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Immediate vs. Deferred Switching from a Boosted Protease Inhibitor (PI/r) Based Regimen to a Dolutegravir (DTG) Based Regimen in Virologically Suppressed Patients with High Cardiovascular Risk or Age ≥50 years: Final 96 Weeks Results of NEAT 022 study / Gatell, J.M., Assoumou, L., Moyle, G., Waters, L., Johnson, M., Domingo, P., Fox, J., Martinez, E., Stellbrink, H., Guaraldi, G., Masia, M., Gompels, M., De Wit, S., Florence, E., Esser, S., Raffi, F., Stephan, C., Rockstroh, J., Giacomelli, A., Vera, J., et al.. - In: CLINICAL INFECTIOUS DISEASES. - ISSN 1058-4838. - 68:4(2019), pp. 597-606. [10.1093/cid/ciy505]

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## Title:

Immediate vs. Deferred Switching from a Boosted Protease Inhibitor (PI/r) Based Regimen to a Dolutegravir (DTG) Based Regimen in Virologically Suppressed Patients with High Cardiovascular Risk or Age ≥50 years: Final 96 Weeks Results of NEAT 022 study

## Authors:

José M Gatell (1), Lambert Assoumou (2), Graeme Moyle (3), Laura Waters (4), Margaret Johnson (5), Pere Domingo (6), Julie Fox (7), Esteban Martinez (1), Hans – Jürgen Stellbrink (8), Giovanni Guaraldi (9), Mar Masia (10), Mark Gompels (11), Stephane De Wit (12), Eric Florence (13), Stefan Esser (14), François Raffi (15), Christoph Stephan (16), Juergen Rockstroh (17), Andrea Giacomelli (18), Jaime Vera (19), José Ignacio Bernardino (20), Alan Winston (21), Maria Saumoy (22), Julien Gras (23), Christine Katlama (24), Anton L Pozniak (3) and NEAT022 Study Group*.

(1) Hospital Clinic/IDIBAPS, University of Barcelona and ViiV Healthcare. Barcelona. Spain, (2) INSERM, Sorbonne Université, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), Paris, France, (3) Chelsea & Westminster Hospital and St Stephens AIDS Trust. London. UK, (4) Mortimer Market Center. London. UK, (5) Royal Free Hospital. London. UK. (6) Hospital de Sant Pau. Barcelona. Spain. (7) Guys and St. Thomas` Hospital. London. UK. (8) ICH Study Centrum. Hamburg. Germany, (9) University of Modena and Reggio Emilia. Modena. Italy, (10) Hospital de Elche. Elche. Spain. (11) Southmead Hospital. Bristol. UK, (12) Saint Pierre Hospital. Université Libre de Bruxelles. Brussels. Belgium, (13) Institute of Tropical Medicine. Antwerp. Belgium, (14) Universitatsklinikum. Essen AoR. Germany, (15) Infectious Diseases University Hospital and CIC UIC 1413 INSERM, CHU Nantes, Nantes. France. (16) Klinikum der Goethe Universitat. Frankfurt. Germany. (17) Medizinische Klinik und Poliklinik. Bonn. Germany. (18) Hospital Luigi Sacco. Milan. Italy. (19) Global Health and Infection. Brighton and Sussex Medical School. Brighton. UK. (20) Hospital La Paz. Madrid. Spain. (21) St. Marys Hospital. London. UK. (22) Hospital de Bellvitge. Barcelona. Spain. (23) Hopital St. Louis. Paris France. (24) Pitie-Salpetriere Hospital. Paris. France.

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## Correspondence to:

Prof. José M Gatell, Hospital Clínic Universitari. Barcelona. Villarroel, 170. 08036 Barcelona. Spain.

Telf: Int-34-932275430, Int-34-609889132, Fax: Int-34-934514438, Email: gatell@fundsoriano.es or jmgatell@clinic.cat

## Short title:

Switching from a PI/r to DTG regimen.

## Short summary:

Both immediate and deferred switching from a PI/r to a DTG regimen in virologically suppressed HIV patients ≥ 50 years old or with a Framingham score ≥10% was highly efficacious, well tolerated and improved lipid profile.

### Abstract

**Background:** Both immediate or deferred switching from a PI/r to DTG may improve lipid profile.

Methods: NEAT022 is a European, open label, randomized, trial. HIV-infected adults ≥ 50 years or with a Framingham score ≥10% were eligible if HIV RNA < 50 copies/mL. Patients were randomized to switch the PI/r to DTG immediately (DTG-I) or to deferred switch at week 48 (DTG-D) . Week 96 end-points were: proportion of patients with HIV RNA < 50 copies/ml, percentage change of lipid fractions and adverse events.

**Results:** 415 patients were randomized: 205 to DTG-I and 210 to continue PI/r plus a deferred switch (DTG-D) at week 48 . The primary objective of non-inferiority at week 48 was met. At week 96, treatment success rate was 92.2 % in DTG-I arm and 87% in DTG-D arm (difference 5.2%, 95% CI -0.6 to 11). There were 5 virological failures in the DTG-I arm and 5 (1 while on PI/r and 4 after switching to DTG) in the DTG-D arm without selection of resistance mutations. There was no significant difference in terms of grade 3 or 4 AE´s or treatment modifying AE´s. Total cholesterol and other lipid fractions (except HDL) significantly ($p<0.001$) improved both after immediate and deferred switching to DTG overall and regardless of baseline PI/r strata.

**Conclusions:** Both immediate and deferred switching from a PI/r to a DTG regimen in virologically suppressed HIV patients ≥ 50 years old or with a Framingham score ≥10% was highly efficacious, well tolerated and improved lipid profile.

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## Introduction:

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) of the HIV-1[1-4] generally well tolerated with a low potential for drug-drug interactions [5], an infrequent emergence of resistance mutations [6] and a neutral lipid profile[7] . In antiretroviral naïve patients has demonstrated non-inferiority to raltegravir[8] and bictegravir [9, 10] and superiority to efavirenz[11] and the ritonavir boosted darunavir[12] and atazanavir[13].

As the HIV-1 infected population ages, there is a need to identify regimens that reduce the risk of adverse outcomes, such as cardiovascular disease. Dolutegravir-based regimens may be ideal for this, based on their efficacy and safety profile. Raltegravir may be another choice, but there is some concern about using it as a switch strategy based on the SWITCHMRK [4] results. In the STRIIVING study [19, a switch of suppressed patients to dolutegravir was virologically non-inferior, but there was no clear benefit with respect to the lipid profile, due to the lower risk of the study population and the heterogeneity of the baseline regimens. From the perspective of the lipid profile, it may be that the evaluation of a population at higher risk of adverse outcomes and on a regimen that includes a boosted protease inhibitor (with a more unfavorable lipid profile) would identify a population that would benefit more significantly from a switch to DTG.

We performed a randomized, non-inferiority, 96 weeks, strategic trial to compare the efficacy, and impact on lipid parameters of immediate switching to DTG (DTG-I group) to that of remaining on a PI/r regimen for first 48 weeks [14] and then a deferred switching to DTG (DTG-D group) in a population with potential high CVD risk.

## Methods:

### Study design and patients:

NEAT022 was a randomized, open-label, non-inferiority trial conducted in 32 European sites (see supplementary Table 1). Patients were recruited between May 2014 and November 2015. Eligible patients were HIV-1-infected adults older than 50 years or older than 18 years with a Framingham CVD risk score 10 year risk score >10%[15, 16]. Participants had to be on a stable (>6 months) triple antiretroviral regimen consisting on a PI/r ) plus two NtRTIs and have a plasma HIV RNA <50 copies per mL for at least the previous 6 consecutive months. See supplementary table 2.

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**Ethics:**

The trial was conducted in accordance to the Good Clinical Practice and ethical principles of the declaration of Helsinki. The protocol was approved by the ethics committees of all participating hospitals. All participants gave their written informed consent . 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 to DTG 50mg/day plus the same two NtRTIs (DTG-I group) or to continue with the same triple therapy regimen including a PI/r for first 48 weeks [14] after which all patients remaining on a PI/r were switched to DTG and followed up to 96 weeks (DTG-D group) . We assigned patients to treatment groups by computer-generated permuted blocks of four and stratified by country. The study design was open-label.

**Study procedures**

Participants attended study centers at screening, baseline, weeks 4 (DTG group only), 12, 24, 36, 48, 52 (DTG-D group only), 60, 72, 84 and 96 weeks. Each visit included a general assessment, and collection of blood samples for full blood cell counts plus serum chemistry. CD4+ cell counts and plasma viral loads were measured at screening, baseline, weeks 24, 48, 72.and week 96. Fasting (overnight or > 6 hours) serum lipids were measured at all visits. Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI method [17]. HIV RNA measurements in plasma and, if indicated, testing for antiretroviral resistance by genotype sequencing were done at local laboratories (the local laboratories were required to meet Clinical Laboratory Improvement Amendments regulations or the country's equivalent). Virological failure was defined as two consecutive measurements of plasma viral load above 50 copies per mL separated at least by 2 weeks during the assigned treatment. A viral blip was defined by a plasma viral load >50 copies of HIV RNA per mL followed by a second measurement <50 copies of HIV RNA per mL. Safety was assessed at all visits by monitoring of all AEs and serious adverse events (SAEs), vital signs, and laboratory values. Adherence during the trial was monitored by participant questioning at each medical visit regarding missed tablets, at any moment during the trial or the prior week. Patients and investigators were advised not to change administration of lipid-lowering agents during the study period unless strictly necessary. Patients were also advised at each medical visit to give up smoking, to exercise daily to pay attention to their body weight, diet and alcohol

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intake, and to control blood pressure using a written predefined healthy life style guidance formulary. AIDS events and deaths, SAEs, 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.

**Endpoints:**

The endpoints at 96 weeks were: 1) the proportion of patients maintaining treatment response (HIV RNA <50 copies per mL with no discontinuation of the study treatment) and, 2) the percentage change from baseline in total cholesterol (TC) to week 96. Non-response was defined as any of the following: virological failure, death from any cause, loss to follow-up, consent withdrawal or permanent change or interruption of randomized treatment for any reason.

Other secondary end-points were: 1) frequency of all clinical and laboratory AEs up to week 96; 2) change in CD4+ cell count from baseline to week 96; 3) percentage change from baseline to week 96 of other lipid fractions: non-HDL cholesterol, LDL cholesterol, HDL cholesterol, triglycerides (TG) and TC:HDL cholesterol ratio and changes from baseline to week 96 of Framingham CVD risk score at 10 years.

**Statistical analyses:**

A total of 420 participants (210 per group) was estimated providing at least 90% power to exclude a non-inferiority margin of 10% for the difference in proportion of participants reaching the primary endpoint, assuming 90% of participants have treatment success in the DTG-D group at week 48 and a one-sided $\alpha$ of 0.025 (two-sided $\alpha$=0.05). The study was powered for the first primary endpoint since this is the criterion that requires the larger sample size. All patients who underwent randomization were included in the intent-to-treat (ITT) population. In the primary, ITT analysis, the proportion of participants who had treatment success was estimated with Kaplan-Meier methods, censoring at week 96 or last follow-up date. The difference in percentage of participants in treatment success (DTG – PI/r) was estimated and two-sided 95% confidence interval (CI) of the difference was obtained with bootstrap standard error (1000 replicates) as proportions were estimated by time-to-event method.

In the pre-specified sensitivity analysis on the per-protocol population, individuals were ignored if they did not fulfil the eligibility criteria, withdrew consent, were lost to follow-up or discontinued study medication for any reasons other than virological failure or adverse event. DTG-I was considered non-inferior to DTG-D if the lower bound of CI was below -10% for both ITT and per protocol analysis.

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The mean percentage change from baseline in lipid fractions: TC, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, TG and TC/HDL cholesterol ratio at week 48, the mean change from baseline in CD4+ cell counts and eGFR to week 48 were analyzed with the ITT population, with the last observation carried forward (LOCF) approach. The non-parametric Mann Whitney test was used to compare the changes from baseline between the 2 groups.

Subgroup analysis were also conducted to study the treatment effect by PI/r at screening (darunavir, atazanavir, other PI), backbone administration of tenofovir or abacavir, Framingham 10-year CVD risk score[15, 16] (<15% vs ≥15%), and Framingham CVD 10 year risk score and age (age≤50yr and CVD risk >10%, age>50yr and CVD risk>10%, age>50yr and CVD risk ≤10%) for the two co-primary endpoints and all other lipid fractions. Safety analysis was performed with randomized patients who received at least 1 time any study treatment. Any AEs, grade 3 and 4 AEs, antiretroviral therapy related AEs (all grade), treatment modifying AEs (all grade), death, SAEs and finally AEs occurring in at least 5% of participants were described and compared by group, using Fisher's exact test.

Variables were summarized as proportions for categorical variables (based on the non-missing sample size), the median and interquartile range (IQR) for continuous baseline variables, and the mean and standard deviation (SD) for continuous variables used as endpoints. All reported p-values are two-tailed with a significance level of 0.05. Analyses were performed with IBM SPSS Statistics version 24 and STATA SE version 13.

## Results:

Of the 455 patients screened 415 (ITT population) were randomized: 205 to switch to a DTG regimen (DTG-I group) and 210 to continue the PI/r regimen for 48 weeks [14] followed by a deferred switching to DTG (DTG-D group). See figure 1 and supplementary table 1. At least one dose of study treatment was received by 412 patients: 204 in the DTG-I group and 208 in the DTG-D treatment group (figure 1). Baseline characteristics were balanced between groups (table1).

### Efficacy:

The primary objective of non-inferiority at week 48 was met [14] (figures 2a and 2b). At week 48, 14 patients in the DTG group and 10 in the PI/r group had experienced treatment failure; corresponding to a treatment success rate of 93.1 % and 95.2 % respectively (difference -2.1%, 95% CI -6.6 to 2.4, non-inferiority demonstrated). At week 96,

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16 patients in the DTG-I group and 27 in the DTG-D group had experienced treatment failure; corresponding to a treatment success rate of 92.2% and 87% respectively (difference 5.2%, 95% CI -0.6 to 11); Figure 2a and Supplementary Figure 1 . The per-protocol analysis gave a similar estimated difference of 3% (95%CI -2.3 to 8.3); Figure 2b. Reasons for non-response were similar between groups. There were 5 protocol defined virological failures in the DTG-I group (plasma viral load at failures ranged from 51 to 130 HIV RNA copies per mL) and 5 (of whom one in the first 48 weeks while receiving PI/r) in the DTG-D group (plasma viral load at failures ranged from 64 to 3373 HIV RNA copies per mL) with no emergent resistance associated mutations in the 3 of the 10 samples that could be amplified (supplementary Figure 2 ). All these 10 patients but 1 reported 100% adherence at all time points. Subgroup analysis can be seen in supplementary figure 3. Overall, 34 episodes of viral blips occurred in 33 participants (supplementary figure 2 ). Mean increases in CD4+ cell count from baseline to week 96 were 33±69 cells per µL in the DTG group and 14±185 cells per µL in the PI/r group (p = 0.18).

**Changes in lipids and in other CVD risk factors**:

At 96 weeks, total cholesterol and other proatherogenic lipid fractions significantly (p<0.001) decreased from baseline at similar levels (p>0.05) in both the DTG-I and DTG-D groups: TC -7.8±14.6% vs -5.8±17.7%, LDL cholesterol –6.9±22.0% vs -4.5±26.5%, non-HDL cholesterol –10.3±20.5% vs -8.1±23.8%, TC/HDL cholesterol ratio –6.4±24.4% vs -7.0%±23.1% and TG –15.6±37.1% vs -12.1±44.1% (Figure 3). Similar significant improvements were detected in both DTG-I and DTG-D groups when analysis of lipid changes was stratified by baseline age and Framingham CVD risk score, by baseline PI/r and also by backbone administration of tenofovir or abacavir (supplementary Figures 4a, 4b, 4c, 4d and 4e ). The change from baseline to week 96 in the percentage of patients receiving lipid lowering agents, receiving or requiring[18] lipid lowering agents (supplementary fig 5 ), currently smoking, taking daily exercise and with high blood pressure was -0.7%, -5.6%, -2.7%, 6.2% and 7.5% respectively in the DTG-I group and 4.3%, 0%, -4.3%, 6.7% and 0% respectively in the DTG-D group. None of these changes were statistically significant. There was a trend towards a reduction in the CVD risk score at 5 years after 48 weeks of immediate or deferred switching to DTG using both Framingham [15] or D:A:D [16] equations (supplementary fig 6 )

**Safety:**

Adverse events, all grades and causalities, were reported in 75% (weeks 0-48) and 77.9% (weeks 48-96) of the patients in the DTG-I arm and in 63.5% (weeks 0-48) and 83.8% (weeks 48-96) in the DTG-D arm of whom 6.4%, 5.8% and 7.2% and 10.1% were SAE´s (p>0.05, table 2). 8 (3.9%) of patients who had received DTG in the DTG-I arm and 9 (4.5%) who had received DTG in the weeks 48-96 in the DTG-D arm vs. 3 (1.4%) of those who had

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received PI/r in the weeks 0-48 in the DTG-D arm interrupted study medication due to AE. Mood disturbances or insomnia were the cause of DTG discontinuation in 13 of 17 patients. The most frequent AEs occurring in ≥5% of patients can be seen in Table 2. A major cardiovascular event occurred in 7 patients in the DTG-I arm and in 8 patients in the DTG-D arm, of whom 2 while still receiving a PI/r (Table 2). Two death events occurred during the trial in the DTG-D group due to an accidental fall with a temporal bone fracture and a subdural hematoma and to a hepatocellular carcinoma.

Grade 3 or 4 laboratory AEs were observed in 2.5% (weeks 0-48) and 3.7% (weeks 48-96) of the patients in the DTG-I arm and in 14.9% (week 0-48 while still on PI/r) and 5.6% (weeks 48-96) in the DTG-D arm ($p<0.01$ and $p=0.47$; table 2). There was also a small but significant ($p<0.001$) decrease in the calculated eGFR) in those who had received DTG (supplementary Figure 7 ).

## Discussion:

This is the first study to specifically examine switching from a regimen containing two NtRTIs plus a PI/r to a regimen with the same backbone plus DTG in virologically stable patients with high CVD risk (61% of the patients were both older than 50 years and with a Framingham risk score > 10%). The primary objective of non-inferiority at week 48 was met [14]. At 96 weeks, the study demonstrated non-inferiority for maintenance of control of HIV RNA in the DTG-I group without an overall significant increase in SAEs or in any grade AEs related with antiretroviral therapy. Importantly in this population we showed significant reduction in proatherogenic lipid fractions.

CVD is a major cause of morbidity and mortality in persons with HIV-1 infection with an estimated risk of 1.5 to 2.0 fold higher compared with the general population[19]. Data from the D:A:D showed that CVD accounts for 11% of deaths among HIV-1-infected persons [20] and the EuroSIDA study showed that cardiovascular events account for about one-third of non–AIDS-defining events [21]. The US National Lipid Association [22] suggests that lipid goals be based on the number of risk factors including LDL cholesterol and non-HDL cholesterol and HIV-1 infection may be counted as a risk factor. The antiretroviral therapy *per-se*[23-25] or through its effect on lipids should also be considered as contributing to risk of CVD[26]. HIV-1 treatment guidelines recommend, in addition to lifestyle changes and lipid-lowering therapy [27], modifications of antiretroviral regimen for CVD risk reduction [28, 29]. There is good evidence from the general population that reducing TC and LDL cholesterol reduces CVD risk[30] and there is an ongoing ACTG study in HIV-1 infected patients to examine the cardiovascular impact of adding pitavastatin .

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Switching antiretrovirals in order to improve lipid profiles can be combined with the use of lipid lowering agents [3, 4, 31, 32]. . TC and other proatherogenic lipid fractions significantly improved both after immediate and deferred switching to DTG even when stratified by baseline age, Framingham risk score and baseline PI/r. Most switching studies have not included in the analysis non-HDL cholesterol that has been recently incorporated into the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines[18]. Switching to DTG significantly decreased this fraction as well as TC:HDL cholesterol ratio, a factor used in some CVD risk equations, which is usually unaffected in other antiretroviral switch studies [4] [3] . After switching to DTG, a reduction of the LDL cholesterol of >5% (approximately 0.3 mmol per L) from baseline values was achieved. This level of reduction in the general population, is associated with a significant reduction in the relative risk of CVD[30]. As 60% of study participants switched away from PI/r regimens containing ritonavir boosted lopinavir[24] or darunavir[25] both independently associated with an increased CVD risk there may be an additional favorable impact. Moreover, there was a trend towards a reduction in the CVD risk scores at 5 years after 48 weeks of immediate or deferred switching to DTG. A limitation of the study was that it was not powered for differences in cardiovascular events and only 15 major cardiovascular events were observed.

There are some risks associated with switching to a new regimen in stable patients tolerating well the older medication. In our study, virological failures were numerically more common after both immediate or deferred switching to DTG (9 versus 1 while still on PI/r) albeit all at low level and not associated with emergent resistance mutations. Although there were few discontinuations, there were more after switching to DTG (17 vs. 3 while still on PI/r) which is often seen when patients are switching from a regimen that they have been tolerating from a long period of time. Of note, 13/17 discontinued due to mood disturbances or insomnia which have been recently highlighted [33, 34] as potential side effect of DTG. We should also recognize that switching to a single pill of DTG/rilpivirine or DTG/lamivudine would be more appealing in the future. Finally, analysis of patient-related outcomes was not included in the protocol that was designed more than 5 years ago.

In conclusion, both immediate and deferred switching from a PI/r based regimen to a DTG regimen in virologically suppressed HIV patients aged 50 years or older or with a Framingham score ≥10% was highly efficacious well tolerated and significantly improved the lipid profile.

## Contributors:

JMG, ALP, SDW, EM, GG and FR designed the study in consultation with the trial steering committee. GM, LW,

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MJ, PD, JF, EM, GG, MM, MG, SDW, EF, SE, CS, JR, AG, JV, JIB, AW, MS, JG and CK enrolled participants into the study. JMG, GM, LW, MJ, PD, JF, ALP, FR, GG, MM, AG, SDW, EM, EF, SE, CS, JR, MG, JV, JIB, AW, MS, JG and CK contributed to the coordination and oversight of the study. LA wrote the statistical plan and did the statistical analysis. All authors participated in data interpretation. The manuscript was drafted by JMG, GM, LW, ALP, LA and PD. All authors provided input to the report and approved the final version of the manuscript.

## Acknowledgements:

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## Declaration of interests:

JMG has received honoraria for lectures or advisory boards and his institution research grant from ViiV Healthcare, Gilead Sciences, MSD and Janssen up to April 30th 2018. Since May 1st 2018 is a full time employee of ViiV Healthcare as Senior Global Medical Director.

LA has no potential conflicts of interest.

GM has received honoraria for lectures or advisory boards from Gilead Sciences, MSD, Tobira Therapeutics and Thera Technologies.

LW has received support for attending conferences or honoraria for lectures or advisory boards from Gilead Sciences, ViiV Healthcare, MSD, AbbVIe and Janssen

MJ has received consultancy fees from Gilead Sciences, ViiV Healthcare and MSD.

PD has received honoraria for lectures or advisory boards and his institution research grant from ViiV Healthcare, Gilead Sciences, MSD and Janssen

JF has received research grant from ViiV Healthcare and gilead Sciences

EM has received honoraria for lectures or advisory boards from ViiV Healthcare, MSD and Janssen and his institution research grant from ViiV Healthcare, Gilead Sciences, MSD and Janssen

HJS has received honoraria for lectures or advisory boards from AbbVie, MSD, Janssen, Gilead Sciences, Teva, and Bristol-Myers Squibb, as well as documentation fees for clinical trials from Gilead, ViiV Healthcare, Janssen, and MSD.

GG has received honoraria for lectures or advisory boards and his institution research grant from ViiV Healthcare, Gilead Sciences, MSD and Janssen.

MM has received honoraria for lectures or advisory boards and his institution research grant from ViiV Healthcare, Gilead Sciences, MSD and Janssen.

MG has received educational support to attend CROI from BMS and is undertaking clinical trial work for Merck Sharp & Dhome, Gilead Sciences and Janssen

SDW has received honoraria for lecture from Janssen and his institution has received research grants from BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare

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EF and his institution have received research grants and honoraria for advisory boards participation from BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare

SE has received honoraria for lectures or advisory boards and his institution research grants from ViiV Healthcare, Gilead Sciences, MSD, AbbVie, BMS, and Janssen

FR has received honoraria for lectures or advisory boards and his institution research grants from Abbvie, ViiV Healthcare, Gilead Sciences, Janssen, Merck and MSD.

CS has received grants or research supports from MSD and honoraria, consultation fees or conference travel grants from AbbVie, MSD, ViiV, BMS, Gilead, Janssen and Astellas.

JR has received honoraria for consulting or for educational lectures from Abbott, Abbvie, Abivax, Gilead Sciences, Hexal, Janssen, MSD and ViiV

AG no potential conflicts of interest

JV no potential conflicts of interest

JIB research grants from Gilead Sciences and personal fees from Gilead Sciences, ViiV, MSD and Janssen

AW research grants or honoraria from Gilead Sciences, ViiV, GSK, BMS, Janssen and MSD

MS no potential conflicts of interest

JG no potential conflicts of interest

CK research grants from Janssen and ViiV and speaker fees from MSD and Janssen

ALP has received honoraria for lectures or advisory boards, and his institution research grants from ViiV Healthcare, Gilead Sciences, MSD and Janssen.

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# Notes:

## (*) NEAT 022 study investigators (32 sites from 6 European countries):

Belgium: Linos Vandekerckhove, Els Caluwé, Stephane De Wit, Coca Necsoi, Eric Florence, and Maartje Van Frankenhuijsen; France: Francois Raffi, Clotilde Allavena, Véronique Reliquet, Morane Cavellec, Audrey Rodallec, Thierry Le Tourneau, Jérôme Connault, Jean-Michel Molina, Samuel Ferret, Miresta Previlon, Yazdan Yazdanpanah, Roland Landman, Véronique Joly, Adriana Pinto Martinez, 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, Berta Torres, Pere Domingo, Gracia Mateo, Mar Gutierrez, Joaquin Portillo, 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; UK: 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.

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## Figures:

**Figure 1:** Study flow chart

Notes:

DTG= Dolutegravir, PI/r= ritonavir boosted protease inhibitors

A genotypic resistance test was available in 19 (47.5%) of the 40 patients assessed for eligibility but not randomized. Presence of resistance mutation was the reason in 2 (5%) of these 40 patients

F**ig 2:** Outcomes at 48 and 96 weeks of primary efficacy end point (Kaplan Meier estimates)

**2a)** Intent-to-treat analysis

2b) Per protocol analysis

**Fig 3:** Changes in fasting lipids concentration from baseline to weeks 48 and 96 (N=415)

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## Table 1. baseline characteristics

| | DTG-I (n=205) | DTG-D (n=210) | Total (n=415) |
|---|---|---|---|
| **Age (years)** | **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** | **173(84.4)** | **180(85.7)** | **353(85.1)** |
| **Mode of HIV-1 transmission** | | | |
| Male homosexual sexual intercourse | **130(63.4)** | **131(62.4)** | **261(62.9)** |
| Heterosexual sexual intercourse | **43(23.9)** | **48(22.9)** | **97(23.4)** |
| Other [a] | **26(12.7)** | **31(14.8)** | **57(13.7)** |
| **CD4+ count (cells per µL)** | **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** | **27(13.4)** | **24(11.6)** | **51(12.5)** |
| **Time since undetectable viral load (< 50 copies per mL); years** | **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 Smokers** | **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** [b] | **72(35.3)** | **79(37.6)** | **151(36.5)** |
| **Daily exercise** [c] | **64(31.2)** | **59(28.2)** | **123(29.7)** |
| **Cardiovascular risk factors** [d] | | | |
| 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)** | | | |
| 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)** |

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| | | | |
|---|---|---|---|
| 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)** | **90.8(80.7-99.7)** | **91.4(78.3-101.8)** | **91.1(80-100.2)** |

Data are n (%) or median (IQR)

[a] Mode of HIV transmission was unknown in 22 (38.6 %) of the 57 and 28 ( 49.1 %) of the 57 were intravenous drugs users

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

[c] Defined as self-reported some exercise (duration not specified) every day

[d] 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 method). DTG-D= Dolutegravir-deferred. DTG-I= Dolutegravir-immediate

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**Table 2:** Adverse events in 412 patients who received either dolutegravir (n=204) or ritonavir boosted protease inhibitor (n=208).

| | DTG-I arm | | | | DTG-D arm | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0-48 weeks (n=204) | | 48-96 weeks (n=190) | | 0-48 weeks[a] (n=208) | | 48-96 weeks (n=198) | | P value 0-48 weeks | P value 48-96 weeks |
| | Patients n(%) | Adverse events (n) | Patients n(%) | Adverse events (n) | Patients n(%) | Adverse events (n) | Patients n(%) | Adverse events (n) | | |
| **Summary of adverse events** | | | | | | | | | | |
| Any adverse event | 153 (75.0) | 395 | 148 (77.9) | 416 | 132 (63.5) | 352 | 166 (83.8) | 558 | 0.014 | 0.156 |
| Grade 3 or 4 adverse events | 12 (5.9) | 17 | 13 (6.8) | 18 | 18 (8.7) | 31 | 21 (10.6) | 34 | 0.344 | 0.212 |
| Serious adverse events | 13 (6.4) | 14 | 11 (5.8) | 15 | 15 (7.2) | 27 | 20 (10.1) | 28 | 0.845 | 0.136 |
| Discontinuation due to adverse events | 8 (3.9)[b] | 8 | 0 (0.0) | 0 | 3 (1.4)[c] | 3 | 9 (4.5)[b] | 9 | 0.137 | 0.004 |
| Any adverse event related to antiretroviral therapy | 25 (12.3)[d] | 40 | 15 (7.9)[d] | 20 | 14 (6.7)[e] | 20 | 42 (21.2)[d] | 74 | 0.064 | <0.001 |
| Death | 0 (0.0) | | 0 (0.0) | | 1 (0.5)[f] | | 1 (0.5)[f] | | 1.000 | 1.000 |
| **Adverse events, any grade, occurring in at least 5% of patients in either group** | | | | | | | | | | |
| Digestive | 41 (20.1) | 52 | 36 (18.9) | 50 | 37 (17.8) | 54 | 56 (28.3) | 89 | 0.615 | 0.032 |
| Muscular or skeletal | 49 (24.0) | 63 | 50 (26.2) | 82 | 40 (19.2) | 52 | 66 (33.3) | 102 | 0.281 | 0.150 |
| Cardiovascular | 10 (4.9)[g] | 12 | 19 (10.0)[g] | 27 | 18 (8.7)[g] | 20 | 18 (9.1)[g] | 22 | 0.170 | 0.863 |
| Respiratory | 63 (30.9) | 90 | 53 (27.9) | 67 | 49 (23.6) | 65 | 61 (30.8) | 80 | 0.098 | 0.578 |
| Dermatological | 36 (17.6) | 43 | 46 (24.2) | 61 | 27 (13.0) | 38 | 53 (26.8) | 77 | 0.218 | 0.641 |
| Genitourinary | 32 (15.7) | 37 | 25 (13.2) | 30 | 14 (6.7) | 26 | 28 (14.1) | 41 | 0.005 | 0.883 |
| Systemic | 26 (12.7) | 28 | 27 (14.2) | 31 | 35 (16.8) | 43 | 42 (21.1) | 55 | 0.269 | 0.084 |
| Neuropsychiatric | 43 (21.1) | 63 | 39 (20.5) | 49 | 36 (17.3) | 46 | 51 (25.8) | 69 | 0.381 | 0.231 |
| **Grade 3 or 4 laboratory adverse events** | | | | | | | | | | |
| Any grade 3 or 4 laboratory adverse event | 5 (2.5) | 10 | 7 (3.7) | 7 | 31 (14.9) | 55 | 11 (5.6) | 12 | <0.001 | 0.472 |
| Alanine aminotransferase concentration >5xULN | 1 (0.5) | 1 | 0 (0.0) | 0 | 1 (0.5) | 1 | 1 (0.5) | 1 | 1.000 | 1.000 |
| Bilirubin >2.5xULN | 2 (1.0) | 4 | 0 (0.0) | 0 | 16 (7.7) | 28 | 1 (0.5) | 1 | 0.001 | 1.000 |
| LDL cholesterol >4.9 mmol/L | 3 (1.5) | 5 | 3 (1.6) | 3 | 15 (7.2) | 22 | 5 (2.5) | 6 | 0.006 | 0.724 |

Data are number of patients (%) or number of events.
DTG-I=Dolutegravir immediate group. DTG-D= Dolutegravir-deferred group.
P-value: comparison of proportion of patients with at least one adverse event between all DTG groups vs. ritonavir boosted protease inhibitors

**a)** During the period 0-48 weeks patients of the DTG-D arm were receiving a ritonavir boosted protease inhibitor

**b)** 1 case each of acute hepatitis C, chest pain and fatige, rash and poor control of diabetes and 13 cases of mood and/or sleep disorders

**c)** 1 case each of hepatitis C, dyspepsia and declining renal function

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**d)** mood and/or sleep disorders in 27 (33%) of the 87 patients who developed adverse events related with antiretroviral therapy while on DTG

**e)** mood and/or sleep disorders in 5 (36%) of the 14 patients who developed adverse events related with antiretroviral therapy while on PI/r

**f)** One case each of an accidental fall with a temporal bone fracture and subdural hematoma and an hepatocellular carcinoma

**g)** 1/10, 6/19, 2/18, 6/18 patients respectively developed a major cardiovascular event

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Figure 1.

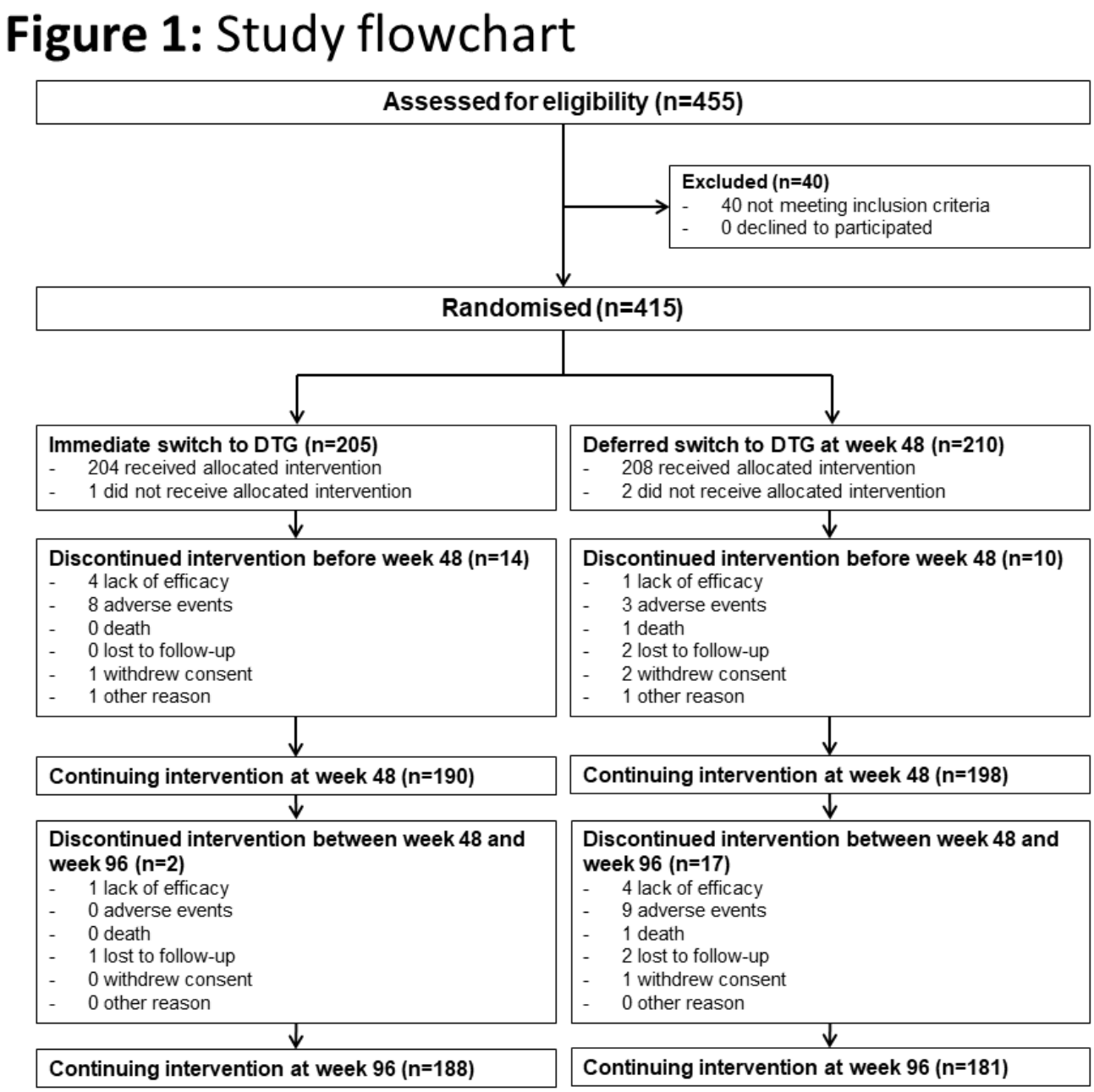


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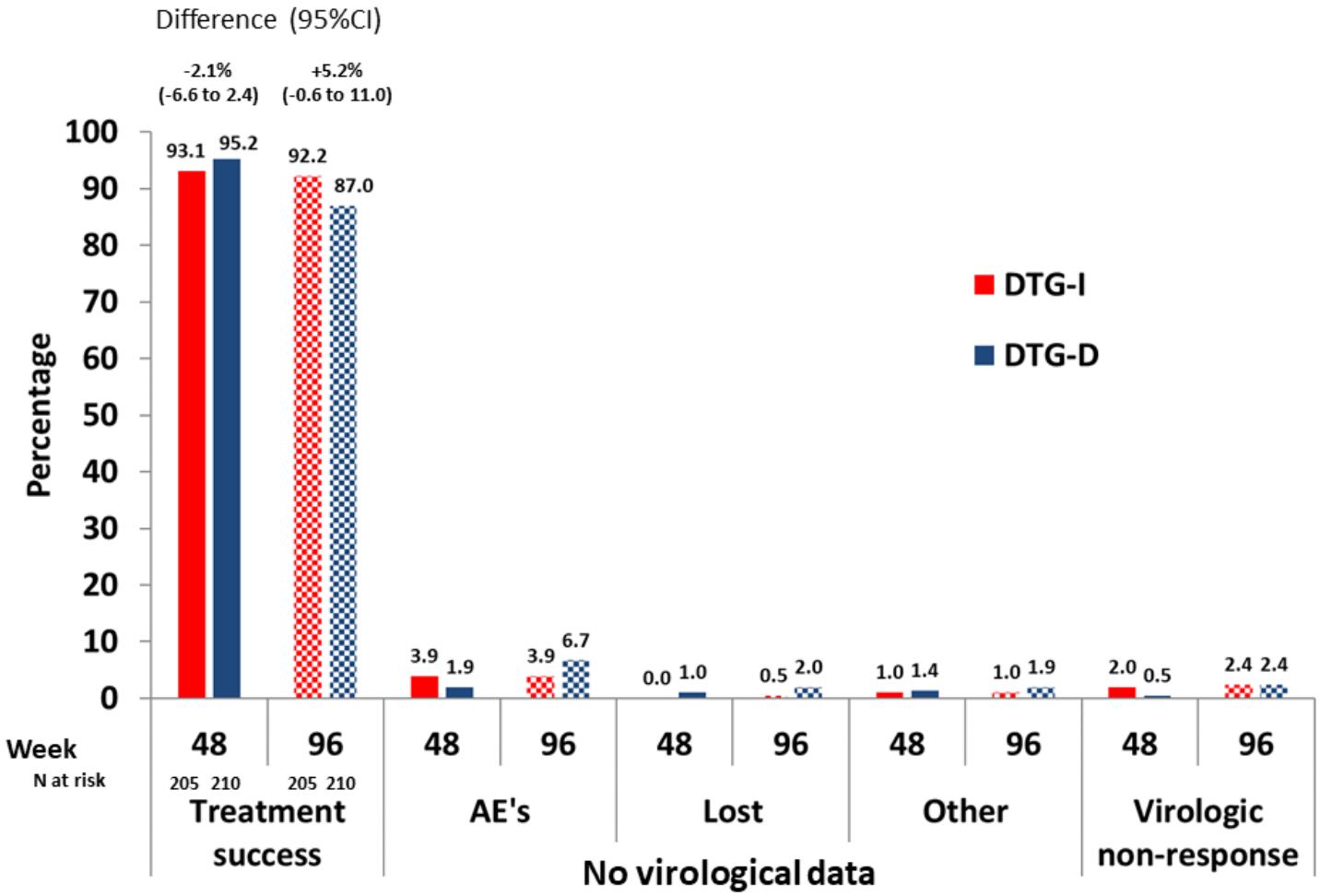
Figure 2a.




ITT population

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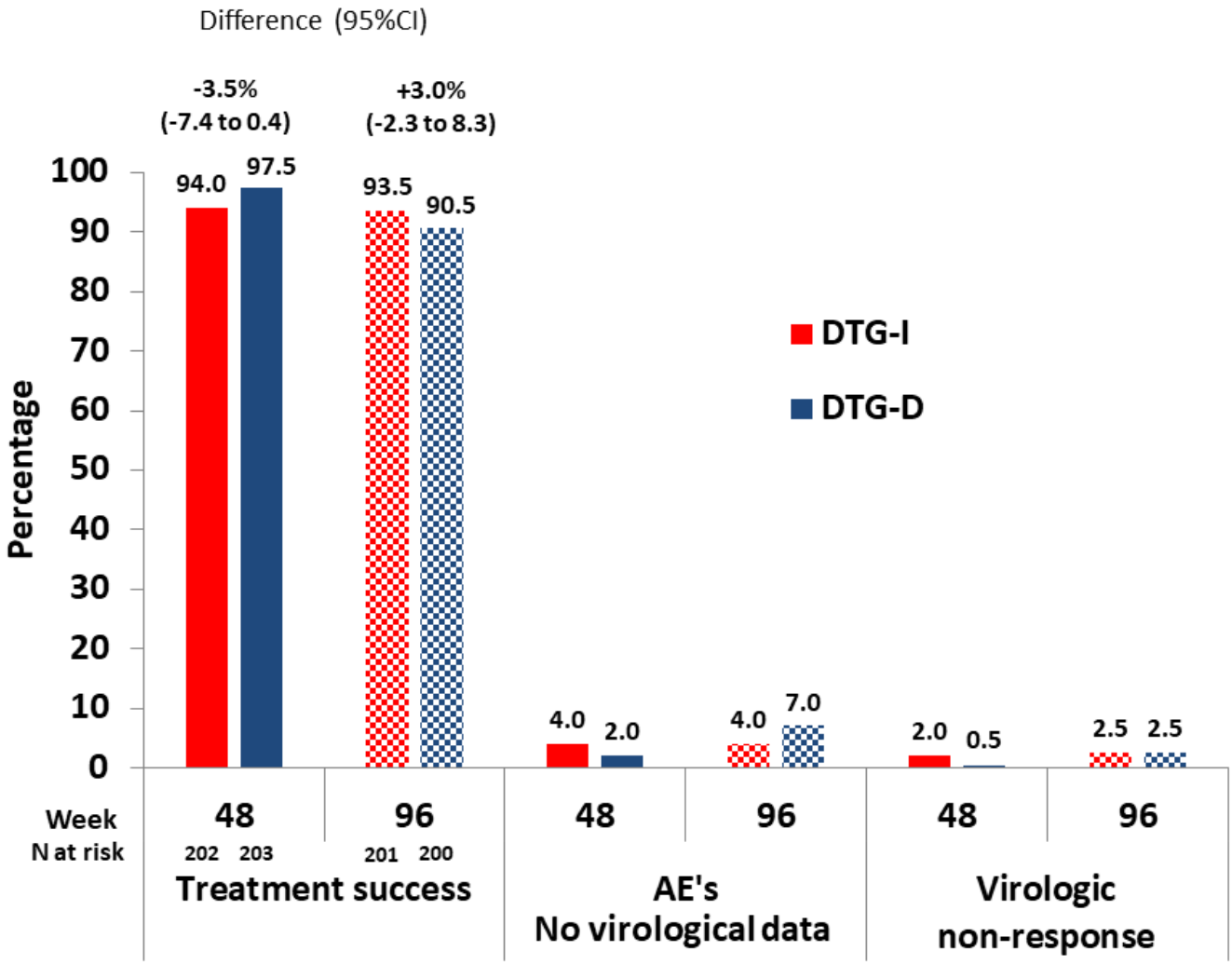
Figure 2b.




PP population

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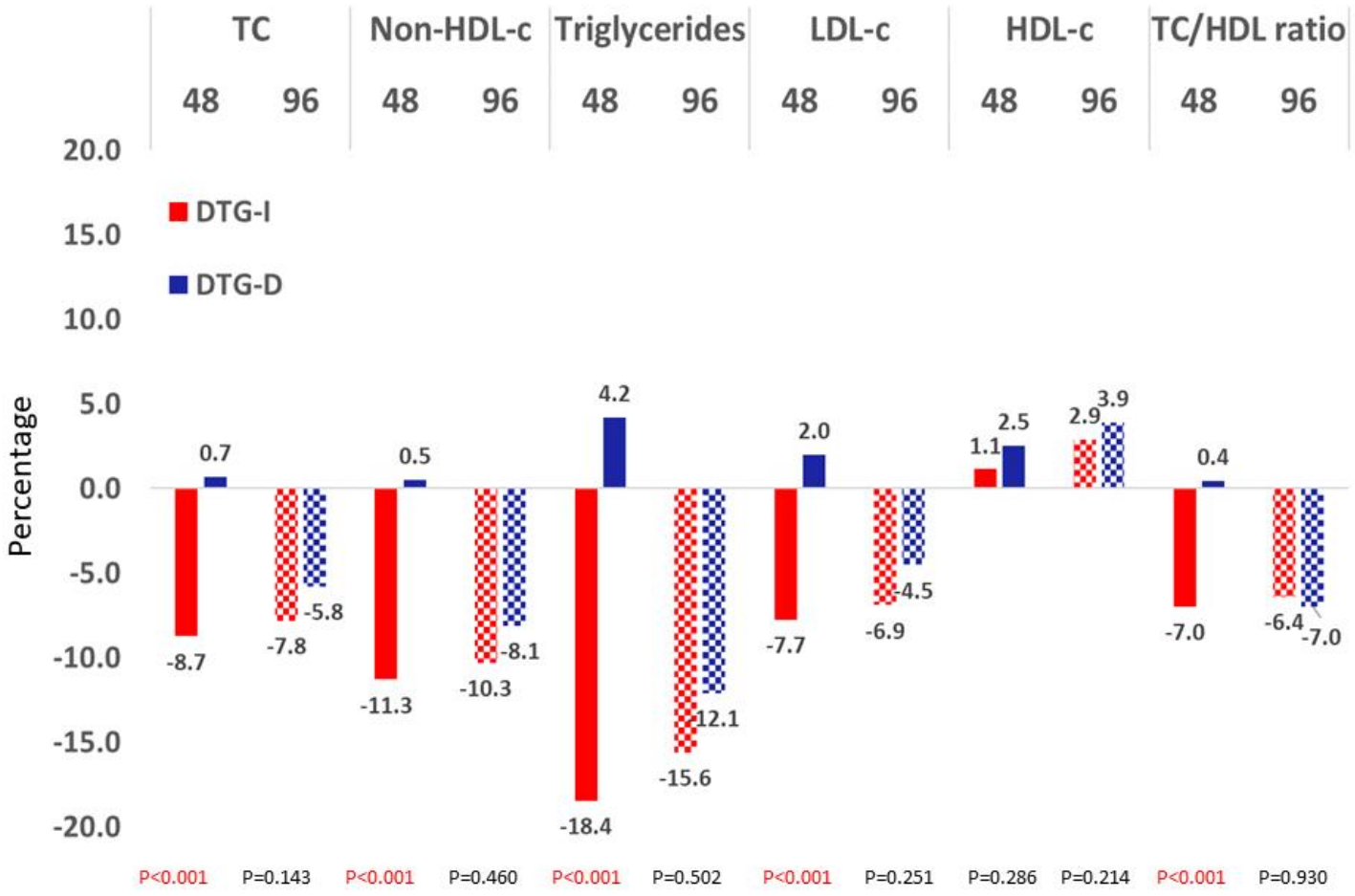
Figure 3.

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