n=412).

	Total	**DTG-IS**	**DTG-DS**
	(n=412)	**(n=204)**	**(n=208)**
Age (years): median (IQR)	54 (51-58)	54 (51-58)	53 (51-57)
<50 years	51 (12.4)	26 (12.7)	25 (12.0)
50-60 years	282 (68.4)	134 (65.7)	148 (71.2)
Age > 60 years	79 (19.2)	44 (21.6)	35 (16.8)
Framingham score at 10 years			
<10%	104 (25.2)	48 (23.5)	56 (26.9)
10-15%	114 (27.7)	61 (29.9)	53 (25.5)
15-20%	94 (22.8)	43 (21.1)	51 (24.5)
>20%	100 (24.3)	52 (25.4)	48 (23.1)
Sex at birth	367 (89.1)	180 (88.2)	187 (89.9)
Male	367 (89.1)	180 (88.2)	187 (89.9)
Female	45 (10.9)	24 (11.8)	21 (10.1)
Race			
White	350 (85.0)	171 (83.8)	179 (86.1)
Black	38 (9.2)	21 (10.3)	17 (8.2)
Other	24 (5.8)	12 (5.9)	12 (5.8)
Mode of HIV-1 transmission			
Men who have sex with men	260 (63.1)	130 (63.7)	130 (62.5)
Heterosexual	96 (23.3)	49 (24.0)	47 (22.6)
Other	56 (13.6)	25 (12.3)	31 (14.9)
CD4+ count (cells per µL): median (IQR)	610 (476-830)	634 (488-819)	584 (470-839)
HIV RNA >50 copies per mL	8 (2.0)	7 (3.4)	1 (0.5)

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Hepatitis C IgG antibodies detected	54 (13.2)	29 (14.4)	25 (12.1)
Time since undetectable viral load (< 50 copies per mL); years: median (IQR)	5.7 (2.7-9.3)	5.5 (2.6-9.6)	5.7 (2.7-8.9)
Duration on cART (years): median (IQR)	7.2 (3.7 - 12.4)	6.8 (3.6 - 12)	7.3 (3.8 - 12.5)
Backbone nucleos(t)ides			
Tenofovir disoproxil fumarate/emtricitabine	268 (65.2)	134 (66.0)	134 (64.4)
Abacavir/lamivudine	132 (32.1)	64 (31.5)	68 (32.7)
Other	11 (2.7)	5 (2.5)	6 (2.9)
PI/r at baseline			
Lopinavir	35 (8.5)	12 (5.9)	23 (11.1)
Darunavir	213 (51.8)	105 (51.7)	108 (51.9)
Atazanavir	148 (36.0)	77 (37.9)	71 (34.1)
Other	15 (3.7)	9 (4.4)	6 (2.9)
Current Smoker	156 (38.0)	78 (38.2)	78 (37.7)
Diabetes mellitus	25 (6.1)	11 (5.4)	14 (6.7)
Family history of cardiovascular disease	176 (43.6)	87 (43.5)	89 (43.6)
Receiving lipid lowering agents	125 (30.3)	63 (30.9)	62 (29.8)
Hypertension*	191 (46.4)	97 (47.5)	94 (45.2)
Antihypertensive agents	91 (22.1)	45 (22.1)	46 (22.1)
Systolic blood pressure (mmHg): median (IQR)	128 (118-138)	129 (118-139)	127 (117-138)
Diastolic blood pressure (mmHg): median (IQR)	80 (72-85)	80 (72-85)	79 (74-85)
Daily exercise	122 (29.6)	64 (31.4)	58 (27.9)
Fasting plasma lipids (mmol/L): median (IQR)			
Total cholesterol	5.1 (4.5-5.7)	5.2 (4.4-5.8)	5.0 (4.5-5.6)
Triglycerides	1.6 (1.2-2.2)	1.6 (1.2-2.3)	1.6 (1.2-2.2)
Non-HDL cholesterol	3.8 (3.2-4.5)	3.9 (3.3-4.6)	3.8 (3.2-4.3)
LDL-cholesterol	3.1 (2.5-3.6)	3.1 (2.5-3.7)	3.1 (2.5-3.6)
HDL-cholesterol	1.2 (1.0-1.4)	1.2 (1.0-1.5)	1.2 (1.0-1.4)
Total cholesterol/HDL cholesterol ratio	4.1 (3.4-5.3)	4.2 (3.4-5.4)	4.1 (3.4-5.2)
Estimated glomerular filtration rate (eGFR, mL/minute): median (IQR)	91.2 (79.8-100.8)	91.0 (80.7-99.7)	91.4 (77.1-102.0)
Body mass index (BMI, Kg/m2): median (IQR)	25.8 (23.5-28.2)	25.8 (23.6-28.0)	25.8 (23.5-28.2)
Obesity (BMI>30 kg/m2)	61 (15.0)	30 (14.8)	31 (15.3)
Weight, Kg: median (IQR)	79.0 (71.0-87.0)	79.5 (72.1-86.0)	78.1 (69.5-87.8)

Data are n (%) unless indicated otherwise.

*SBP ≥130 mmHg and/or DBP ≥85 mmHg

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Table 1B. Baseline characteristics (people without hypertension or antihypertensive agents, n=197).

	Total	DTG-IS	DTG-DS	P-value
	(n=197)	(n=98)	(n=99)	
Age (years): median (IQR)	53 (51-57)	53 (51-57)	53 (51-57)	0,831
<50 years	26 (13.2)	15 (15.3)	11 (11.1)	0,510
50-60 years	138 (70.1)	65 (66.3)	73 (73.7)	
Age > 60 years	33 (16.8)	18 (18.4)	15 (15.2)	
Framingham score at 10 years				0,478
<10%	74 (37.6)	34 (34.7)	40 (40.4)	
10-15%	59 (29.9)	34 (34.7)	25 (25.3)	
15-20%	43 (21.8)	19 (19.4)	24 (24.2)	
>20%	21 (10.7)	11 (11.2)	10 (10.1)	
Sex et birth				0,227
Male	168 (85.3)	87 (88.8)	81 (81.8)	
Female	29 (14.7)	11 (11.2)	18 (18.2)	
Race				0,316
White	170 (86.3)	81 (82.7)	89 (89.9)	
Black	15 (7.6)	9 (9.2)	6 (6.1)	
Other	12 (6.1)	8 (8.2)	4 (4.0)	
Mode of HIV-1 transmission				0,390
Men who have sex with men	124 (62.9)	66 (67.3)	58 (58.6)	
Heterosexual	48 (24.4)	20 (20.4)	28 (28.3)	
Other	25 (12.7)	12 (12.2)	13 (13.1)	
CD4+ count (cells per µL): median (IQR)	604 (474-818)	634 (476-816)	582 (472-830)	0,650
HIV RNA >50 copies per mL	2 (1.0)	2 (2.0)	0 (0.0)	0,246
Hepatitis C IgG antibodies detected	28 (14.4)	16 (16.7)	12 (12.2)	0,419
Time since undetectable viral load (< 50 copies per mL); years: median (IQR)	5.0 (2.2-9.0)	4.9 (2.3-9.7)	5.0 (2.1-8.8)	0,484
Duration on cART (years): median (IQR)	6.8 (3.5-11.4)	6.9 (3.5-10.9)	6.6 (3.4-12.3)	0,919
Backbone nucleos(t)ides				0,822
Tenofovir disoproxil fumarate/emtricitabine	142 (72.4)	72 (74.2)	70 (70.7)	
Abacavir/lamivudine	49 (25)	23 (23.7)	26 (26.3)	
Other	5 (2.6)	2 (2.1)	3 (3)	
PI/r at baseline				0,418
Darunavir	96 (49)	46 (47.4)	50 (50.5)	
Atazanavir	73 (37.2)	40 (41.2)	33 (33.3)	
Other	27 (13.8)	11 (11.3)	16 (16.2)	
Current Smoker	77 (39.1)	39 (39.8)	38 (38.4)	0,884
Diabetes mellitus	6 (3.0)	2 (2.0)	4 (4.0)	0,683
Family history of cardiovascular disease	76 (39.6)	40 (42.1)	36 (37.1)	0,555
Receiving lipid lowering agents	42 (21.3)	21 (21.4)	21 (21.2)	>0.999

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Systolic blood pressure (mmHg): median (IQR)	118 (112.5-125)	118 (112.5-125)	118.5 (113-125)	0,945
Diastolic blood pressure (mmHg): median (IQR)	74 (70-79.5)	72 (68.5-79.5)	75 (70-79.5)	0,231
Daily exercise	68 (34.5)	32 (32.7)	36 (36.4)	0,654
Fasting plasma lipids (mmol/L): median (IQR)				
Total cholesterol	5.2 (4.5-5.7)	5.2 (4.3-5.7)	5.2 (4.6-5.8)	0,322
Triglycerides	1.5 (1.1-2.1)	1.4 (1.1-2)	1.6 (1.1-2.2)	0,273
Non-HDL cholesterol	3.9 (3.3-4.5)	3.8 (3.2-4.5)	3.9 (3.3-4.5)	0,632
LDL-cholesterol	3.1 (2.6-3.6)	3.1 (2.5-3.6)	3.1 (2.6-3.6)	0,891
HDL-cholesterol	1.2 (1-1.5)	1.2 (0.9-1.5)	1.2 (1-1.5)	0,400
Total cholesterol/HDL cholesterol ratio	4.1 (3.3-5.3)	4.1 (3.4-5.3)	4.2 (3.3-5.3)	0,783
Estimated glomerular filtration rate (eGFR, mL/minute): median (IQR)	91.4 (78.5-100.8)	91.1 (80.6-100.1)	91.7 (77.2-101)	0,791
Body mass index (BMI, Kg/m2): median (IQR)	25 (22.6-26.9)	25 (23.1-26.7)	24.7 (22.4-26.9)	0,864
Obesity (BMI>30 kg/m2)	15 (7.7)	6 (6.1)	9 (9.2)	0,592
Weight, Kg: median (IQR)	75.9 (66.9-82.2)	77.1 (66.9-81.8)	74.8 (66.8-83.4)	0,367

Data are n (%) unless indicated otherwise.

Table 2. Factors associated with hypertension at baseline in the whole population (n=412).

		Hypertension at baseline				**Univariable analysis**				**Multivariable analysis**			
	Parameter	No N=221 (53.6%)		Yes N=191 (46.4%)		P value	OR	(95% CI)		P value	OR	(95% CI)	
		N	%	N	%								
Age, years						0,458							
	< 50	30	58,8%	21	41,2%		1						
	50-60	153	54,3%	129	45,7%	0,547	1,204	0,658	2,205				
	> 60	38	48,1%	41	51,9%	0,233	1,541	0,757	3,139				
Framingham 10-year CVD risk score						**<0.001**				**<0.001**			
	≤ 15%	145	66,5%	73	33,5%		1				1		
	> 15%	76	39,2%	118	60,8%	<0.001	3,084	2,062	4,613	<0.001	2,996	1,961	4,577
Sex at birth						**0,066**							
	Male	191	52,0%	176	48,0%		1						

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	Female	30	66,7%	15	33,3%	0,066	0,543	0,282	1,042				
PI at baseline						0,137							
	Darunavir	104	48,8%	109	51,2%		1						
	Atazanavir	86	58,1%	62	41,9%	0,083	0,688	0,451	1,050				
	Other	30	60,0%	20	40,0%	0,157	0,636	0,340	1,190				
Backbone nucleos(t)ides						**0,018**							
	Tenofovir disoproxil fumarate/Emtricitabine	154	57,5%	114	42,5%		1						
	Abacavir /Lamivudine	58	43,9%	74	56,1%	0,011	1,724	1,132	2,624				
	Other	8	72,7%	3	27,3%	0,323	0,507	0,131	1,952				
Race						0,510							
	White	188	53,7%	162	46,3%		1						
	Black	18	47,4%	20	52,6%	0,457	1,289	0,659	2,521				
	Other	15	62,5%	9	37,5%	0,405	0,696	0,297	1,633				
Transmission group						0,938							
	MSM	138	53,1%	122	46,9%		1						
	Heterosexual	53	55,2%	43	44,8%	0,720	0,918	0,573	1,469				
	Other	30	53,6%	26	46,4%	0,946	0,980	0,549	1,749				
Positive Hep C antibody						0,358							
	No	186	52,5%	168	47,5%		1						
	Yes	32	59,3%	22	40,7%	0,358	0,761	0,426	1,362				
Obesity (BMI>30 Kg/m2)						**<0.0001**				**0,013**			
	No	200	57,0%	151	43,0%		1				1		
	Yes	20	33,3%	40	66,7%	<0.001	2,649	1,488	4,716	0,013	2,203	1,184	4,099
Current smokers						0,525							
	No	1	52,	1	47,		1						

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		34	5%	21	5%								
	Yes	87	55,8%	69	44,2%	0,525	0,878	0,589	1,311				
Diabetes						0,321							
	No	210	54,3%	177	45,7%		1						
	Yes	11	44,0%	14	56,0%	0,321	1,510	0,669	3,410				
Family history of cardiovascular disease						**0,124**							
	No	129	56,6%	99	43,4%		1						
	Yes	86	48,9%	90	51,1%	0,124	1,364	0,919	2,024				
Receiving lipid lowering agents						**0,052**							
	No	163	56,8%	124	43,2%		1						
	Yes	58	46,4%	67	53,6%	0,052	1,518	0,996	2,316				
Antihypertensive agents						**<0.001**				**<0.001**			
	No	197	61,4%	124	38,6%						1		
	Yes	24	26,4%	67	73,6%	<0.001	4,435	2,643	7,442	<0.001	4,080	2,378	7,000
Daily exercise						**0,039**							
	No	146	50,3%	144	49,7%		1						
	Yes	75	61,5%	47	38,5%	0,039	0,635	0,413	0,978				
CD4 cells/mm3						0,812							
	<500	62	55,4%	50	44,6%		1						
	≥500	154	54,0%	131	46,0%	0,812	1,055	0,680	1,637				
Time since undetectable viral load (< 50 copies per mL); years						0,646							
	< 5	104	55,0%	85	45,0%		1						
	≥5	115	52,8%	103	47,2%	0,646	1,096	0,741	1,620				
Duration on cART; years						0,526							

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	< 5	85	55,6%	68	44,4%		1						
	≥5	135	52,3%	123	47,7%	0,526	1,139	0,762	1,702				
Glucose, mmol/L						**0,010**							
	<4.8	78	62,9%	46	37,1%		1						
	4.8-5.4	88	54,3%	74	45,7%	0,146	1,426	0,884	2,299				
	>5.4	52	43,3%	68	56,7%	0,002	2,217	1,328	3,704				
Total cholesterol, mmol/L						0,923							
	<4.6	69	54,8%	57	45,2%		1						
	4.6-5.5	84	53,8%	72	46,2%	0,878	1,038	0,648	1,662				
	>5.5	68	52,3%	62	47,7%	0,694	1,104	0,675	1,804				
HDL cholesterol, mmol/L						0,279							
	<1.0	61	54,5%	51	45,5%		1						
	1.0-1.4	92	49,7%	93	50,3%	0,429	1,209	0,755	1,935				
	>1.4	68	59,1%	47	40,9%	0,478	0,827	0,489	1,399				
LDL cholesterol, mmol/L						0,357							
	<2.6	63	54,8%	52	45,2%		1						
	2.6-3.4	76	48,7%	80	51,3%	0,324	1,275	0,787	2,067				
	>3.4	75	56,8%	57	43,2%	0,748	0,921	0,557	1,523				
Triglycerides, mmol/L						**0,155**							
	<1.3	83	59,3%	57	40,7%		1						
	1.3-1.9	64	54,2%	54	45,8%	0,415	1,229	0,749	2,015				
	>1.9	74	48,1%	80	51,9%	0,054	1,574	0,992	2,499				
TC/HDL ratio at baseline						0,513							
	<3.7	79	57,7%	58	42,3%		1						
	3.7-4.8	69	51,5%	65	48,5%	0,308	1,283	0,795	2,072				
	>4.8	73	51,8%	68	48,2%	0,324	1,269	0,790	2,037				
Non-HDL-c, mmol/L						0,365							
	<3.4	7	56,	5	43,		1						

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		4	9%	6	1%								
	3.4-4.2	71	49,0%	74	51,0%	0,187	1,377	0,856	2,217				
	>4.2	76	55,5%	61	44,5%	0,812	1,061	0,654	1,721				
Estimated glomerular filtration rate (e-GFR), ml/min						0,558							
	<90	99	52,1%	91	47,9%		1						
	≥90	121	55,0%	99	45,0%	0,558	0,890	0,603	1,314				

Table 3A. Baseline factors associated with incident hypertension at week 48 among participants without hypertension or antihypertensive agents at baseline (n=197).

						Univariable analysis				**Multivariable analysis**			
	Parameter	N pts in group	Person-years	Nb events	IR per 100 P-Y	P value	IRR	(95% CI)		P value	IRR	(95% CI)	
								lower	upper			lower	upper
Randomisation group						0,5755							
	DTG-I	98	71,9	29	40,3		1						
	DTG-D	99	77,8	27	34,7	0,5755	0,861	0,510	1,454				
Age, years						0,0298				0,0044			
	< 50	26	21,7	3	13,8		1				1		
	50-60	138	104,9	39	37,2	0,0988	2,688	0,831	8,699	0,0335	3,594	1,105	11,689
	> 60	33	23,2	14	60,5	0,0204	4,372	1,257	15,214	0,0048	6,131	1,740	21,600
Framingham 10-year CVD risk score						0,0924							
	≤ 15%	133	103,9	33	31,8		1						
	> 15%	64	45,8	23	50,2	0,0924	1,580	0,928	2,690				
Sex at birth						0,0350				0,0057			
	Male	168	125,0	53	42,4		1				1		
	Female	29	24,7	3	12,1	0,0350	0,286	0,089	0,916	0,0057	0,185	0,056	0,612
PI at baseline						0,8752							
	Darunavir	96	74,2	26	35,1		1						
	Atazanavir	73	54,8	22	40,1	0,6397	1,145	0,649	2,021				
	Other	27	20,5	7	34,	0,94	0,9	0,4	2,24				

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					1	74	72	22	0				
Backbone nucleos(t)ides						0,7865							
	Tenofovir disoproxil fumarate/Emtricitabine	142	109,5	39	35,6		1						
	Abacavir /Lamivudine	49	36,7	14	38,1	0,8265	1,071	0,581	1,972				
	Other	5	3,3	2	60,5	0,4654	1,698	0,410	7,030				
Race						0,1860				0,0756			
	White	170	131,6	46	35,0		1				1		
	Black	15	8,9	7	78,8	0,0451	2,255	1,018	4,994	0,0137	2,844	1,238	6,529
	Other	12	9,3	3	32,2	0,8913	0,922	0,287	2,964	0,7498	0,824	0,251	2,706
Transmission group						0,8087							
	MSM	124	93,8	36	38,4		1						
	Heterosexual	48	35,6	14	39,3	0,9398	1,024	0,552	1,899				
	Other	25	20,3	6	29,5	0,5504	0,769	0,324	1,824				
Positive Hep C antibody						0,7644							
	No	166	125,4	47	37,5		1						
	Yes	28	21,5	9	41,8	0,7644	1,115	0,547	2,275				
Obesity (BMI>30 Kg/m2)						0,9239							
	No	181	138,1	51	36,9		1						
	Yes	15	11,4	4	35,1	0,9239	0,952	0,344	2,633				
Current smokers						0,3345							
	No	120	89,4	37	41,4		1						
	Yes	77	60,3	19	31,5	0,3345	0,762	0,438	1,324				
Diabetes						0,0470							
	No	191	145,7	52	35,7		1						
	Yes	6	4,0	4	100,0	0,0470	2,803	1,014	7,749				
Family history of cardiovascular disease						0,2039							
	No	116	92,3	28	30,3		1						
	Yes	76	55,5	24	43,2	0,2039	1,424	0,826	2,456				
Receiving lipid lowering agents						0,9764							
	No	155	117,9	44	37,3		1						
	Yes	42	31,8	12	37,7	0,9764	1,010	0,533	1,912				

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Daily exercise						0,0172				0,0089			
	No	129	94,0	44	46,8		1				1		
	Yes	68	55,7	12	21,5	0,0172	0,460	0,243	0,872	0,0089	0,420	0,219	0,804
CD4 cells/mm3						0,7352							
	<500	56	41,8	15	35,8		1						
	≥500	136	103,3	41	39,7	0,7352	1,107	0,613	2,001				
Time since undetectable viral load (< 50 copies per mL); years						0,3658							
	< 5	98	77,6	26	33,5		1						
	≥5	97	70,3	30	42,7	0,3658	1,274	0,754	2,154				
Duration on cART; years						0,5982							
	< 5	82	65,1	22	33,8		1						
	≥5	114	84,4	33	39,1	0,5982	1,156	0,674	1,983				
Glucose, mmol/L						0,8523							
	<4.8	72	54,4	22	40,4		1						
	4.8-5.4	79	59,3	23	38,8	0,8916	0,960	0,535	1,723				
	>5.4	43	33,3	11	33,0	0,5839	0,817	0,396	1,685				
Total cholesterol, mmol/L						0,1785							
	<4.6	56	42,8	18	42,1		1						
	4.6-5.5	79	63,1	17	27,0	0,1879	0,641	0,330	1,243				
	>5.5	62	43,9	21	47,8	0,6913	1,136	0,605	2,132				
HDL cholesterol, mmol/L						0,0912							
	<1.0	51	38,5	20	52,0		1						
	1.0-1.4	84	65,7	17	25,9	0,0343	0,498	0,261	0,950				
	>1.4	62	45,6	19	41,7	0,4905	0,802	0,428	1,502				
LDL cholesterol, mmol/L						0,6332							
	<2.6	51	38,2	17	44,5		1						
	2.6-3.4	70	54,0	18	33,3	0,3949	0,750	0,387	1,455				
	>3.4	70	53,8	18	33,4	0,3988	0,752	0,387	1,459				
Triglycerides, mmol/L						0,6083							
	<1.3	76	59,1	19	32,2		1						
	1.3-1.9	59	45,2	20	44,3	0,3184	1,377	0,735	2,579				
	>1.9	62	45,5	17	37,4	0,6509	1,163	0,605	2,238				

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TC/HDL ratio at baseline						0,4288							
	<3.7	71	53,7	21	39,1		1						
	3.7-4.8	60	45,9	13	28,3	0,3599	0,724	0,363	1,446				
	>4.8	66	50,1	22	43,9	0,7017	1,124	0,618	2,044				
Non-HDL-c, mmol/L						0,5575							
	<3.4	61	46,1	20	43,4		1						
	3.4-4.2	67	52,4	16	30,5	0,2934	0,703	0,364	1,357				
	>4.2	69	51,2	20	39,0	0,7374	0,899	0,484	1,672				
Estmated glomerular filtration rate (e-GFR), ml/min						0,4855							
	<90	88	64,9	27	41,6		1						
	≥90	108	84,0	29	34,5	0,4855	0,830	0,491	1,402				

Table 3B. Baseline factors associated with incident hypertension at week 96 among participants without hypertension or antihypertensive agents at baseline (n=197).

						Univariable analysis				**Multivariable analysis**			
	Parameter	N pts in group	Person-years	Nb events	IR per 100 P-Y	P value	IRR	(95% CI)		P value	IRR	(95% CI)	
								lower	upper			lower	upper
Randomisation group						0,7196							
	DTG-I	98	124,3	48	38,6		1						
	DTG-D	99	127,8	53	41,5	0,7196	1,074	0,727	1,587				
Age, years						0,0050							
	< 50	26	39,54	7	17,7		1						
	50-60	138	176,7	71	40,2	0,0385	2,270	1,044	4,934				
	> 60	33	35,92	23	64,0	0,0029	3,616	1,552	8,428				
Framingham 10-year CVD risk score						0,0112				0,0011			
	≤ 15%	133	181,2	61	33,7		1				1		
	> 15%	64	70,92	40	56,4	0,0112	1,675	1,124	2,496	0,0011	2,125	1,352	3,340
Sex at birth						0,0308				0,0287			
	Male	168	205,	91	44		1				1		

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			7		,2								
	Female	29	46,42	10	21,5	0,0308	0,487	0,254	0,936	0,0287	0,4656	0,2348	0,9235
PI at baseline						0,8184							
	Darunavir	96	126,6	50	39,5		1						
	Atazanavir	73	90,26	38	42,1	0,7657	1,066	0,699	1,626				
	Other (lopinavir;saquinavir;fosamprenavir)	27	35	12	34,3	0,6606	0,868	0,463	1,631				
Backbone nucleos(t)ides						0,7472							
	Tenofovir disoproxil fumarate/Emtricitabine	142	181,6	74	40,8		1						
	Abacavir /Lamivudine	49	64,71	23	35,5	0,5665	0,872	0,546	1,392				
	Other	5	5,615	3	53,4	0,6458	1,311	0,413	4,158				
Race						0,3793							
	White	170	223,5	85	38,0		1						
	Black	15	14,88	9	60,5	0,1857	1,590	0,800	3,161				
	Other	12	13,77	7	50,8	0,4606	1,337	0,618	2,889				
Transmission group						0,9677							
	MSM	124	155,9	62	39,8		1						
	Heterosexual	48	62,38	26	41,7	0,8401	1,048	0,663	1,657				
	Other	25	33,8	13	38,5	0,9133	0,967	0,532	1,759				
Positive Hep C antibody						0,9057							
	No	166	211,4	86	40,7		1						
	Yes	28	35,62	14	39,3	0,9057	0,966	0,549	1,700				
Obesity (BMI>30 Kg/m2)						0,7128							
	No	181	231,7	91	39,3		1						
	Yes	15	20,15	9	44,7	0,7128	1,137	0,573	2,256				
Current smokers						0,0719				0,0085			
	No	120	147,4	68	46,1		1				1		
	Yes	77	104,8	33	31,5	0,0719	0,683	0,450	1,035	0,0085	0,55	0,3523	0,8587
Diabetes						0,0579				0,0517			
	No	191	246,7	96	38,9		1				1		
	Yes	6	5,385	5	92,9	0,0579	2,387	0,971	5,865	0,0517	2,503	0,993	6,308
Family history of cardiovascular disease						0,9189							
	No	116	153,	60	39		1						

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			5		,1								
	Yes	76	96,69	37	38,3	0,9189	0,979	0,650	1,475				
Receiving lipid lowering agents						0,3378							
	No	155	199,5	76	38,1		1						
	Yes	42	52,62	25	47,5	0,3378	1,247	0,794	1,960				
Daily exercise						0,0024				0,0008			
	No	129	154,3	77	49,9		1				1		
	Yes	68	97,87	24	24,5	0,0024	0,491	0,311	0,777	0,0008	0,448	0,280	0,717
CD4 cells/mm3						0,9498							
	<500	56	72,31	30	41,5		1						
	≥500	136	171,1	70	40,9	0,9498	0,986	0,643	1,513				
Time since undetectable viral load (< 50 copies per mL); years						0,1204							
	< 5	98	133,8	46	34,4		1						
	≥5	97	115,1	54	46,9	0,1204	1,366	0,922	2,024				
Duration on cART; years						0,1129							
	< 5	82	113,2	37	32,7		1						
	≥5	114	138,7	63	45,4	0,1129	1,389	0,925	2,084				
Glucose, mmol/L						0,9909							
	<4.8	72	90,73	37	40,8		1						
	4.8-5.4	79	100,4	41	40,8	0,9955	1,001	0,642	1,562				
	>5.4	43	55,69	22	39,5	0,9057	0,969	0,572	1,642				
Total cholesterol, mmol/L						0,3782							
	<4.6	56	72,23	32	44,3		1						
	4.6-5.5	79	107	36	33,7	0,2578	0,760	0,472	1,223				
	>5.5	62	72,92	33	45,3	0,9318	1,022	0,628	1,661				
HDL cholesterol, mmol/L						0,0227				0,0223			
	<1.0	51	60,46	31	51,3	0,0181	1,806	1,106	2,94889	0,1528	1,453	0,871	2,426
	1.0-1.4	84	116,3	33	28,4		1				1		
	>1.4	62	75,42	37	49,1	0,0223	1,728	1,081	2,763	0,0036	2,121	1,278	3,521
LDL cholesterol, mmol/L						0,7541							
	<2.6	51	65,15	28	43,0		1						
	2.6-3.4	70	88,98	37	41,6	0,8955	0,968	0,592	1,581				

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	>3.4	70	91,54	33	36,1	0,4941	0,839	0,507	1,388				
Triglycerides, mmol/L						0,9892							
	<1.3	76	100,9	40	39,7		1						
	1.3-1.9	59	75,57	30	39,7	0,9966	1,001	0,624	1,607				
	>1.9	62	75,69	31	41,0	0,8929	1,033	0,646	1,651				
TC/HDL ratio at baseline						0,9998							
	<3.7	71	92,49	37	40,0		1						
	3.7-4.8	60	77,48	31	40,0	0,9994	1,000	0,621	1,612				
	>4.8	66	82,15	33	40,2	0,9862	1,004	0,628	1,606				
Non-HDL-c, mmol/L						0,5396							
	<3.4	61	77	36	46,8		1						
	3.4-4.2	67	88,05	32	36,3	0,2998	0,777	0,483	1,251				
	>4.2	69	87,08	33	37,9	0,3836	0,811	0,505	1,300				
Estmated glomerular filtration rate (e-GFR), ml/min						0,0429							
	<90	88	105,3	52	49,4		1						
	≥90	108	145,8	48	32,9	0,0429	0,667	0,450	0,987				

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