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## Switching from boosted PIs to dolutegravir in HIV-infected patients with high cardiovascular risk: 48 week effects on subclinical cardiovascular disease

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**Title:** Switching from boosted protease inhibitors to dolutegravir in HIV-infected patients with high cardiovascular risk: 48-week effects on subclinical cardiovascular disease.

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**Key points:** Relative to continuing on PI/r, switching PI/r to DTG in virologically suppressed patients with high cardiovascular risk showed consistent favorable although non-significant effects on carotid ultrasonography progression at 48 weeks relative to continuing PI/r.

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**Synopsis** (word count: 249)

Background: Switching from boosted protease inhibitors (PIr) to dolutegravir (DTG) in virologically suppressed HIV-infected patients with high cardiovascular risk significantly decreased total cholesterol and other proatherogenic lipid fractions at 48 weeks. The impact of this strategy on subclinical cardiovascular disease is unknown.

Methods: NEAT022 is a European, multicenter, open-label, randomized, non-inferiority trial. HIV-infected adults >50 years or with a Framingham score >10% were eligible if plasma HIV RNA <50 copies/mL for >24 weeks on a PI/r-based regimen. Patients were randomized 1:1 to switch from PI/r to DTG or to continue on PI/r. Common carotid arteries intima media thickness (CIMT) and pulse wave velocity (PWV) were measured following a standardized protocol in a sub-group of NEAT022 study participants at baseline and at week 48.

Results: One hundred and fifty-six patients participated in the ultrasonography and arterial stiffness sub-studies respectively. In each sub-study, population characteristics did not differ between arms and matched those of the main study. At 48 weeks, patients who switched to DTG had lower mean progression of both right (+4 vs. +14.6  $\mu\text{m}$ ) and left (-6.1 vs. +1.6  $\mu\text{m}$ ) CIMT and also smaller increase in mean PWV (-0.49 vs. -0.21 m/s) than patients continuing on PI/r although differences were not statistically significant. CIMT trends were consistent across Framingham score, age, and country. Inconsistent effects were seen in arterial stiffness.

Conclusions: Relative to continuing on PI/r, switching to DTG in virologically suppressed patients with high cardiovascular risk showed consistent favorable although non-significant effects on CIMT progression at 48 weeks.

## Introduction

Effective antiretroviral therapy has changed the natural course of HIV infection from a fatal condition to a chronic manageable disease. HIV-infected patients have a longer life expectancy and their major medical problems have shifted from AIDS-related conditions to non-AIDS comorbidities (1, 2). Atherosclerotic cardiovascular disease has emerged as an increasing cause of morbidity among HIV-infected adults (3-6). Multiple studies across different settings have shown a risk of ischemic heart disease in HIV-infected adults 1.5- to 2-fold higher than that of the general population (3, 6-8). Traditional cardiovascular risk factors such as smoking, dyslipidemia, diabetes and hypertension are more prevalent in HIV-infected persons than in the general population (9, 10). Factors directly linked to HIV infection such as immune depression, chronic inflammation, and immune activation also play a role (4, 11-13). Although antiretroviral therapy has a doubtless overall benefit on HIV infection, some antiretroviral drugs have been linked to a higher risk of cardiovascular disease (CVD). Exposure to first-generation protease inhibitors (14) and to lopinavir/ritonavir (15) was associated with an increased risk of cardiovascular disease at least in part due to drug effects on plasma lipids. More recently, darunavir/ritonavir has been also associated with an increase in CVD due to unknown mechanisms (16). Current guidelines recommend antiretroviral therapy modification switching to non-nucleoside reverse transcriptase inhibitors, integrase inhibitors or another protease inhibitor known to cause less metabolic disturbances and/or lower CVD risk in HIV-infected adults with a 10-year cardiovascular risk score of 10% or higher as a first step to prevent CVD (17).

Because cardiovascular events are rare, interventional studies with clinical endpoints will need thousands of patients and many years of follow-up (18). Subclinical CVD progression may be more accurate than use of predictive scores and more cost-effective than detection of cardiovascular events to assess CVD (19). Carotid artery intima-media thickness (CIMT) has been commonly used

as an anatomical surrogate marker of CVD in the general (20-22) and HIV-infected (23-29) populations. Increased pulse wave velocity (PWV) is associated with arterial stiffening and has been proposed as a marker of microvascular structure and function that may contribute to tissue damage, particularly in susceptible high flow organs such as the heart, brain and kidneys (30-33).

The NEAT022 study has shown that switching the ritonavir-boosted protease inhibitor (PI/r) component to dolutegravir (DTG) in virologically suppressed HIV-infected adults with high cardiovascular risk was non-inferior and significantly improved lipid profile after 48 weeks of follow-up (34). Patients switched to DTG had a 7.7% LDL cholesterol reduction from baseline values after 48 weeks. In the general population, this level of LDL cholesterol reduction is associated with a significant reduction in the relative risk of major cardiovascular events in all baseline strata of cardiovascular risk (35, 36). As 60% of study participants switched away from regimens containing ritonavir-boosted lopinavir or darunavir, both independently associated with an increased CVD risk in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study through mechanisms other than dyslipidaemia (15, 16), there might have been additional favorable effects on CVD. Moreover, switching from a PI/r regimen to an integrase inhibitor regimen may have additional potential benefits in reducing inflammation (37, 38), immune activation (39) and residual viral replication (40, 41). In the NEAT022 study, there were only 3 major cardiovascular events throughout 48 weeks (34). Although the study was not powered to detect differences in cardiovascular events, there might be measurable anatomical or functional benefits of the switching strategy on subclinical CVD. We hypothesized that switching from PI/r to DTG in virologically suppressed HIV-infected patients with high cardiovascular risk would have a favorable impact on the progression of subclinical CVD.

## **Methods**

### Patients

NEAT022 is an open-label, randomized, non-inferiority trial conducted in 32 clinical sites in 6 European countries. Briefly, eligible patients were HIV-infected adults older than 50 years or older than 18 years with a 10-year Framingham CVD risk score higher than 10%. They required to be treated with a stable triple antiretroviral regimen consisting on a PI/r plus two nucleoside reverse transcriptase analogues and to have a plasma HIV RNA <50 copies per mL for at least the previous six months. Patients with prior evidence of primary viral resistance to backbone nucleos(t)ides or previous episodes of documented virological failures were excluded. Eligible participants were randomly assigned (1:1) to switch the PI/r component to DTG 50mg/day maintaining the two NtRTIs unchanged or to continue with the same PI/r-based triple therapy regimen for 48 weeks and subsequently all patients in the PI/r arm were switched to DTG (34). Of 415 patients randomized in NEAT022, 100 and 56 respectively agreed to participate in the CIMT ultrasonography and arterial stiffness sub-studies. Ultrasonography of common CIMT and arterial stiffness (PWV) were measured locally following a standardized protocol at baseline and at week 48. These evaluations were performed by independent experts blinded to patient's therapy. The subclinical CVD substudy protocol was approved by the ethics committees of all participating centres. All participants gave their written informed consent prior to study procedures. The study is registered on ClinicalTrials.gov NCT02098837 and EudraCT 2013-003704-39.

### Carotid intima media thickness

CIMT measurement procedures followed the Mannheim consensus (42). Measurements were performed on both common carotid arteries using a commercially validated ultrasound scanner equipped with a linear 7-10 MHz probe following a standardized procedure. CIMT was automatically assessed on the far wall of the common carotid artery at one centimeter from the

bulb to avoid inter-individual variability. Plaque was defined as an area with localized carotid thickness >1.5 mm as measured from the intima-lumen interface to the media-adventitia interface.

#### Arterial stiffness

Measurement of brachial cuff blood pressure (BP) was performed prior to central hemodynamic assessment. After resting for a period of 5 minutes in seated position, brachial BP was recorded as the mean of two readings in the non-dominant arm using an oscillometric BP monitor. Pulse wave analysis was used to determine central BP by non-invasive tonometry with one of two validated devices, SphygmoCor (AtCorMedical, Sydney, Australia) or Complior (Alam Medical, Saint Quentin Fallavier, France), on the same arm used for brachial BP measurements. The central systolic, diastolic and pulse pressures were calculated following manufacturer's instructions. Collected data included augmentation index (Aix), which is the supplementary increase in systolic BP as determined by the reflected pressure waves according to the following formula  $Aix = (AP/PP) \times 100$ , where AP is the pressure difference between the shoulder of the wave and the peak systolic pressure and PP is the pulse pressure. Because of their dependence on heart rate, the data are automatically normalized to 75 b.p.m. ( $Aix@HR75$ ). Carotid-femoral pulse wave velocity (cfPWV) was then obtained using ECG-gated pulse waveforms over the carotid and femoral arteries in supine position. PWV was calculated as the distance between recording sites measured over the surface of the body, divided by the time interval between the feet of the pressure waves. PWV measurements were collected in duplicate and averaged. Only high-quality recordings, defined as an in-device quality index of > 80%, were accepted for analysis. Central BP and PWV were assessed at baseline and at week 48.

#### Statistical analysis

As there are no reliable data on arterial stiffness progression, sample size estimation was based on CIMT progression. Considering the CIMT changes from baseline in A5260s (28), a sub-study of the randomized clinical trial A5257 evaluating two PI/r versus the integrase inhibitor raltegravir (43), we estimated that the pooled changes in the PI/r arm would be 11.4  $\mu\text{m}/\text{year}$  with a standard deviation of 0.92  $\mu\text{m}$ . We assumed that DTG would obtain similar results of CIMT changes as those observed with raltegravir in A5260s, i.e. 10.7  $\mu\text{m}$  per year. Therefore, the expected difference between the DTG arm and the PI/r arm would be at least 0.7  $\mu\text{m}$  per year. With 38 patients per arm, the study would have more than 90% power to detect a between treatment difference of 0.7  $\mu\text{m}$  per year in the mean change from baseline in the CIMT, with a standard deviation of 0.92  $\mu\text{m}$ , a type I error of 0.05, and a two-tailed test.

The mean change and mean percentage change from baseline in right and left common CIMT ( $\mu\text{m}$ ) at week 48 were compared between DTG and PI/r arms using the non-parametric Mann Whitney test. The mean change and mean percentage change from baseline in arterial stiffness parameters (PWV (m/s) and  $\text{Alx@HR75}$  (%)) at week 48 were compared using the non-parametric Mann Whitney test. Subgroups analyses were also conducted to study the treatment effect across groups: PI/r drugs at screening (darunavir, atazanavir, other PI), age and cardiovascular risk score (<50yr and >10%,  $\geq 50\text{yr}$  and >10%,  $\geq 50\text{yr}$  and  $\leq 10\%$ ), cardiovascular risk score (<15% vs  $\geq 15\%$ ) and participating country (France, Italy, and Spain) for all parameters. Differences in outcomes between intervention arms were also assessed by t-tests and interaction between randomisation arms and strata were assessed by an analysis of variance. The 95% two sided confidence intervals of the difference in the change from baseline in parameters at week 48 between randomisation arms (DTG containing regimen – PI/r containing regimen) were calculated. We used local readings of CIMT and arterial stiffness for the analysis because the availability of data was higher than that of central readings. There was a high degree of concordance between both assessments (**Figure 1**).



## Results

### Carotid intima media thickness (CIMT)

Population characteristics in the CIMT sub-study (**Table 1**) did not differ between arms and matched those of the main study: >50 years 88%, Framingham score  $\geq 10\%$  72%, men 80%, Caucasian 89%, median time with undetectable viral load 4.2 years, current smokers 55%, diabetes 5%, family history of cardiovascular disease 36%, hypertension 26%, and lipid-lowering therapy 32%.

Mean absolute progression was lower in both right (4.0 vs. 14.6  $\mu\text{m}$ ) and left (-6.1 vs. 1.6  $\mu\text{m}$ ) common CIMT in patients switched to DTG as compared with patients continuing on PI/r, respectively (**Figure 2**). There was also a lower mean percentage change from baseline in both right (3% vs. 3.2%) and left (0.4% vs. 0.6%) common CIMT in patients switched to DTG as compared with patients continuing on PI/r (**Figure 2**). However, differences were not statistically significant because of the high dispersion of the results.

Patients with a Framingham score  $\geq 15\%$  (vs.  $< 15\%$ ), treated with PIs other than darunavir or atazanavir (almost all patients not receiving darunavir or atazanavir were treated with lopinavir/ritonavir), those with an age  $< 50$  years and a Framingham score  $> 10\%$ , and those from France or Italy (vs. Spain) showed more favorable right common CIMT changes with DTG switch at 48 weeks (**Table 2**).

At baseline, 38.5% patients in the DTG arm and 43.8% in the PI/r arm had carotid plaques detected without differences between arms. At week 48, the percentages rose to 40.4% and 45.8%, respectively. The change from baseline in the proportion of patients with carotid plaques at week 48 showed no difference between the two groups (**Figure 3**).

### Arterial stiffness

Population characteristics in the arterial stiffness sub-study (**Table 3**) did not differ between arms and reflected also those of the main study: >50 years 89%, Framingham score  $\geq 10\%$  70%, men 86%, Caucasian 84%, median undetectable viral load 3.9 years, current smokers 52%, diabetes 9%, family history of cardiovascular disease 51%, hypertension 32%, and lipid-lowering therapy 25%.

**Figure 4** shows the mean change and mean percentage change from baseline in PWV and  $\text{Alx@HR75}$  at week 48. Mean PWV change and mean percentage PWV change showed smaller increases in patients switched to DTG compared with patients continuing on PI/r (0.18 vs. 0.39 m/s, and 4.47 vs. 5.77%, respectively) although these differences were not statistically significant. There were higher mean  $\text{Alx@HR75}$  (1.59 vs. -0.36) and a higher mean percent  $\text{Alx@HR75}$  (43.99% vs. 5.86%) changes in patients switched to DTG as compared with patients continuing on PI/r, but none of these differences was statistically significant. **Table 4** shows the subgroup analysis for change from baseline in PWV at week 48. Patients treated with atazanavir (vs. darunavir) showed more favorable PWV changes with DTG switch at 48 weeks.

## Discussion

This sub-study of NEAT 022 study was unable to detect significant changes between arms in subclinical cardiovascular disease progression at 48 weeks as measured by both ultrasonography and arterial stiffness. Due to the scarcity of reliable arterial stiffness data, sample size calculation was based on 1-year CIMT changes in A5260s (28), a sub-study of the randomized clinical trial A5257 (43), that compared first-line atazanavir/r, darunavir/r and raltegravir in combination with emtricitabine-tenofovir disoproxil. In contrast with the NEAT022 sub-study, patients in the A5260s sub-study were antiretroviral-naïve and had a low cardiovascular risk (28). Although the magnitude of mean CIMT changes in the A5260s and NEAT022 sub-studies was similar, the variability of CIMT measurements found in the NEAT022 sub-study was unexpectedly higher than that reported in the A5260s sub-study.

Relative to continuing PI/r, switching the PI/r component to DTG in virologically suppressed patients with high cardiovascular risk showed consistent although not significant effects on absolute and percent CIMT progression in both common carotid arteries. In contrast to CIMT changes, the changes in A1x@HR75 and PWV were not consistent. While both absolute and relative PWV showed smaller increases in patients switching to DTG relative to patients remaining on PI/r, both absolute and relative A1x@HR75 values increased and this is inconsistent with the smaller increases in PWV and CIMT seen in those patients. Increases in both PWV and A1x@HR75 suggest worse subclinical cardiovascular status; however, they do not measure exactly the same. PWV is considered the non invasive gold standard measure of arterial stiffness. Although A1x is frequently referred as an arterial stiffness measure, it is the result of several arterial factors, including (but not limited to) arterial stiffness (32). Altogether these data suggest that arterial stiffness may be less reliable than CIMT as an indicator of subclinical cardiovascular disease in virologically suppressed HIV-infected patients with high cardiovascular risk.

Subgroup CIMT analyses showed that patients switching to DTG had more favorable CIMT changes when Framingham Score (rather than age) was higher or when the PI switched was other than darunavir or atazanavir, a proxy of lopinavir/ritonavir. A high Framingham score gives an estimate of the risk of developing cardiovascular disease and points out who is most likely to benefit from prevention. Lopinavir/ritonavir is associated with higher lipid values than atazanavir/ritonavir (44) or darunavir/ritonavir (45); furthermore, lopinavir/ritonavir has been associated with an additional lipid-independent higher risk of cardiovascular disease (15). Despite having similar lipid impact, atazanavir and darunavir have shown very distinct cardiovascular profiles [16,46].

Integrase inhibitors in general and dolutegravir in particular have been associated with more weight gain than PI or non-nucleoside reverse transcriptase inhibitors in randomized clinical trials (46). Beyond favorable lipid effects, integrase inhibitors may promote weight gain and other unfavorable metabolic changes which might also impact on cardiovascular health of the HIV infected population. Most studies evaluating the possible effects of antiretroviral drug switching strategies on cardiovascular health have been focused on plasma lipid changes. A few randomized studies have directly assessed subclinical atherosclerosis (28,29), but these studies were addressed to patients starting antiretroviral therapy. There are no data available on switching strategies addressed to reduce CVD in patients with high cardiovascular risk. NEAT022 sub-studies aimed to evaluate subclinical atherosclerosis with both anatomical and functional parameters. Although the observed CIMT trends were in agreement with the improvement in lipid profile after 48 weeks of follow-up (34), changes were not statistically significant.

The main limitation of this substudy was the lack of power. A higher number of patients with longer follow-up would have been necessary to allow for detection of significant effects. The negative results of this study are important as they contribute to a better knowledge of the topic and can inform other scientists with similar objectives. Results suggest that the 1-year impact of

antiretroviral therapy switch on subclinical CVD is scarce at most and cannot be taken as given by lipid effects only.

In summary, switching the PI/r component to DTG in virologically suppressed patients with high cardiovascular risk showed consistent favorable although non-significant effects on CIMT progression at 48 weeks relative to continuing on PI/r. These findings may be useful in designing future studies.

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**Contributions**

AG-C, MC, MD, JMG and EM designed the study. MC and MD established standardized protocols on carotid ultrasonography and arterial stiffness respectively, trained the operators on local sites, and performed central measurements. LA undertook the statistical analyses. AG-C, MC, MD, GG, PD, SR, FR, CK, MM, JIB, MS, AP, JMG, and EM were involved in the interpretation of data. AG-C and EM drafted the manuscript. All authors critically reviewed and subsequently approved the final version.



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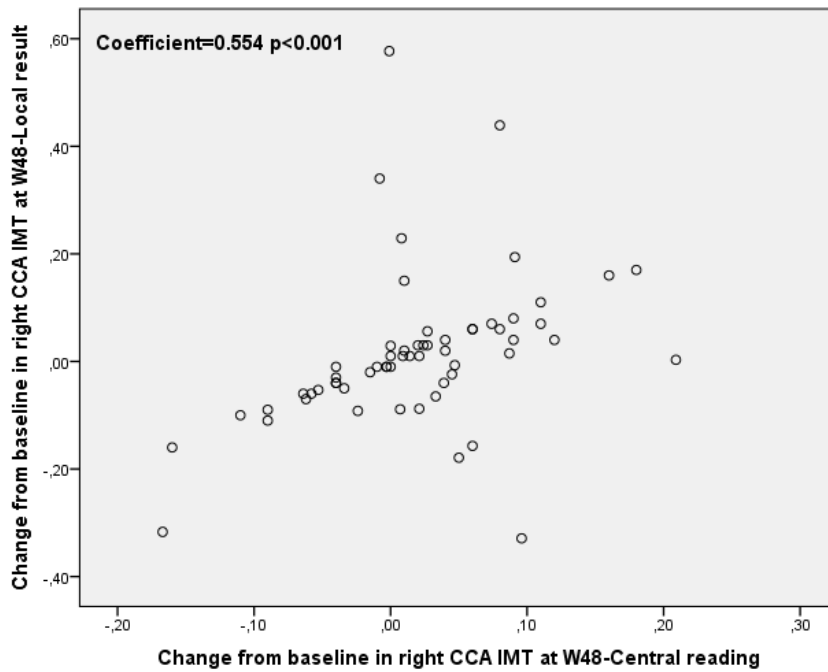
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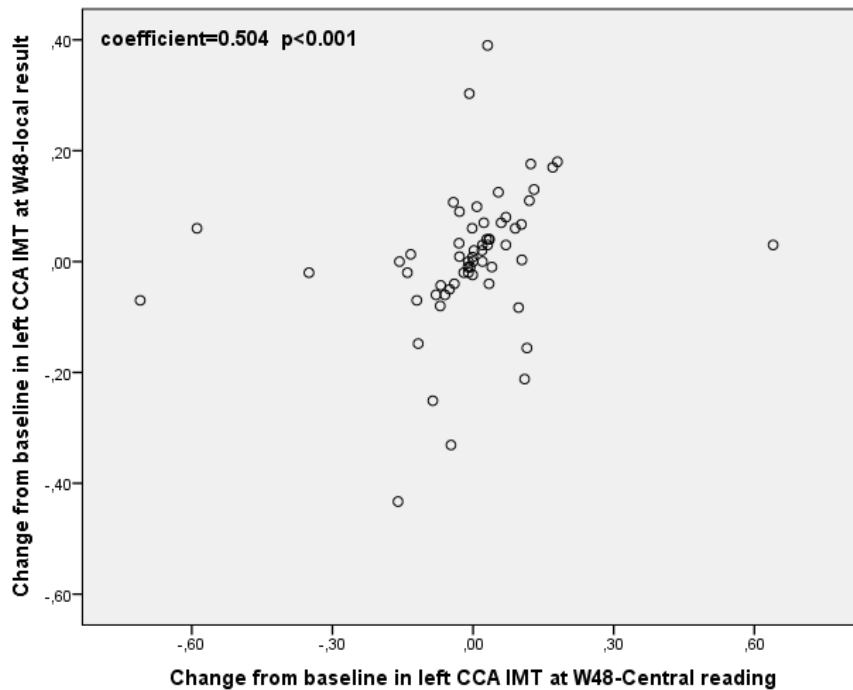


Figure 1. Correlation between local and central readings in right and left common carotid intima media thickness (CCA IMT), pulse wave velocity, and augmentation index.

Right common CIMT

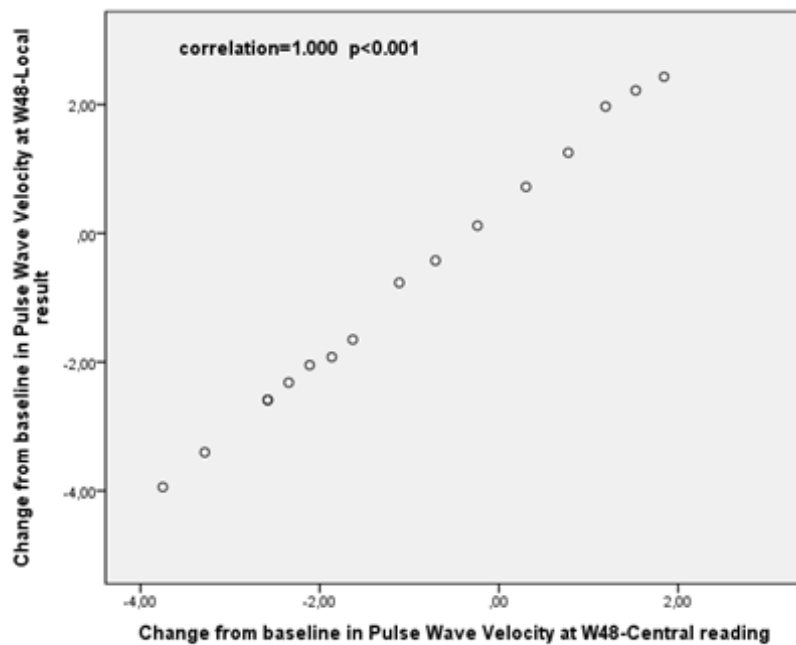


Left common CIMT





### Pulse wave velocity (PWV)



### Augmentation index (AIx@HR75)

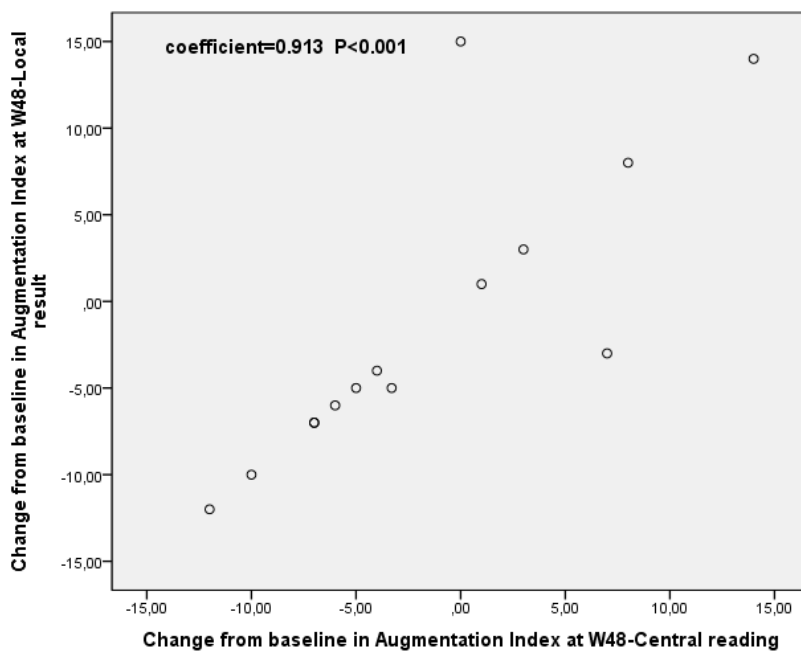
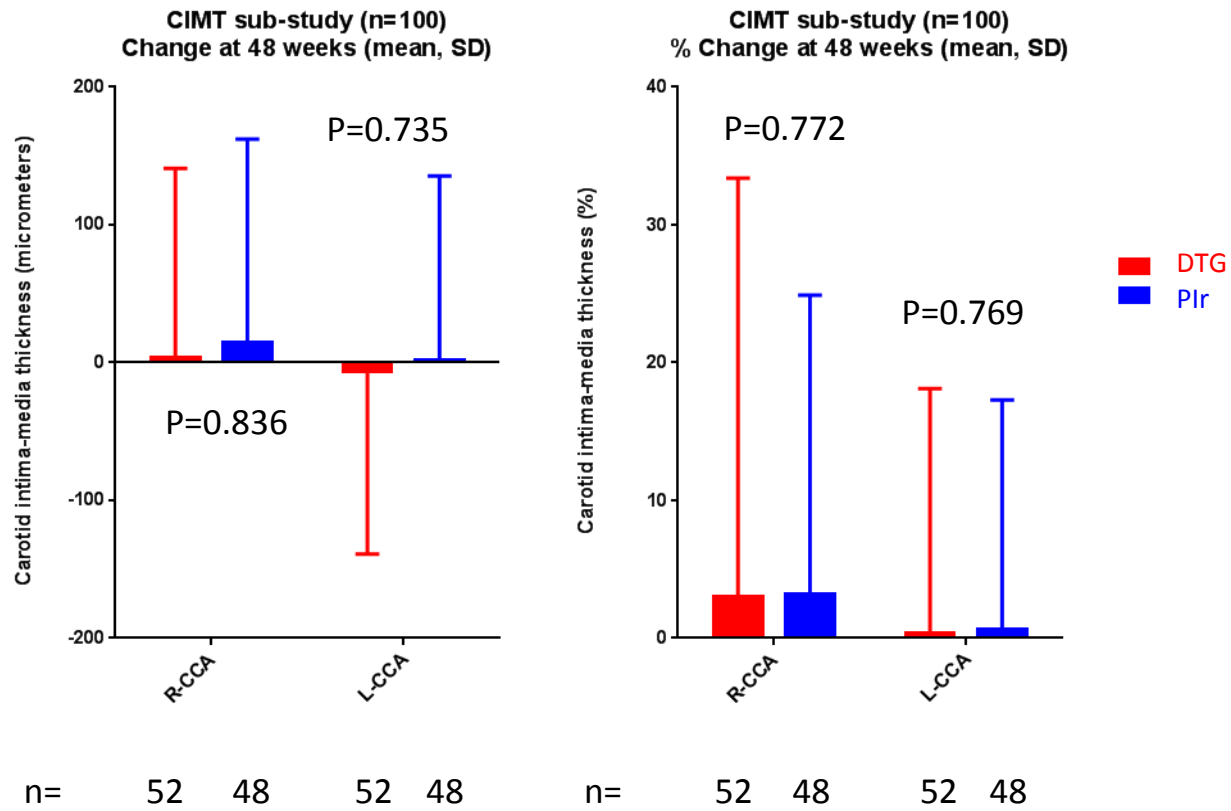
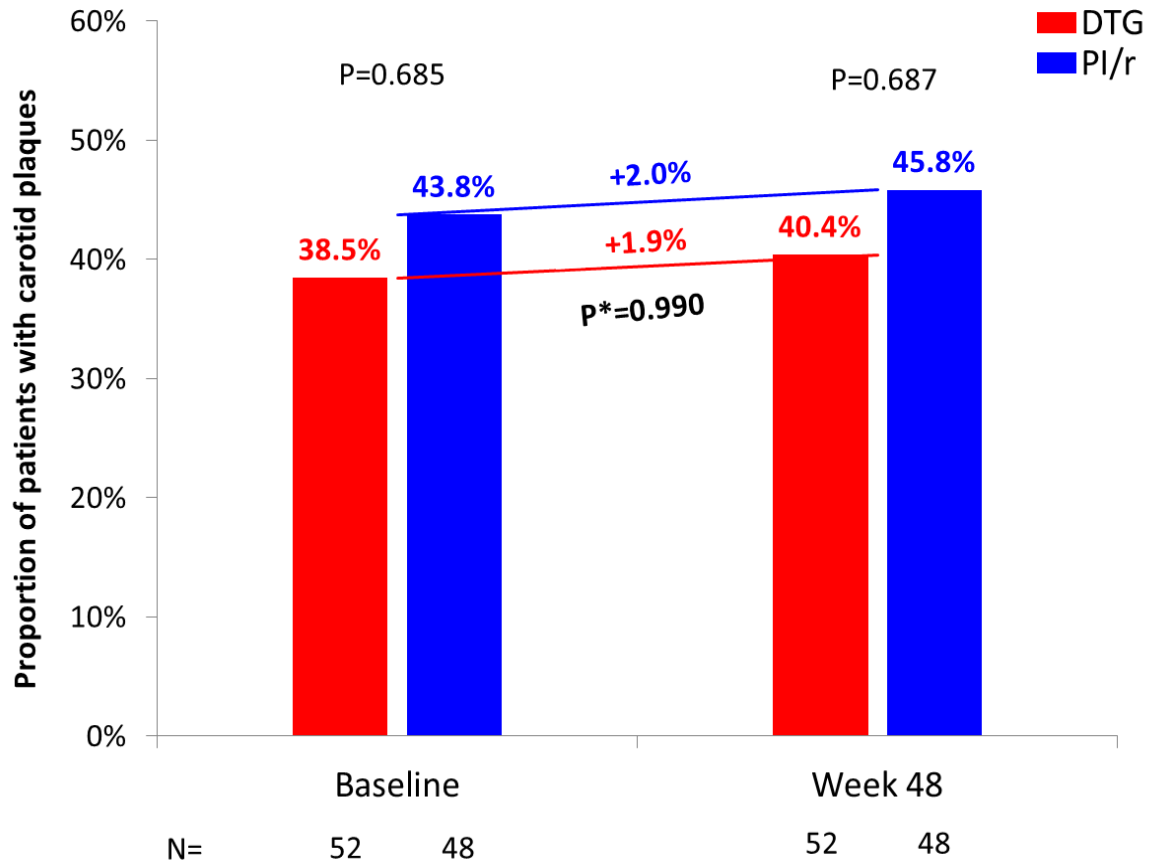


Figure 2. Mean change and mean percentage change from baseline in right (R-CCA) and left (L-CCA) common carotid intima media thickness (CIMT).



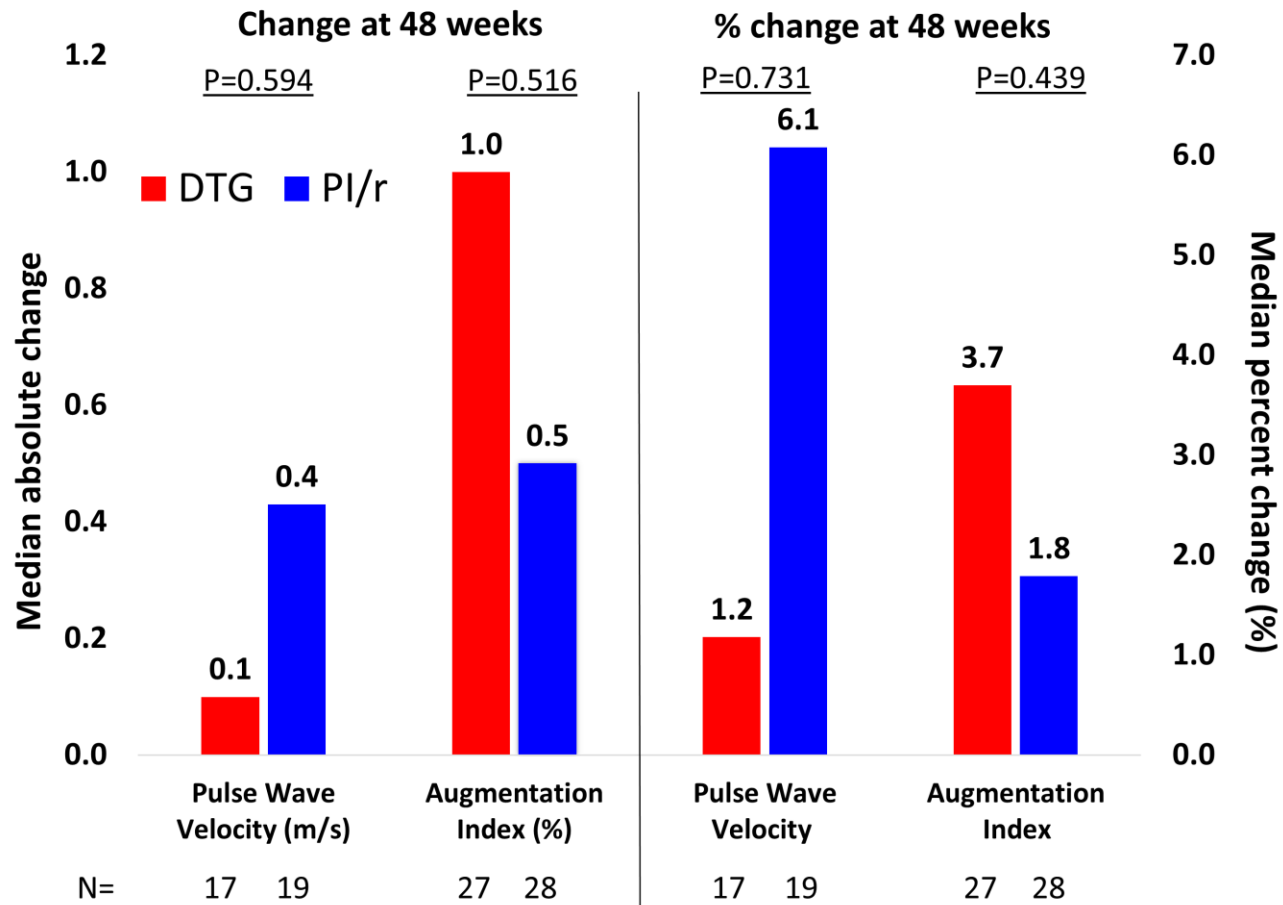
**Figure 3. Carotid plaques**

Change from baseline in the proportion of patients with carotid plaques at week 48 between the 2 groups, using a GEE model



GEE: Generalized estimating equation

Figure 4. Mean change and mean percentage change from baseline in pulse wave velocity (PWV) and augmentation index (Aix@HR75).



No significant changes were observed in each arm

**Table 1. Characteristics of the population included in the common carotid intima media thickness (CIMT) sub-study (N=100).**

	<b>DTG (n=52)</b>	<b>PI/r (n=48)</b>	<b>Total (n=100)</b>
<b>Age, years, median(IQR)</b>	53 (51 – 57)	54 (52 – 56)	54 (51 – 57)
<b>Age &gt; 50 years</b>	<b>44(84.6)</b>	<b>44(92.7)</b>	<b>88(88.0)</b>
<b>Framingham score at 10 years</b>			
<10%	13 (25.0)	15 (31.3)	28 (28.0)
10-15%	17 (32.7)	14 (29.2)	31 (31.0)
15-20%	12 (23.1)	8 (16.7)	20 (20.0)
>20%	10 (19.2)	11 (22.9)	21 (21.0)
<b>Male gender</b>	41 (78.8)	39 (81.3)	80 (80.0)
<b>White race</b>	<b>45(86.5)</b>	<b>44(91.7)</b>	<b>89(89.0)</b>
<b>Mode of HIV transmission</b>			
Male homosexual sexual intercourse	22 (42.3)	23 (47.9)	45 (45.0)
Heterosexual sexual intercourse	20 (38.5)	16 (33.3)	36 (36.0)
Other	10 (19.2)	9 (18.8)	19 (19.0)
<b>CD4+ count (cells per µL)</b>	672 (571 – 928)	610 (427 – 878)	657 (552 – 920)
<b>HIV RNA &gt;50 copies/mL</b>	<b>1(2.9)</b>	<b>0(0.0)</b>	<b>1(1.0)</b>
<b>Hepatitis C IgG antibodies</b>	<b>10 (19.2)</b>	<b>11 (24.4)</b>	<b>21 (21.0)</b>
<b>Time since undetectable viral load (&lt; 50 copies per mL); years</b>	<b>3.6 (1.7 – 6.8)</b>	<b>5.7 (2.8 – 8.9)</b>	<b>4.2 (2.2 – 8.2)</b>
<b>Bacbone nucleos(t)ides</b>			
Tenofovir disoproxil fumarate/Emtricitabine	<b>34 (65.4)</b>	<b>27 (56.3)</b>	<b>61 (61.0)</b>
Abacavir /Lamivudine	<b>16 (30.8)</b>	<b>19 (39.6)</b>	<b>35 (35.0)</b>
Other	<b>2 (3.8)</b>	<b>2 (4.2)</b>	<b>4 (4.0)</b>
<b>PI/r at baseline</b>			
Lopinavir	26 (50.0)	27 (56.3)	53 (53.0)
Darunavir	21 (40.4)	12 (25.0)	33 (33.0)
Atazanavir	5 (9.6)	9 (18.7)	14 (14.0)
<b>Current Smokers</b>	<b>30 (57.7)</b>	<b>25 (52.1)</b>	<b>55 (55.0)</b>
<b>Diabetes mellitus</b>	<b>2 (3.8)</b>	<b>3 (6.3)</b>	<b>5 (5.0)</b>
<b>Family history of cardiovascular disease</b>	<b>21 (40.4)</b>	<b>15 (31.3)</b>	<b>36 (36.0)</b>
<b>Receiving lipid lowering agents</b>	<b>16(30.8)</b>	<b>16(33.3)</b>	<b>32 (32.0)</b>
<b>High blood pressure <sup>a</sup></b>	<b>13(25.0)</b>	<b>13(27.1)</b>	<b>26(26.0)</b>
<b>Daily exercise</b>	<b>9(17.3)</b>	<b>10(20.8)</b>	<b>19(19.0)</b>
<b>Cardiovascular risk factors <sup>b</sup></b>			
0	<b>13 (25.0)</b>	<b>10 (20.8)</b>	<b>23 (23.0)</b>
1	<b>16 (30.8)</b>	<b>18 (37.5)</b>	<b>34 (34.0)</b>
2	<b>14 (26.9)</b>	<b>14 (29.2)</b>	<b>28 (28.0)</b>
≥3	<b>9 (17.3)</b>	<b>6 (12.5)</b>	<b>15(15.0)</b>
<b>Fasting plasma lipids (mmol/L)</b>			
Total cholesterol	<b>5.3(4.4-5.6)</b>	<b>5.2(4.4-5.8)</b>	<b>5.2(4.4-5.6)</b>
Triglycerides	<b>1.7(1.1-2.3)</b>	<b>1.6(1.1-2.2)</b>	<b>1.7(1.1-2.3)</b>
Non-HDL cholesterol	<b>4.0(3.5-4.4)</b>	<b>3.9(3.3-4.6)</b>	<b>4.0(3.3-4.5)</b>
LDL-cholesterol	<b>3.2(2.5-3.7)</b>	<b>3.1(2.6-3.6)</b>	<b>3.2(2.6-3.7)</b>
HDL-cholesterol	<b>1.2(0.9-1.4)</b>	<b>1.1(1.0-1.4)</b>	<b>1.1(1.0-1.4)</b>

Total Cholesterol/HDL cholesterol ratio	<b>4.4(3.4-5.6)</b>	<b>4.3(3.5-5.7)</b>	<b>4.3(3.5-5.7)</b>
<b>eGFR (mL/minute)</b>	<b>94(81-98)</b>	<b>94(76-101)</b>	<b>94(81-100)</b>

Data are n (%) or median (IQR)

a Defined by systolic blood pressure >140mmHg or diastolic blood pressure > 110 mmHg or receiving anti-hypertensive treatment addition

b An addition of male patients with age more than 50 years or female patients with age more than 60 years, current or past smoker within the last 3 years, HDL CHOLESTEROL less than 1 mmol/L, high blood pressure, diabetes mellitus, family history of cardiovascular diseases. HDL CHOLESTEROL levels above 1.5 mmol/L, implicates a subtraction of one risk factor.

eGFR=estimated glomerular filtration rate (CKD-EPI method54). PI/r= ritonavir boosted protease inhibitors. DTG= dolutegravir

**Table 2. Subgroup analysis for change from baseline in Right CCA IMT ( $\mu\text{m}$ ) at week 48 (Total N=100)**

Subgroup	Percentage in group	DTG mean (SE)	PI/r mean (SE)	Mean difference (95% CI)	P Value for interaction
<b>All participants</b>	100	+4.0 (19.7)	+14.6 (20.5)	-10.6 (-67.2;+45.8)	
<b>Framingham Cardiovascular risk score</b>					0.446
<15%	59	-1.5 (24.2)	-9.1 (24.2)	+7.6 (-61.1; +76.4)	
$\geq$ 15%	41	+9.4 (35.0)	+47.3 (37.7)	-37.9 (-141.9 ; +66.2)	
<b>PI/r regimen</b>					0.603
Darunavir	54	+16.3 (34.2)	+18.7 (33.5)	-2.4 (-98.5; +93.6)	
Atazanavir	33	-1.0 (16.3)	-7.8 (21.5)	+6.8 (-41.2; +61.9)	
Others	13	-59.3 (72.7)	+32.3 (48.5)	-91.6 (-283.9; +100.8)	
<b>Age and Framingham Cardiovascular (CVS) risk</b>					0.527
Age $\geq$ 50yr and CVS $\leq$ 10%	28	+15.1 (38.6)	-24.8 (35.9)	+39.9 (-68.5;+148.2)	
Age $\geq$ 50yr and CVS>10%	60	+7.4 (23.1)	+33.2 (23.8)	-25.8 (-92.2; +40.6)	
Age<50yr and CVS>10%	12	-27.4 (77.5)	+28.3 (109.5)	-55.6 (-354.5; +243.3)	
<b>Country</b>					0.830
France	18	-8.2 (21.8)	+37.1 (27.3)	-45.3 (-119.5; +28.8)	
Italy	27	-12.8 (33.1)	-4.6 (34.3)	-8.2 (-106.5; +90.0)	
Spain	53	+22.2 (34.2)	-18.0 (32.3)	+4.2 (-90.1; +98.6)	

**Table 3. Characteristics of the population included in the arterial stiffness sub-study (N=56).**

	<b>DTG (n=27)</b>	<b>PI/r (n=29)</b>	<b>Total (n=56)</b>
<b>Age, years, median(IQR)</b>	55 (53 – 59)	54 (52 – 56)	54 (52 – 58)
<b>Age &gt; 50 years</b>	26(96.3)	27(96.6)	56(88.9)
<b>Framingham score at 10 years</b>			
<10%	9 (33.3)	8 (27.6)	17 (30.4)
10-15%	6 (22.2)	7 (24.1)	13 (23.2°)
15-20%	6 (22.2)	5 (17.2)	11 (19.6)
>20%	6 (22.2)	9 (31.0)	15 (26.8)
<b>Male gender</b>	21 (77.8)	25 (86.2)	46 (86.1)
<b>White race</b>	22(81.5)	25(86.2)	47(83.9)
<b>Mode of HIV transmission</b>			
Male homosexual sexual intercourse	8 (29.6)	15 (51.7)	23 (41.1)
Heterosexual sexual intercourse	13 (48.1)	8 (27.6)	21 (37.5)
Other	6 (22.2)	6 (20.7)	12 (21.4)
<b>CD4+ count (cells per µL)</b>	654 (547 – 938)	731 (482 – 1024)	658 (547 – 970)
<b>HIV RNA &gt;50 copies/mL</b>	0(0.0)	0(0.0)	0(0.0)
<b>Hepatitis C IgG antibodies</b>	4 (15.4)	6 (21.4)	10 (18.5)
<b>Time since undetectable viral load (&lt; 50 copies per mL); years</b>	3.5 (2.2 – 6.3)	4.3 (2.9 – 8.8)	3.9 (2.4 – 6.9)
<b>Backbone nucleos(t)ides</b>			
Tenofovir disoproxil fumarate/Emtricitabine	18 (66.7)	15 (51.7)	33 (58.9)
Abacavir /Lamivudine	8 (29.6)	13 (44.8)	21 (37.5)
Other	1 (3.7)	1 (3.4)	2 (3.6)
<b>PI/r at baseline</b>			
Lopinavir	10 (37.0)	14 (48.3)	24 (42.9)
Darunavir	15 (55.6)	9 (31.0)	24 (42.9)
Atazanavir	1 (3.7)	6 (20.7)	7 (12.5)
Other	1(3.7)	0(0.0)	1(1.8)
<b>Current Smokers</b>	14 (51.9)	15 (51.7)	29 (51.8)
<b>Diabetes mellitus</b>	1 (3.7)	4 (13.8)	5 (8.9)
<b>Family history of cardiovascular disease</b>	14 (53.8)	13 (48.1)	27 (50.9)
<b>Receiving lipid lowering agents</b>	6(22.2)	8(27.6)	14(25.0)
<b>High blood pressure <sup>a</sup></b>	7(25.9)	11(37.9)	18(32.1)
<b>Daily exercise</b>	4(16.7)	7(28.0)	11(22.4)
<b>Cardiovascular risk factors <sup>b</sup></b>			
0	7 (25.9)	7 (24.1)	14 (25.0)
1	7 (25.9)	7 (24.1)	14 (25.0)
2	8 (29.6)	8 (27.6)	16 (28.6)
≥3	5 (18.5)	7 (24.1)	12 (21.4)
<b>Fasting plasma lipids (mmol/L)</b>			
Total cholesterol	5.2(4.3-5.6)	5.1(4.2-5.8)	5.2(4.2-5.8)
Triglycerides	1.6(1.1-2.3)	1.6(1.2-2.2)	1.6(1.2-2.2)
Non-HDL cholesterol	3.9(3.0-4.7)	3.8(3.2-4.6)	3.8(3.0-4.6)
LDL-cholesterol	3.1(2.3-3.7)	3.0(2.2-3.6)	3.0(2.3-3.7)
HDL-cholesterol	1.1(0.9-1.4)	1.1(1.0-1.4)	1.1(1.0-1.4)



Total Cholesterol/HDL cholesterol ratio	4.4(3.4-6.0)	4.0(3.3-5.6)	4.2(3.3-5.7)
<b>eGFR (mL/minute)</b>	94(81-98)	99(90-106)	96(82-103)

Data are n (%) or median (IQR)

a Defined by systolic blood pressure >140mmHg or diastolic blood pressure > 110 mmHg or receiving anti-hypertensive treatment addition

b An addition of male patients with age more than 50 years or female patients with age more than 60 years, current or past smoker within the last 3 years, HDL CHOLESTEROL less than 1 mmol/L, high blood pressure, diabetes mellitus, family history of cardiovascular diseases. HDL CHOLESTEROL levels above 1.5 mmol/L, implicates a subtraction of one risk factor.

eGFR=estimated glomerular filtration rate (CKD-EPI method54). PI/r= ritonavir boosted protease inhibitors. DTG= dolutegravir

**Table 4. Subgroup analysis for change from baseline in Pulse Wave Velocity (m/s) at week 48 (Total N=36)**

Subgroup	Percentage in group	DTG mean (SE)	PI/r mean (SE)	Mean difference (95% CI)	P Value for interaction
<b>All participants</b>	100	+0.18 (0.42)	+0.39(0.40)	-0.21 (-1.37;+0.96)	
<b>Framingham Cardiovascular risk score</b>					<b>0.765</b>
<15%	57.6	+0.09 (0.50)	+0.47 (0.43)	-0.38 (-1.77;+1.01)	
≥15%	42.4	+0.09 (0.86)	+0.08 (0.86)	+0.01 (-2.6;+2.7)	
<b>PI/r regimen</b>					<b>0.012</b>
Darunavir	40.0	+1.53(0.78)	-0.12 (0.58)	+1.65 (-0.48;+3.78)	
Atazanavir	45.7	-0.36 (1.96)	+1.26 (0.63)	-1.62 (-3.24 ;+0.00)	
Others*	14.3				
<b>Age and Framingham Cardiovascular (CVS) risk</b>					<b>0.795</b>
Age≥50yr and CVS≤10%	38.9	+0.49 (0.54)	+0.46 (0.47)	+0.03(-1.53;+1.60)	
Age≥50yr and CVS>10%	58.3	+0.04 (0.64)	+0.33 (0.61)	-0.29 (-2.15; +1.57)	
Age<50yr and CVS>10%**	2.8				
<b>Country</b>					<b>0.101</b>
France	30.6	-0.52 (0.70)	+0.89 (0.76)	-1.41 (-3.75; +0.93)	
Italy	41.7	-0.26 (0.34)	+0.19 (0.32)	-0.45 (-1.47; +0.57)	
Spain***	27.8	+2.00 (1.18)	+0.23 (0.96)	+1.77 (-1.75; +5.28)	

PI/r= ritonavir boosted protease inhibitors. DTG= dolutegravir. SE= Standard error

\*Not estimated because there are only 1 patient in the DTG arm and 6 in the PI/r arm

\*\*Not estimated because there are only 1 patient in the DTG arm and 1 in the PI/r arm

\*\*\*Included 1 patient from Germany and 1 from UK