Subgroup Analysis of Randomized Clinical Trials Comparing Dolutegravir Treatment Regimens With Non–Integrase Strand Transfer Inhibitor Treatment Regimens in Antiretroviral-Naive Patients at 48 Weeks by Race

ACTHIV-9

M. Keith Rawlings,[1] Richard Grove,[2] Romina Quercia,[2] Trevor Mole,[2] Jean van Wyk,[2] Ralph DeMasi[1]

[1]ViiV Healthcare, Research Triangle Park, NC; [2]ViiV Healthcare, Brentford, UK

Introduction

- Throughout the highly active antiretroviral therapy era there has been a difference in the rate of viral suppression (VS) by race, particularly in the United States
- The current demographics of people living with HIV make it imperative to determine if there are therapeutic interventions that can lessen the racial disparities in VS
- This analysis aims to evaluate dolutegravir (DTG) treatment regimen efficacy in antiretroviral therapy (ART)–naive participants by subgroups

Methods

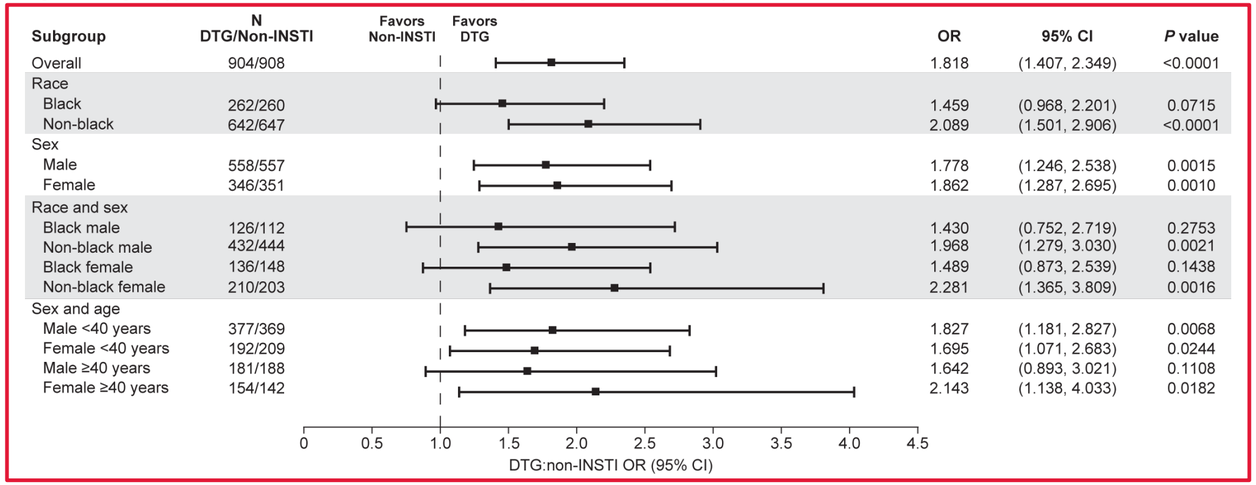
- A pooled analysis of 3 randomized phase III or IIIb trials comparing DTG with non–integrase strand transfer inhibitor (non-INSTI) regimens in treatment-naive individuals infected with HIV-1 (ARIA, FLAMINGO, and SINGLE) was performed
  - ARIA was an open-label study of DTG/abacavir (ABC)/lamivudine (3TC) vs ritonavir-boosted atazanavir (ATV/r) plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) in women
  - FLAMINGO was an open-label study of DTG vs ritonavir-boosted darunavir (both groups could have either ABC/3TC or TDF/FTC)
  - SINGLE was a double-blind study of DTG plus ABC/3TC vs efavirenz/TDF/FTC
- This analysis evaluated the effect of DTG relative to non-INSTIs in ART-naive participants for subgroups of interest
  - Race (black vs non-black)
  - Sex (male vs female)
  - Race and sex (black vs non-black male) and (black vs non-black female)
  - Sex and age (<40 years vs ≥40 years)
- Because none of the individual studies were specifically powered to establish efficacy within subgroups, we combined study data to more precisely estimate treatment regimen effects within subgroups
- The primary endpoint was VS (HIV-1 RNA <50 c/mL) at Week 48 using the US Food and Drug Administration snapshot algorithm
- Efficacy and safety endpoints were assessed using original study reporting
- Unadjusted VS rates were estimated using a fixed-effects meta-analysis inverse-variance weighted combination of individual study estimates
- Baseline covariate adjusted treatment regimen odds ratios (DTG:non-INSTI) were estimated using a fixed effects meta-analysis logistic regression of VS
- All *P* values are 2 sided and provide supportive evidence of treatment regimen effects
- All comparisons between the treatment regimens are reported with 95% confidence intervals for the difference
- Bayesian posterior probabilities for a treatment benefit for DTG vs non-INSTI are reported where indicated

Results

Study Participants

- Overall, 1812 ART-naive participants were included in this pooled analysis for the ARIA (DTG, n=248; comparator, n=247), FLAMINGO (DTG, n=242; comparator, n=242), and SINGLE (DTG, n=414; comparator, n=419) trials
- DTG and non-INSTI arms were balanced on baseline factors
  - 29% identified as black, and 38% identified as female
  - Median age was 36 years; 63% were <40 years of age
- A higher percentage of participants completed 48 weeks of treatment for the DTG group overall (87% vs 81% for the non-INSTI group) and in each of the subgroups assessed

Figure. Virologic Suppression at 48 Weeks of Treatment: Treatment Regimen Odds Ratios by Participant Factors



DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; OR, odds ratio.

Efficacy

- The treatment regimen odds ratios for VS at Week 48 favored DTG vs non-INSTI in all subgroups (Figure)
- The probability of a benefit in VS at Week 48 for DTG vs non-INSTI was >0.95 in the majority of subgroups investigated (range, 0.862–1.000; Table 1)
- No statistical evidence of varying treatment effects were observed within subgroups based on the interaction odds ratios from the logistic regression analysis
- The probability that VS at Week 48 is higher in the DTG arm than in the non-INSTI arm was 0.966 for black participants
- Differences in the rate of VS at Week 48 were numerically higher for the DTG group than the non-INSTI group in each subgroup
  - The most pronounced VS rate differences were observed in female participants <40 years old (10.8%) and in non-black female participants (12.1%)
  - The least pronounced VS rate differences were observed in male participants ≥40 years old (5.2%)
- Mean CD4+ cell count change from baseline favored DTG for all subgroups (Table 2)
- VS rates were ~10% lower in black vs non-black participants (Table 3)
- Black participants had higher percentages of discontinuations for "other reasons" than non-black participants in both the DTG and non-INSTI groups

Table 1. Virologic Suppression at Week 48 by Subgroup

Subgroup	DTG, n/N (%)[a]	Non-INSTI, n/N (%)[a]	Difference, % (95% CI)[a]	Posterior probability[b]
Overall	786/904 (87.5)	717/908 (79.8)	7.7 (4.4, 11.1)	1.000
Black	208/262 (79.8)	187/260 (72.6)	7.2 (−0.0, 14.5)	0.966
Non-black	578/642 (90.3)	529/647 (82.3)	8.0 (4.3, 11.7)	1.000
Male	500/558 (89.7)	464/557 (83.6)	6.2 (2.2, 10.1)	0.999
Female	286/346 (82.7)	253/351 (72.1)	10.6 (4.4, 16.7)	1.000
Black male	104/126 (82.9)	86/112 (77.1)	5.8 (−4.4, 15.9)	0.862
Non-black male	396/432 (91.7)	377/444 (85.1)	6.6 (2.4, 10.8)	0.999
Black female	104/136 (77.8)	101/148 (68.6)	9.2 (−0.9, 19.4)	0.930
Non-black female	182/210 (86.9)	152/203 (74.9)	12.1 (4.6, 19.6)	0.999
Male <40 years	339/377 (90.2)	307/369 (83.5)	6.7 (1.9, 11.5)	0.997
Female <40 years	151/192 (79.1)	142/209 (68.3)	10.8 (2.3, 19.4)	0.989
Male ≥40 years	161/181 (89.0)	157/188 (83.8)	5.2 (−1.8, 12.2)	0.948
Female ≥40 years	135/154 (88.4)	111/142 (78.8)	9.5 (1.1, 17.9)	0.993

DTG, dolutegravir; INSTI, integrase strand transfer inhibitor. [a]Inverse-variance weighted percentages presented. [b]Posterior probability odds ratio (DTG:non-INSTI) >1.

Table 2. Analysis of Change From Baseline to Week 48 in CD4+ Cell Count: Treatment Regimen Effect by Subgroup

Subgroup	DTG mean,[a] cells/mm^3	Non-INSTI, mean,[a] cells/mm^3	Difference, mean[a] (95% CI)	*P* value
All	255.21	220.5	34.70 (3.21, 66.20)	0.0384
Black	235.77	210.23	25.54 (−8.44, 59.52)	0.1323
Non-black	262.43	223.88	38.55 (8.45, 68.65)	0.0218
Male	250.06	208.57	41.49 (3.39, 79.58)	0.0386
Female	266.84	243.88	22.95 (−15.63, 61.54)	0.2062

DTG, dolutegravir; INSTI, integrase strand transfer inhibitor. [a]Baseline covariate adjusted mean.

Table 3. Combined Pooled Virologic Analysis at Week 48, by Race (Snapshot)

HIV-1 RNA <50 c/mL	DTG, n (%)[a]	Non-INSTI, n (%)[a]
Black, N	**262**	**260**
Virologic suppression	208 (79.4)	187 (71.9)
Virologic nonresponse	20 (7.6)	34 (13.1)
Data in window, not <50 c/mL	5 (1.9)	9 (3.5)
Discontinued for lack of efficacy	5 (1.9)	2 (0.8)
Discontinued while not <50 c/mL	9 (3.4)	23 (8.8)
Change in ART	1 (0.4)	0 (0)
No virologic data	34 (13.0)	39 (15.0)
Discontinued because of AE or death	8 (3.1)	17 (6.5)
Discontinued for other reasons	23 (8.8)	19 (7.3)
Missed data during window but on study	3 (1.1)	3 (1.2)
Non-black, N	**642**	**647**
Virologic suppression	578 (90.0)	529 (81.8)
Virologic nonresponse	30 (4.7)	45 (7.0)
Data in window, not <50 c/mL	9 (1.4)	22 (3.4)
Discontinued for lack of efficacy	7 (1.1)	10 (1.5)
Discontinued while not <50 c/mL	10 (1.6)	12 (1.9)
Change in ART	4 (0.6)	1 (0.2)
No virologic data	34 (5.3)	73 (11.3)
Discontinued because of AE or death	13 (2.0)	49 (7.6)
Discontinued for other reasons	18 (2.8)	21 (3.2)
Missed data during window but on study	3 (0.5)	3 (0.5)

AE, adverse event; ART, antiretroviral therapy; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor. [a]Unadjusted percentages determined as n/N*100.

Safety

- Adverse drug reactions (ADRs; investigational product–related adverse events [AEs]) and AEs leading to withdrawal were numerically higher in the non-INSTI group and for each of the subgroups assessed
  - Overall ADRs: 39% DTG vs 59% non-INSTI
  - Overall AEs leading to withdrawal: 4% DTG vs 10% non-INSTI
- Overall and grade 3/4 AE incidence rates were comparable for all subgroups
  - Overall: 89% DTG vs 90% non-INSTI; Grade 3/4 AEs: 15% DTG vs 18% non-INSTI

Conclusions

- Prior studies in randomized, controlled trials; meta-analyses; and clinical cohorts have demonstrated disparities in VS and viral failure by race[1-7]
- This meta-analysis provided evidence that DTG improved VS rates vs non-INSTI regimens in ART-naive HIV-1–infected participants in all subgroups without additional risk to participant safety
  - The VS rate in both black and non-black participants was numerically higher for DTG compared with non-INSTIs at Week 48
  - Black participants on DTG had VS rates similar to those seen in non-black participants on non-INSTI regimens

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