Evaluation of Incident Hypertension and Blood Pressure Changes Among People Living With HIV-1 (PLWH) Receiving Dolutegravir (DTG)-Based Regimens or Comparator Antiretroviral Therapy (cART) in Randomized Clinical Trials Through 96 Weeks

LBEPB12

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Key Takeaways

- **In people living with HIV-1 (PLWH) without hypertension (HTN) at baseline, the odds of developing incident HTN through Week 96 did not differ between participants initiating dolutegravir (DTG)-based regimens and comparator antiretroviral therapy (cART)**
- **In participants without evidence of baseline HTN, blood pressure (BP) increases were small and did not clinically or significantly differ between the DTG and cART groups through Week 96**
- **ViiV randomized controlled trial data do not support an association between increased BP and DTG in treatment-naive PLWH**

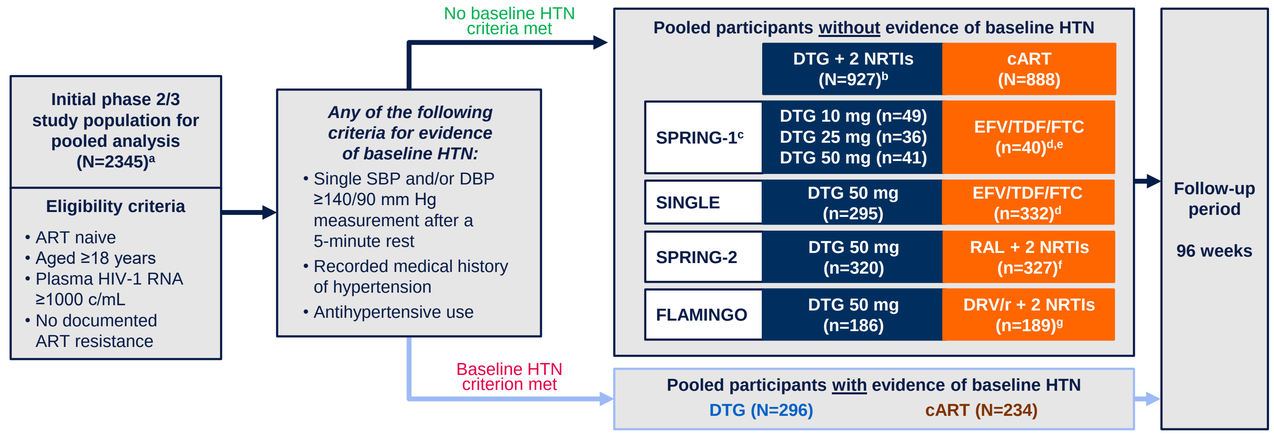
Introduction

- With longer life expectancy due to effective ART, PLWH are aging and affected by metabolic complications, including HTN[1,2]
- Estimated prevalence of HTN is as high as 53% among PLWH on ART[3-6]
  - Immunological activation and inflammation due to HIV may exacerbate HTN and cardiovascular disease risk[6]
- Data are conflicting regarding the role of INSTI-based regimens in HTN incidence
  - RESPOND found a higher incidence of HTN with use of INSTIs compared with NNRTIs, but not compared with boosted PIs[7]
  - REPRIEVE found no association between HTN and INSTI- vs non–INSTI-based regimens[8]
- Currently, data describing changes in BP with DTG-based regimens are limited
- We evaluated BP changes and incident HTN in ART-naive PLWH without evidence of baseline HTN initiating DTG + 2 NRTIs or cART from pooled phase 2/3 randomized studies through Week 96

Methods

- Data from ART-naive PLWH randomized to DTG + 2 NRTIs (either TDF/FTC or ABC/3TC) or cART were pooled from the phase 2 SPRING-1 and phase 3 SINGLE, SPRING-2, and FLAMINGO clinical trials
- BP and weight measurements were taken at baseline and Weeks 48 and 96
  - SPRING-1 took additional measurements at Weeks 2, 4, 12, 24, 60, 72, and 84
  - SINGLE and SPRING-2 took additional measurements at Week 24
- Data were analyzed separately based on evidence of potential baseline HTN (Figure 1)
  - Primary aim: to evaluate treatment-emergent BP changes and incident HTN in participants without evidence of baseline HTN
  - Secondary aim: to evaluate BP changes in participants with evidence of baseline HTN
- Incident HTN was defined as any of the following at any post-baseline visit:
  - Single SBP and/or DBP ≥140/90 mm Hg measurement
  - Antihypertensive use
  - Reported HTN adverse event

Figure 1. Study Population in Pooled Analysis



cART, comparator ART; DBP, diastolic BP; HTN, hypertension; SBP, systolic BP. [a]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 TDF/FTC or ABC/3TC. [b]All DTG doses were administered QD. [c]All DTG dose groups were combined in pooled study analyses that included SPRING-1 data. [d]EFV 600 mg QD. [e]n=12 received EFV + ABC/3TC. [f]RAL 400 mg BID. [g]DRV/r 800 mg/100 mg QD.

- Endpoints evaluated in participants without evidence of baseline HTN:
  - Adjusted proportion experiencing incident HTN through Week 96
  - Baseline covariates associated with incident HTN
  - Adjusted mean change from baseline in BP at Weeks 48 and 96
- Mixed-models repeated-measures (MMRM) analyses were used to evaluate BP changes with adjustment for relevant baseline variables and pooled treatment (DTG or cART)
- Logistic regression was used to calculate adjusted odds ratios for incident HTN

Results

Participants

- Among 2345 randomized participants, 1815 (77%) did not have evidence of potential baseline HTN
  - Of these, 927 received DTG-based ART and 888 received cART consisting of either EFV (41%), RAL (37%), or DRV/r (21%), each with 2 NRTIs (Figure 1)
- Baseline characteristics were generally balanced between treatment groups, except for greater TDF/FTC use for cART vs DTG (77% vs 43%; Table 1)

Table 1. Baseline Characteristics of Participants Without Baseline HTN

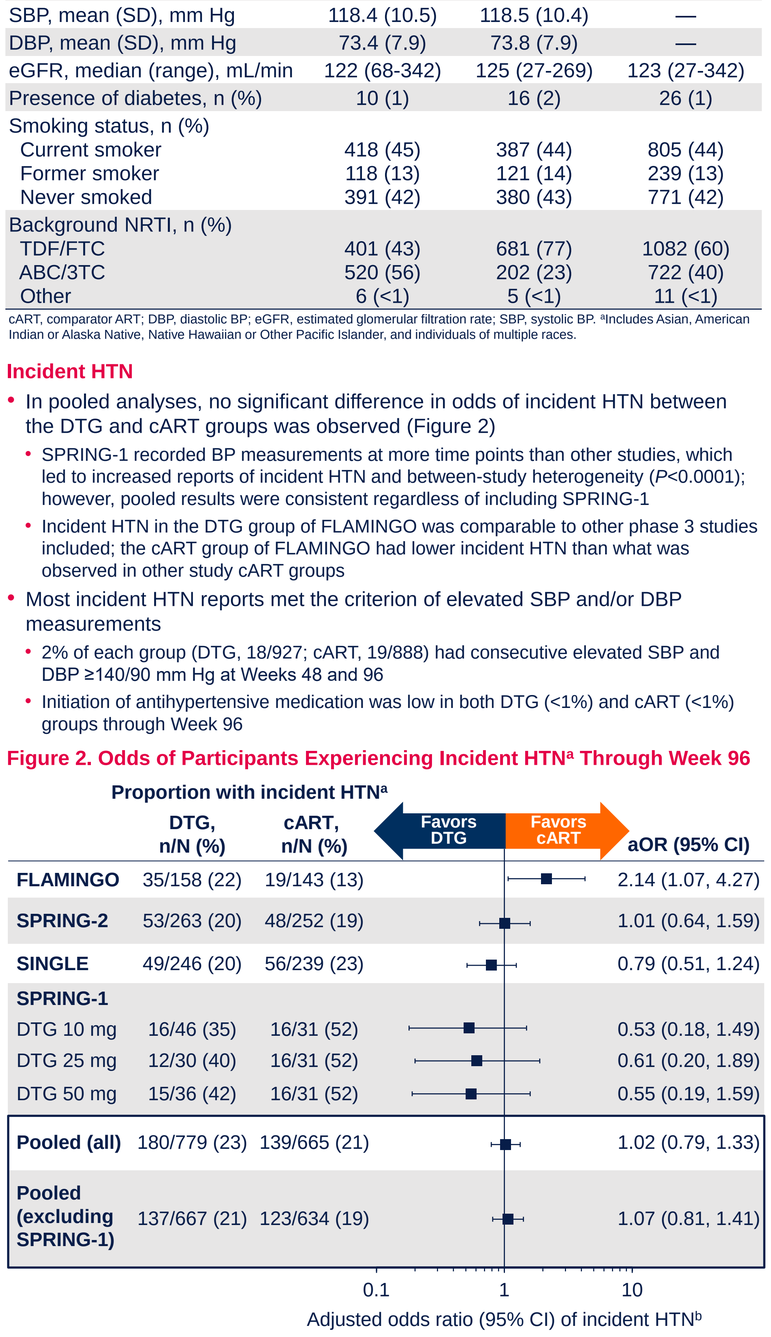
Characteristic	DTG regimen (N=927)	cART (N=888)	Pooled total (N=1815)
Age, median (range), years	34 (18-68)	34 (18-85)	34 (18-85)
≥50, n (%)	66 (7)	66 (7)	132 (7)
Female sex at birth, n (%)	128 (14)	136 (15)	264 (15)
Race, n (%)			
White	728 (79)	693 (78)	1421 (78)
Black or African American	143 (15)	130 (15)	273 (15)
Other races[a]	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)
Weight, median (range), kg	72.3 (39-145)	73.0 (36-132)	73.0 (36-145)
BMI, median (range), kg/m^2	23.6 (15-50)	23.7 (15-46)	23.7 (15-50)
HIV-1 RNA, median (range), c/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, mean (SD), mm Hg	118.4 (10.5)	118.5 (10.4)	—
DBP, mean (SD), mm Hg	73.4 (7.9)	73.8 (7.9)	—
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)

cART, comparator ART; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; SBP, systolic BP. [a]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and individuals of multiple races.

Incident HTN

- In pooled analyses, no significant difference in odds of incident HTN between the DTG and cART groups was observed (Figure 2)
  - SPRING-1 recorded BP measurements at more time points than other studies, which led to increased reports of incident HTN and between-study heterogeneity (P<0.0001); however, pooled results were consistent regardless of including SPRING-1
  - Incident HTN in the DTG group of FLAMINGO was comparable to other phase 3 studies included; the cART group of FLAMINGO had lower incident HTN than what was observed in other study cART groups
- Most incident HTN reports met the criterion of elevated SBP and/or DBP measurements
  - 2% of each group (DTG, 18/927; cART, 19/888) had consecutive elevated SBP and DBP ≥140/90 mm Hg at Weeks 48 and 96
  - Initiation of antihypertensive medication was low in both DTG (<1%) and cART (<1%) groups through Week 96

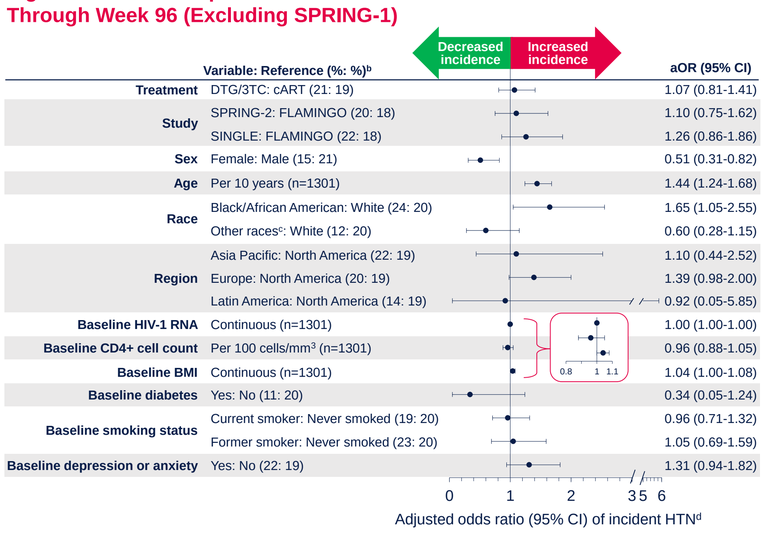
Figure 2. Odds of Participants Experiencing Incident HTN[a] Through Week 96



cART, comparator ART; DBP, diastolic BP; HTN, hypertension; SBP, systolic BP. [a]Defined as any of the following at any post-baseline visit: single SBP and/or DBP ≥140/90 mm Hg measurement, antihypertensive use, or a reported HTN adverse event. [b]Logistic regression analysis adjusted for study, age, sex, race, region, baseline CD4+ cell count, baseline HIV-1 RNA, baseline BMI, diabetes, smoking status, and depression or anxiety.

- Study treatment was not associated with incident HTN
- Covariates associated with increased adjusted odds of incident HTN included increasing age (per 10 years), Black or African American race (vs White), higher baseline HIV-1 RNA, and higher baseline BMI (Figure 3)
  - Female sex at birth (vs male) was associated with decreased adjusted odds of incident HTN
  - Results were consistent regardless of including SPRING-1

Figure 3. Relationship Between Baseline Covariates and Incident HTN[a] Through Week 96 (Excluding SPRING-1)

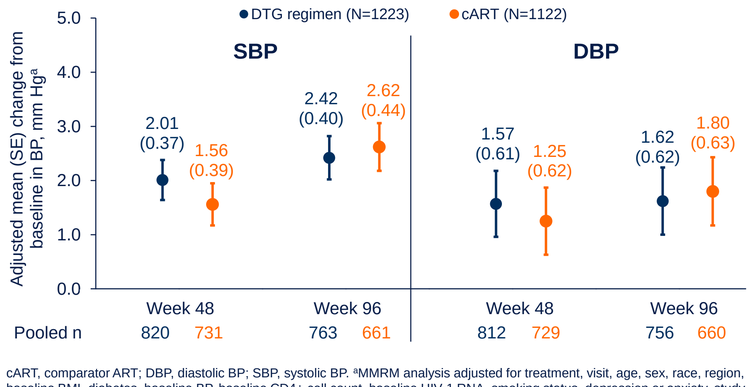


cART, comparator ART; HTN, hypertension. [a]Defined as any of the following at any post-baseline visit: single SBP and/or DBP ≥140/90 mm Hg measurement, antihypertensive use, or a reported HTN adverse event. [b]Proportion with incident HTN. [c]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and individuals of multiple races. [d]Logistic regression analysis adjusted for study, age, sex, race, region, baseline CD4+ cell count, baseline HIV-1 RNA, baseline BMI, diabetes, smoking status, and depression or anxiety.

Blood Pressure Changes From Baseline

- Adjusted mean BP increased slightly from baseline up to 96 weeks in **both** treatment groups (Figure 4)
  - Significant predictors (P<0.05) of increased BP included increasing age, female sex at birth, higher baseline viral load, and higher baseline BMI

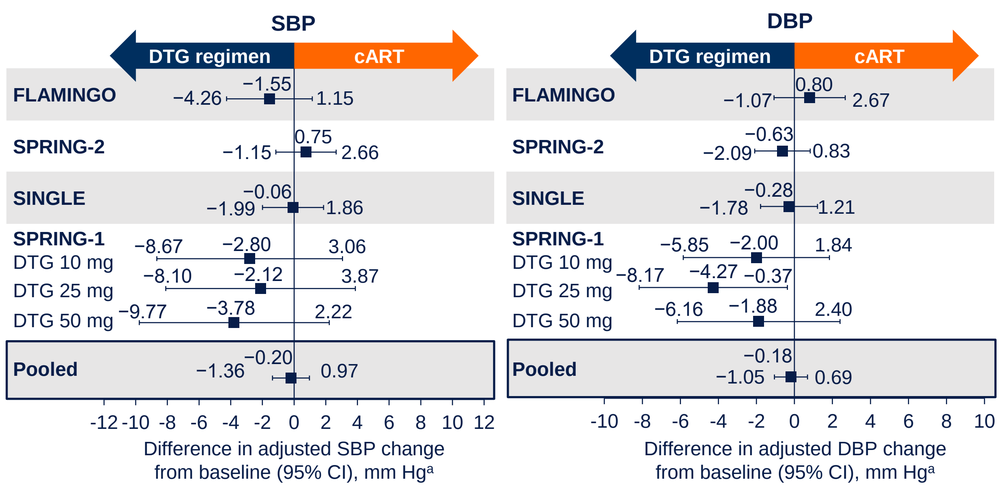
Figure 4. Adjusted Mean BP Change From Baseline at Weeks 48 and 96



cART, comparator ART; DBP, diastolic BP; SBP, systolic BP. [a]MMRM 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 repeated factor and study as random effect.

- At Week 96, no significant changes from baseline in SBP or DBP were observed between treatment groups across pooled and individual studies (Figure 5)
  - There was no evidence of heterogeneity between studies (SBP, P=0.425; DBP, P=0.312)

Figure 5. Treatment Difference in Adjusted SBP and DBP Change From Baseline at Week 96 for Pooled and Individual Studies



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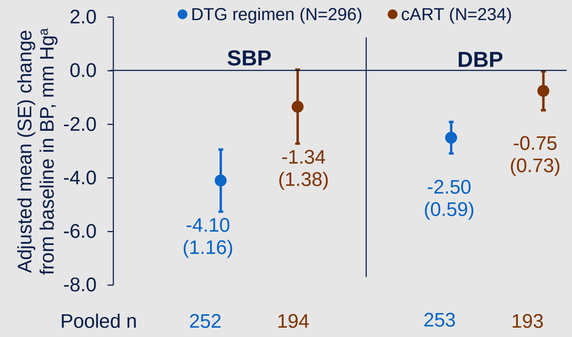
Results for Pooled Population With Evidence of Baseline HTN

- Of the 2345 total randomized participants, 530 (23%) had evidence of potential baseline HTN:
  - 372 (70%) had single SBP and/or DBP ≥140/90 mm Hg measurement
  - 271 (51%) had medical history of HTN
  - 17 (3%) recorded antihypertensive use
- Baseline characteristics were generally similar between participants with vs without evidence of baseline HTN, respectively, with the following differences:
  - Higher proportion aged ≥50 years (25% vs 7%)
  - Higher proportion identifying as Black or African American (28% vs 15%)
  - Higher proportion with diabetes at baseline (10% vs 1%)
  - Higher median baseline BMI (26.4 vs 23.7 kg/m^2)
- At Week 96, adjusted mean change from baseline in BP decreased in both treatment groups and was not significantly different between groups (Figure 6)
  - SBP treatment difference (95% CI): −2.76 (−5.58, 0.06) mm Hg
  - DBP treatment difference (95% CI): −1.75 (−3.60, 0.10) mm Hg
  - There was no evidence of heterogeneity between studies (SBP, P=0.610; DBP, P=0.864)
- Week 48 individual and pooled study analysis results were generally consistent with Week 96

Figure 6. Adjusted Mean BP Change From Baseline at Week 96 Among Participants With Evidence of Baseline HTN



cART, comparator ART; DBP, diastolic BP; SBP, systolic BP. [a]MMRM 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 repeated factor and study as random effect.

Discussion

- HTN development is multifactorial; a variety of HIV- and non–HIV-associated factors can impact HTN risk and contribute to wider cardiovascular risks
- Strengths of this analysis include the following:
  - Adjustment of results for covariates known to have significant impact on BP to estimate the true treatment effect
  - Use of multiple BP readings over time vs single time point assessment
  - Separate analyses with and without baseline HTN to account for potential imbalance in high cardiovascular risk or pre-existing HTN between treatments among participants
- Limitations of this analysis include the following:
  - Multiple BP readings increase the risk of higher estimated rate of HTN
  - Non-standardization of BP measurements across sites with no protocol specification to average BP from repeated measurements at each time point
  - Differences in population demographics and regional HTN prevalence driven by geographic location of study sites
  - Inability to directly extrapolate results to a suppressed-switch population
  - Different comparator classes and trial designs introduce heterogeneity

Conclusions

- Among ART-naive PLWH without evidence of baseline HTN
  - No difference in adjusted odds of incident HTN were observed between the DTG and cART groups at Week 96
  - Older age, Black or African American race, higher baseline HIV-1 RNA, and higher baseline BMI were associated with increased adjusted odds of incident HTN through Week 96 but not study treatment
  - Increases in adjusted mean BP from baseline through Week 96 were small, with no clinical or statistical difference between treatments, and unlikely to be clinically relevant
- In ART-naïve PLWH with evidence of baseline HTN
  - Decreases in adjusted mean BP from baseline through Week 96 were observed in both the DTG and cART groups and were not statistically different
- Healthcare providers should continue to monitor and manage BP as clinically appropriate, especially in individuals with relevant HTN and/or cardiovascular risk factors

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References: 1. Smit et al. *Lancet Infect Dis.* 2015;15:810-818. **2.** Deeks et al. *Lancet.* 2013;382:1525-1533. **3.** Gelpi et al. *Clin Infect Dis.* 2018;67:579-586. **4.** Lake et al. *AIDS.* 2018;32:49-57. **5.** Xu et al. *J Am Soc Hypertens.* 2017;11:530-540. **6.** Tsuro et al. *Int J Environ Res Public Health.* 2022;19:11196. **7.** Byonanebye et al. *HIV Med.* 2022;23:895-910. **8.** Kileel et al. *Open Forum Infect Dis.* 2021;8:ofab537.

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