Switch to dolutegravir (DTG) from a boosted protease inhibitor (PI/r) associated with significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial

Laura Waters[1], Lambert Assoumou[2], Stefano Rusconi[3], Pere Domingo[4], Mark Gompels[5], Stephane de Wit[6], Francois Raffi[7], Christoph Stefan[8], Juergen Rockstroh[9], Christine Katlama[10], Georg Behrens[11], Jose Gatell[12], Anton Pozniak[13,14], Esteban Martinez[1]

1. Mortimer Market Centre, CNWL, London, UK; 2. INSERM, Sorbonne Université, Paris, France; 3. Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Italy; 4. Hospital de Sant Pau' Barcelona. Spain; 5. Southmead Hospital. Bristol. UK ; 6. Saint Pierre Hospital, Université Libre de Bruxelles. Brussels. Belgium; 7. University Hospital of Nantes. Nantes. France; 8. Goethe University Hospital, Frankfurt, Germany; 9. University of Bonn, Bonn, Germany; 10. Sorbonne Université , Infectious Diseases Pitié Salpétriere, Paris, France; 11. . Medizinische Hochschule, Hannover Germany: 12. University of Barcelona. Barcelona. Spain; 13. Chelsea & Westminster Hospital. London. UK; 14. London School of Hygiene & Tropical Medicine, London, UK.

Background

- Several trials and cohorts report weight gain on integrase inhibitors:
  - SPRING-1 (phase 2b) showed more weight gain on all doses of DTG than efavirenz [1]; weight was not analysed in phase 3 DTG trials
  - Cohorts show weight gain on integrase inhibitors [2-4] & one cohort found significant weight gain on DTG after <12 months, most markedly in women on DTG co-formulated with abacavir & lamivudine [5]
- We performed a post-hoc weight analysis of NEAT-022

NEAT-022 background

- NEAT-022 was a randomised, open-label non-inferiority trial to compare efficacy & safety of switching to a DTG-based from a PI/r-based regimen
- Participants with potential high CVD risk (age over 50 or Framingham >10%), stable & suppressed for ≥6/12 on a PI/r based triple regimen were randomised to immediate switch for 96 weeks (**DTG-I**) or to remain on PI/r for 48 weeks followed by deferred switch to DTG (**DTG-D**) for 48 weeks
- Final results are published; switch to DTG was well-tolerated, virologically non-inferior and was associated with significant lipid improvements

Methods

Patient population

- 415 individuals were randomised: 205 to **DTG-I** and 210 to **DTG-D**
- Baseline characteristics were similar in both arms; key characteristics are:
  - Median age 53 years, 88% aged >50 years, 89% male, 85% white;
  - Framingham >10% in 74%,
  - Virally suppressed for median 5 years; baseline PI/r: **51% darunavir/r, 37% atazanavir/r, 9% lopinavir/r & 4% other PI/r**

Weight analysis

- We assessed 48-week and 96-week changes in weight (kg) and body mass index (BMI, kg/m^2)
- Factors associated with the evolution of BMI within the first 48-week on DTG (DTG-I [0-48w] and DTG-D [48-96w]

Statistical methods

•Weight/BMI change was estimated using mixed models with random effects.

•Mixed models were used to compare slopes between & within groups

•Univariable & multivariable analyses identified factors associated with BMI evolution (mixed models with random effects).

•Variables considered included: age, Framingham (≤15% vs >15%), sex, race, HIV acquistion mode, CD4, baseline HIV-, HCV IgG, duration of viral suppression, time on cART, NRTI backbone, PI/r at baseline, eGFR & CVD risk factors*, Multivariable analysis was adjusted by baseline BMI

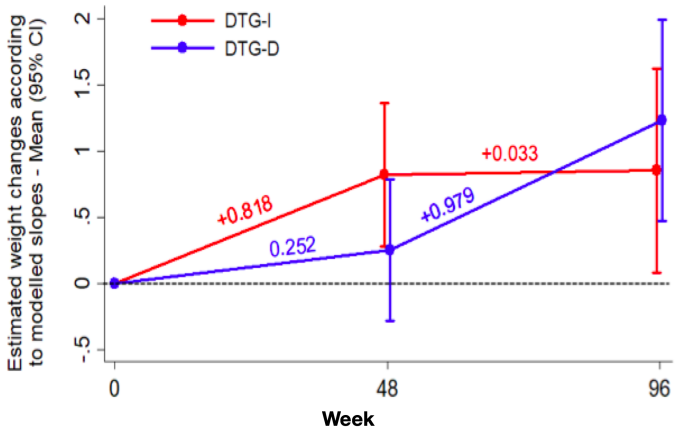
•Variables were summarised as proportions for categorical variables. median and interquartile range (IQR) for continuous baseline variables. and mean and standard error (SE) for body mass index and weight at each time point.

•All p-value are two-sided with a significance level of 5%. Analysis used SAS® statistical analysis software v9.4 and IBM SPSS statistics v24

Results

- Baseline median BMI was 25.9 (IQR : 23.7–28.3)
- **Mean BMI change**
  - **From W0-W48:** +0.272/+0.064kg in the **DTG-I**/**DTG-D**, significant for **DTG-I** but not **DTG-D** (p=0.003/0.471 respectively); difference between arms was statistically significant (p=0.008)
  - **From W48-W96:** -0.002/+0.332 on **DTG-I**/**DTG-D**, significant for **DTG-D** but not **DTG-I** (p=0.984/0.004 respectively); difference between arms was statistically significant (p=0.002)
- **Median weight change (see figure 1)**
  - **From W0-W48:** +0.82kg in **DTG-I** arm vs +0.25kg in **DTG-D** arm; between arm difference statsitically significant (p=0.008)
  - **From W48-W96:** +0.03kg in **DTG-I** arm vs +0.98kg in **DTG-D** arm between arm difference statsitically significant (p=0.002)
- **Factors associated with BMI gain on DTG in multivariable analysis:**
  - Framingham >15% (P=0.042) & hypertension (P=0.035). **Protective** factors were switching from PIs other than DRV/ATV (P=0.032), current smoking (P=0.006), daily exercise (P=0.036), and HDL-chol (P<0.001)
- **After adjustment for baseline BMI, switching from darunavir was the only independent factor associated with BMI gain (P=0.018).**

Fig 1: Change in weight (kg) according to modelled slopes
see adjacent text for p-values



Conclusions

- In virologically suppressed patients with high CV risk, switch from PI/r to DTG was associated with small but statistically significant weight & BMI gain over 48 weeks; risk of weight gain was higher amongst individuals switching from darunavir/r vs other protease inhibitors.
- These findings confirm weight gain as a potential result of integrase inhibitor-based therapy, warranting further analyses of other randomised trials, studies to elucidate body mass composition changes on DTG, and their pathogenesis.
- **Weight gain is an important side effect to people with HIV and we call for all phase 3 trials to routinely include analyses of weight, an easily and routinely collected parameter, in the presentation & publication of antiretroviral trial results.**

References: 1. Van Lunzen J *et* al. Lancet Infect Dis. 2012;12(2):111-8; 2. Norwood J et al. J Acquir Immune Defic Syndr. 2017;76(5):527-531; 3. Taramasso L et al. Open Forum Infect Dis. 2017;4(4):ofx239; 4. Bakal D et al. ID Week 2017; 5. Menard A et al. AIDS 2017; 31(10): 1499-1500; 6. Gatell JM *et al*. Clin Infect Dis 2018.

**current smoking, diabetes mellitus, glucose, FH CVD, LDL-c >4.1 mmol/L, lipid lowering agents, hypertension, daily exercise, no. CVD risk factors, lipid paramaters*