No Relevant Difference in Incident Hypertension Observed by Gender, Race, Baseline BMI, or Other Key Subgroups Through Week 96 Among People Living With HIV-1 (PLWH) Receiving Dolutegravir (DTG)-Based Regimens or Comparator Antiretroviral Therapy (cART) in Pooled Randomized Clinical Trials

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Key Takeaways

- **Blood pressure (BP) changes and incident hypertension (HTN) were assessed among key subgroups of people living with HIV (PLWH) naive to antiretroviral therapy (ART) without evidence of baseline HTN in pooled Phase 2/3 trials through 96 weeks.**
- **No statistical difference in the odds of developing incident HTN was observed between dolutegravir (DTG) and efavirenz (EFV)-, raltegravir (RAL)-, or darunavir/ritonavir (DRV/r)-based comparator ART (cART), both overall and by age, sex at birth, race, region, and baseline body mass index (BMI) category through Week 96.**
- **Study treatment was not associated with the development of incident HTN through Week 96.**
- **Adjusted mean changes in SBP and DBP across subgroups were similar to those observed in the overall population.**

Introduction

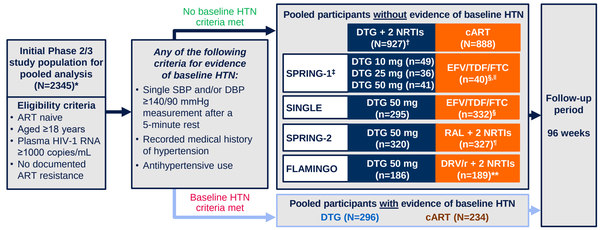
- With longer life expectancy from effective ART, PLWH are increasingly experiencing age-related comorbidities and metabolic complications, such as HTN.[1,2]
- Higher rates of HTN have been observed in PLWH with baseline BMI ≥30 kg/m^2 and Black race.[3]
- Data regarding the association of HTN and integrase strand transfer inhibitor (INSTI) and tenofovir alafenamide (TAF)-based therapy are conflicting and limited, particularly among key populations of PLWH.
  - The RESPOND study found a higher incidence of HTN with the use of INSTIs compared with non-nucleoside reverse transcriptase inhibitors;[4] however, no association between HTN and INSTI-based regimens was observed in the REPRIEVE study.[5]
  - In the ADVANCE trial, Grade 1 treatment-emergent HTN, treatment-emergent obesity, and weight gain were significantly higher in participants receiving a DTG and TAF-containing regimen of TAF/emtricitabine (FTC)/DTG vs. tenofovir disoproxil (TDF)/FTC/EFV.[6,7]
  - In the ADVANCE and NAMSAL trials, DTG was significantly associated with higher risks for treatment-emergent HTN, especially when combined with TAF.[7]
- No statistical or clinical differences in BP changes and incident HTN were observed between DTG 3-drug regimens and EFV-, RAL-, or DRV/r-based cART among ART-naive PLWH without evidence of baseline HTN through 96 weeks in pooled Phase 2/3 trials.[8]
- Here, we assessed BP changes and incident HTN among key subgroups of ART-naive participants without evidence of baseline HTN in pooled Phase 2/3 trials through 96 weeks.

Methods

- Data from ART-naive PLWH without evidence of baseline HTN were pooled from the SPRING-1, SPRING-2, SINGLE, and FLAMINGO clinical trials.
- Participants were randomized to DTG plus two nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir/lamivudine [ABC/3TC] or TDF/FTC) or EFV, RAL, or DRV/r, each combined with two NRTIs (**Figure 1**).
- BP and weight measurements were assessed at baseline and Weeks 48 and 96.
  - SPRING-1 had additional measurements at Weeks 2, 4, 12, 24, 60, 72, and 84.
  - SINGLE and SPRING-2 had additional measurements at Week 24.
- 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 measured after a 5-minute rest, investigator-reported HTN adverse event, and/or antihypertensive medication use.
- **Endpoints assessed through Week 96:**
  - Mean BP changes by subgroup (age, sex at birth, race, region, and baseline BMI).
  - Baseline covariates associated with incident HTN.
  - HTN event incidence by subgroup.
- Logistic regression was used to calculate adjusted odds ratios (aORs) for incident HTN, and mixed model for repeated measures analyses were used to evaluate BP changes from baseline with adjustment for factors known to impact BP.*
- Heterogeneity was assessed by including a treatment-by-study interaction term in the models.

*Adjusted for treatment, visit, age, sex, race, region, baseline BMI, diabetes, baseline BP, baseline CD4⁺ cell count, baseline HIV-1 RNA level, smoking status, depression or anxiety, study, and study as a random effect. The mixed model for repeated measures analyses were also adjusted for baseline BP-by-visit interaction and treatment-by-visit interaction, with visit as a repeated factor.

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 2 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.
ABC/3TC, abacavir/lamivudine; ART, antiretroviral therapy; BID, twice daily; cART, comparator antiretroviral therapy; DBP, diastolic blood pressure; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; HTN, hypertension; NRTI, nucleoside reverse transcriptase inhibitor; QD, once daily; RAL, raltegravir; SBP, systolic blood pressure; TDF/FTC, tenofovir disoproxil/emtricitabine.

Results

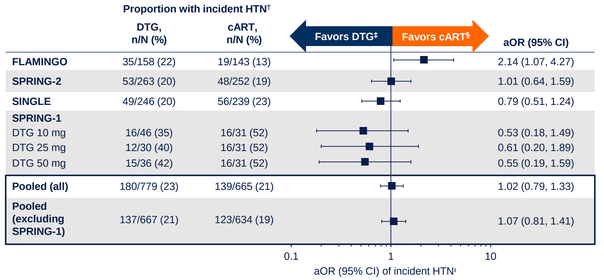
Table 1. Baseline Characteristics of Participants Without Baseline HTN

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)
Geographic region, n (%)			
Europe	576 (62)	565 (64)	1141 (63)
North America	325 (35)	301 (34)	626 (34)
Asia Pacific	22 (2)	18 (2)	40 (2)
Latin America	4 (<1)	4 (<1)	8 (<1)
BMI, median (range), kg/m^2†	23.6 (15–50)	23.7 (15–46)	23.7 (15–50)
<25 kg/m^2, n (%)	613 (66)	570 (64)	1183 (65)
≥25 to <30 kg/m^2, n (%)	248 (27)	249 (28)	497 (27)
≥30 kg/m^2, 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/mm^3	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)	—
eGFR, median (range), mL/min	122 (68–342)	125 (27–269)	123 (27–342)
Presence of diabetes, n (%)	10 (1)	16 (2)	26 (1)
Smoking status, n (%)			
Current smoker	418 (45)	387 (44)	805 (44)
Former smoker	118 (13)	121 (14)	239 (13)
Never smoked	391 (42)	380 (43)	771 (42)
Background NRTI, n (%)			
TDF/FTC	401 (43)	681 (77)	1082 (60)
ABC/3TC	520 (56)	202 (23)	722 (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.
ABC/3TC, abacavir/lamivudine; BMI, body mass index; cART, comparator antiretroviral therapy; DBP, diastolic blood pressure; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; HTN, hypertension; NRTI, nucleoside reverse transcriptase inhibitor; SBP, systolic blood pressure; SD, standard deviation; TDF/FTC, tenofovir disoproxil/emtricitabine.

- Among 1815 participants without evidence of baseline HTN, 927 received a DTG-based regimen and 888 received cART.
- Baseline characteristics were generally balanced between treatment groups, except for greater TDF/FTC use for cART vs. DTG (77% vs. 43%) and greater ABC/3TC use for DTG vs. cART (56% vs. 23%).
- At baseline, 7% of participants were ≥50 years of age, 85% were male (sex at birth), 15% were of Black or African American race, and 7% had a BMI ≥30 kg/m^2.

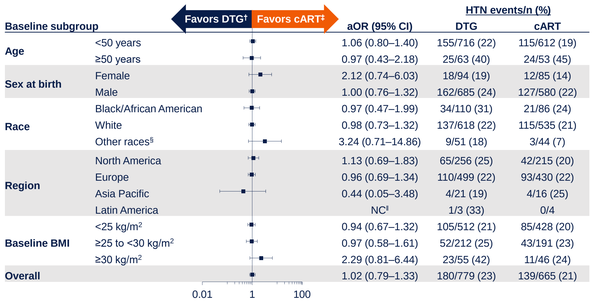
Figure 2. Odds of Participants Experiencing Incident HTN Through Week 96*



*Data previously presented (Patel P, et al. IAS 2023 (Poster LBEPB12)). †Defined as any of the following at any post-baseline visit: single SBP and/or DBP ≥140/90 mmHg measurement, antihypertensive use, or a reported HTN adverse event. ‡Indicates lower incidence of HTN with DTG. §Indicates lower incidence of HTN with cART. ‖Logistic regression analysis adjusted for study, age, sex, race, region, baseline CD4⁺ cell count, baseline HIV-1 RNA level, baseline BMI, diabetes, smoking status, and depression or anxiety.
aOR, adjusted odds ratio; BMI, body mass index; cART, comparator antiretroviral therapy; CI, confidence interval; DBP, diastolic blood pressure; DTG, dolutegravir; HTN, hypertension; SBP, systolic blood pressure.

- Overall, no difference in the odds of HTN between DTG and cART was observed through Week 96 (aOR 1.02 [95% confidence interval, 0.79–1.33]; between-study heterogeneity was observed based on the differing data collection frequency) (**Figure 2**).
- Incident HTN in the DTG group of FLAMINGO was comparable to the other Phase 3 studies included; the cART group of FLAMINGO had lower incident HTN than that observed in other study cART groups.

Figure 3. HTN Event Incidence by Subgroup Between Treatments Through Week 96*



*Defined as any of the following at any post-baseline visit: single SBP and/or DBP ≥140/90 mmHg measurement, antihypertensive use, or a reported HTN adverse event. †Indicates lower incidence of HTN with DTG. ‡Indicates lower incidence of HTN with cART. §Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and individuals of multiple races. ¶Could not be calculated with n=0 HTN events reported for cART. ‖Logistic regression adjusted for age, sex, race, region, baseline BMI, diabetes, baseline CD4⁺ cell count, baseline HIV-1 RNA level, smoking status, depression or anxiety, and study.
aOR, adjusted odds ratio; BMI, body mass index; cART, comparator antiretroviral therapy; CI, confidence interval; DBP, diastolic blood pressure; DTG, dolutegravir; HTN, hypertension; NC, not calculated; SBP, systolic blood pressure.

- No differences in the odds of incident HTN between treatments were observed through Week 96 across subgroups of age, sex at birth, race, region, and baseline BMI region (**Figure 3**).

Figure 4A. Difference in Adjusted SBP Change From Baseline at Week 96 by Subgroup

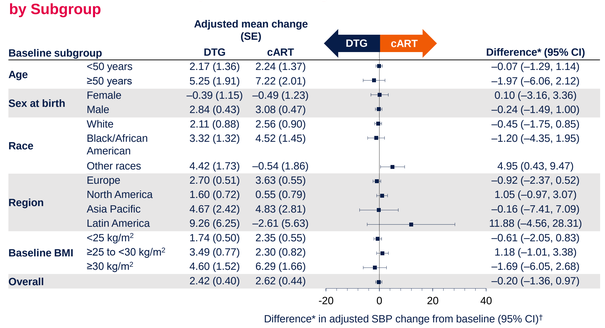
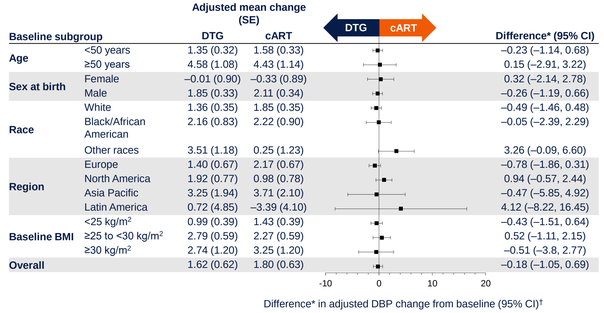


Figure 4B. Difference in Adjusted DBP Change From Baseline at Week 96 by Subgroup



*Difference: DTG – non-DTG. †Mixed model for repeated measures analysis adjusted for treatment, visit, age, sex, race, region, baseline BMI, diabetes, baseline BP, baseline CD4+ cell count, baseline HIV-1 RNA, smoking status, depression or anxiety, study, baseline BP-by-visit interaction, and treatment-by-visit interaction, with visit as a repeated factor and study as a random effect.
BMI, body mass index; BP, blood pressure; cART, comparator antiretroviral therapy; CI, confidence interval; DBP, diastolic blood pressure; DTG, dolutegravir; SBP, systolic blood pressure; SE, standard error.

- There were no statistically and clinically significant changes from baseline in SBP or DBP observed across subgroups at Week 96 (**Figure 4A** and **4B**).

Conclusions

- In treatment-naive PLWH without evidence of HTN at baseline:
  - No statistical difference in the odds of developing incident HTN was observed between DTG and EFV-, RAL-, or DRV/r-based cART, both overall and by age, sex at birth, race, region, and baseline BMI category through Week 96.
  - Study treatment was not associated with the development of incident HTN through Week 96.
  - Adjusted mean changes in SBP and DBP across subgroups were similar to those observed in the overall population.
  - Routine clinical monitoring and management of cardiovascular disease risk and HTN in PLWH is recommended.

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