P-575

# Evaluation of Weight Gain on Incident Hypertension Among People Living With HIV-1 Receiving Dolutegravir (DTG)-Based Regimens or Comparator Antiretroviral Therapy (cART) in Randomized Clinical Trials Through 96 Weeks


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## Key Takeaways

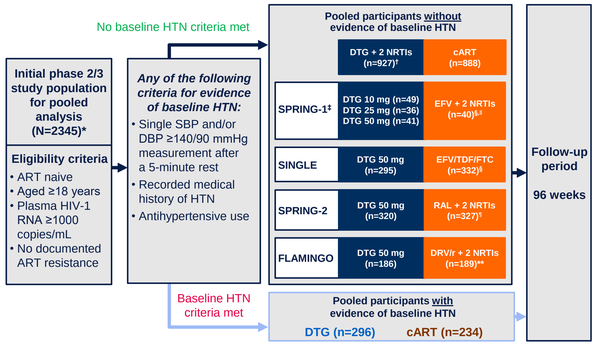
- **Using Bayesian joint models, we evaluated the relationship between ART regimen, weight gain, and hypertension (HTN) risk among participants without baseline (BL) HTN receiving three-drug, dolutegravir (DTG)-based regimens or EFV, RAL, and DRV/r comparator ART (cART) in pooled phase 2/3 studies**
- **Weight gain was found to be independently associated with HTN risk through Week 96, consistent with non-HIV populations**
- **ART was not found to be an independent risk factor for HTN risk**
- **No clear relationship was identified between weight gain post-initiation of DTG and increased risk of HTN over 96 weeks**

## Introduction

- Given longer life expectancy with modern ART, people living with HIV are increasingly experiencing age-related comorbidities and metabolic complications, such as HTN[1,2]
- An association between HTN and integrase strand transfer inhibitor (INSTI)–based regimens has been reported in some observational studies, although data are conflicting and limited[3-5]
- Apart from the known contribution of weight gain to HTN risk, no clear potential mechanism exists to support a causal association for the reported HTN risk in people living with HIV receiving INSTI- and TAF-based regimens[6-9]
- A pooled analysis of four phase 2/3 trials found no difference in the odds of incident HTN among participants without BL HTN receiving three-drug, DTG-based regimens or cART through Week 96[10]
  - Rates of incident HTN were 23% (n=180/779) for DTG vs 21% (n=139/665) for cART (adjusted odds ratio, 1.02; 95% confidence interval [CI], 0.79-1.33; *P*=0.864) through Week 96[10]
- Here, we evaluated the relationship between ART regimen, weight gain, and HTN risk among participants without BL HTN receiving DTG-based regimens or cART in pooled phase 2/3 studies

## Methods

### Figure 1. Study Population in Pooled Analysis




*Pooled: DTG, N=1223; cART, N=1122. SPRING-1: DTG 10 mg, n=53; DTG 25 mg, n=51; DTG 50 mg, n=51; cART, n=50. SINGLE: DTG, n=414; cART, n=419. SPRING-2: DTG, n=411; cART, n=411. FLAMINGO: DTG, n=243; cART, n=242. All ART regimens included two NRTIs, either ABC/3TC or TDF/FTC. †All DTG doses were administered QD. ‡All DTG dose groups were combined in pooled study analyses that included SPRING-1 data. §EFV 600 mg QD. ¶n=12 received EFV + ABC/3TC. **RAL 400 mg BID, **DRV/r 800 mg/100 mg QD.
BID, twice daily; cART, comparator antiretroviral therapy; DBP, diastolic blood pressure; HTN, hypertension; NRTI, nucleoside reverse transcriptase inhibitor; QD, once daily; SBP, systolic blood pressure.

- Data from participants naive to ART randomized to either DTG-based ART or cART were pooled from the dose-ranging phase 2b SPRING-1 (NCT00951015) and phase 3 SINGLE (NCT01263015), SPRING-2 (NCT01227824), and FLAMINGO (NCT01449929) clinical trials (Figure 1)

**The primary aims of this analysis were to:**

1. Evaluate the independent effect of ART and weight increase over time on HTN risk
2. Evaluate the interaction between ART and weight gain on HTN risk

**Data Collected**

- Blood pressure (BP) and weight measurements were assessed at BL, Week 4, Week 12, Week 24, Week 48, and Week 96*
- Evidence of HTN at each time point was defined as a single systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, initiating antihypertensives, or a reported HTN adverse event post-BL

*Week 2 and Week 12 only included data from SPRING-1 (other studies did not include weight evaluations at these time points). Evaluations at Week 24 did not contain data from FLAMINGO (the study did not include a weight evaluation at this time point).

**Statistical Models**

- Adjusted change from BL in weight was evaluated via mixed-model repeated-measures
- Associations between treatment, weight change, and their interaction with HTN risk were evaluated using Bayesian joint models
  - The joint models evaluated BP (BL, Weeks 48 and 96) and weight (BL, Weeks 4, 12, 24, 48, and 96)
  - Models were adjusted for key BL variables: age, sex, race, HIV-1 RNA (log-transformed), and study ID along with treatment (DTG vs cART) and time

## Results

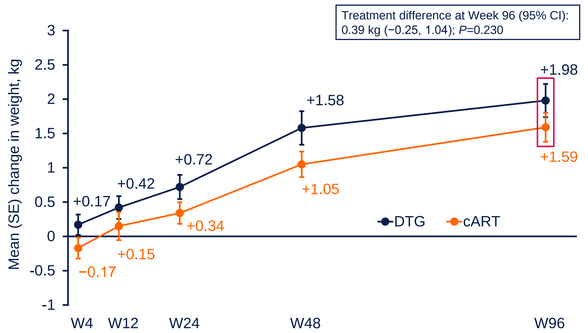
### Table 1. Baseline Characteristics

| Characteristic | DTG regimen (N=927) | cART (N=888) | Pooled total (N=1815) |
|---|---|---|---|
| Age, median (range), years | 34 (18-68) | 34 (18-85) | 34 (18-85) |
| ≥50 years, n (%) | 66 (7) | 66 (7) | 132 (7) |
| Female sex at birth, n (%) | 128 (14) | 136 (15) | 264 (15) |
| Race, n (%) | | | |
| White | 728 (79) | 693 (78) | 1421 (78) |
| Black or African American | 143 (15) | 130 (15) | 273 (15) |
| Other races* | 55 (6) | 64 (7) | 119 (7) |
| BMI, median (range), kg/m²† | 23.6 (15-50) | 23.7 (15-46) | 23.7 (15-50) |
| <25, n (%) | 613 (66) | 570 (64) | 1183 (65) |
| ≥25 to <30, n (%) | 248 (27) | 249 (28) | 497 (27) |
| ≥30, n (%) | 65 (7) | 67 (8) | 132 (7) |
| Weight, median (range), kg | 72.3 (39-145) | 73.0 (36-132) | 73.0 (36-145) |
| HIV-1 RNA, median (range), copies/mL | 38,879 (39-4,054,706) | 40,620 (255-4,963,110) | 39,857 (39-4,963,110) |
| CD4+ cell count, mean (SD), cells/mm³ | 369.8 (164.7) | 372.0 (168.5) | 370.9 (166.5) |
| SBP, median (range), mmHg | 120.0 (80-139) | 120.0 (86-139) | — |
| DBP, median (range), mmHg | 73.5 (46-89) | 74.0 (39-89) | — |
| Presence of diabetes, n (%) | 10 (1) | 16 (2) | 26 (1) |
| Background NRTI, n (%) | | | |
| TDF/FTC | 401 (43) | 681 (77) | 1082 (60) |
| ABC/3TC | 520 (56) | 202 (23) | 720 (40) |
| Other | 6 (<1) | 5 (<1) | 11 (<1) |

*Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and individuals of multiple races. †DTG, n=926; cART, n=886; total, n=1812.
BMI, body mass index; cART, comparator antiretroviral therapy; DBP, diastolic blood pressure; NRTI, nucleoside reverse transcriptase inhibitor; SBP, systolic blood pressure; SD, standard deviation.

- Among 2345 participants, 23% (n=530) were excluded for BL HTN; of the remaining participants, 927 received DTG-based ART and 888 received cART
- Overall, 35% (n=629) of participants had a BMI in the overweight (27%, n=497) or obesity (7%, n=132) categories (Table 1)

### Figure 2. Adjusted Mean Change (SE) in Weight Through Week 96*




*MMRM analysis adjusted for: treatment, visit, age, sex, race, region, diabetes, baseline NRTI, baseline CD4+ cell count, baseline HIV-1 RNA, smoking status, depression or anxiety, hepatitis C co-infection, study, baseline by visit, treatment by visit, with visit as repeated factor and study as a random effect.
cART, comparator antiretroviral therapy; CI, confidence interval; MMRM, mixed-model repeated-measures; NRTI, nucleoside reverse transcriptase inhibitor; SE, standard error; W, Week.

- At BL, mean (SD) weight was 73.7 (13.6) kg for DTG-based regimens and 74.3 (13.1) kg for cART
- At Week 96, adjusted mean (standard error) change in weight was 1.98 (0.242) kg for DTG-based regimens vs 1.59 (0.212) kg for cART (treatment difference, 0.39 kg; 95% CI, −0.25, 1.04; *P*=0.230) (Figure 2)

### Table 2. Evaluating Individual Effects of Treatment, Weight Change, and Key BL Factors on Incident HTN Risk*

| Variables of interest | Mean hazard ratio (95% CrI) |
|---|---|
| Age | 1.026 (1.008, 1.044) |
| Sex at birth (female vs male) | 0.669 (0.456, 0.971) |
| Race (Other races vs White) | 0.691 (0.384, 1.126) |
| Race (Black or African American vs White) | 1.086 (0.795, 1.468) |
| Baseline HIV-1 RNA | 0.994 (0.850, 1.169) |
| **Treatment (DTG vs cART)** | **1.099 (0.876, 1.370)** |
| **Weight change (per 1 kg increase)** | **1.012 (1.004, 1.020)** |

*Main effects model assessing the independent effect of each covariate on incident HTN risk (a joint model looking at only the main effects).
cART, comparator antiretroviral therapy; CrI, credible interval; HTN, hypertension.

- Treatment (DTG-based regimen vs cART) was not independently associated with HTN risk through Week 96 (mean hazard ratio, 1.099; 95% credible interval [CrI], 0.876, 1.370) (Table 2)
- On average, a 1 kg increase in weight was estimated to increase HTN risk by 1.2% (hazard ratio, 1.012; 95% CrI, 1.004, 1.020)

### Table 3. Assessing the Relationship Between Treatment-Induced Weight Gain on Incident HTN Risk*

| Variables of interest | Mean hazard ratio (95% CrI) |
|---|---|
| Age | 1.025 (1.007, 1.043) |
| Sex at birth (female vs male) | 0.658 (0.441, 0.963) |
| Race (Other races vs White) | 0.682 (0.384, 1.128) |
| Race (Black or African American vs White) | 1.075 (0.791, 1.445) |
| Baseline HIV-1 RNA | 0.997 (0.854, 1.158) |
| **Treatment (DTG vs cART)†** | **0.837 (0.289, 2.664)** |
| **Weight change with cART** | **1.009 (0.998, 1.020)** |
| **Weight change with DTG** | **1.013 (1.003, 1.022)** |

*Interaction model assessing the relationship between weight gain caused by treatment initiation and the effect on incident HTN risk while adjusting for key BL factors. †Treatment effect when weight change equals 0.
cART, comparator antiretroviral therapy; CrI, credible interval; HTN, hypertension.

- There was no evidence that the risk of HTN due to weight change varied between treatment groups (hazard ratio [95% CrI]: DTG-based regimen, 1.013 [1.003, 1.022]; cART, 1.009 [0.998, 1.020]) (Table 3)
- No clear relationship suggesting a difference in treatment effect on the risk of HTN was observed when accounting for post-BL weight change

## Conclusions

- Weight gain was found to be independently associated with HTN risk through Week 96, consistent with non-HIV populations
- ART (DTG-based regimens vs EFV, RAL, and DRV/r-based cART) was not found to be an independent risk factor for HTN risk
- The effect of treatment-induced weight gain on HTN risk did not exhibit a clear difference between DTG-based regimens and cART
- In summary, no clear relationship was identified between weight gain post-initiation of DTG and increased risk of HTN over 96 weeks


**Acknowledgments:** This study was funded by ViiV Healthcare. Editorial assistance was provided by Daniel Williams of Nucleus Global, with funding provided by ViiV Healthcare. Data included in this poster have previously been presented in full at European Meeting on HIV & Hepatitis; May 22-24, 2024; Barcelona, Spain; Poster 76.



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