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MAJOR ARTICLE

Evaluating Diversity in Randomized Clinical Trials of Dolutegravir-Based Antiretroviral Therapy Regimens: Pooled 48-Week Analyses by Race, Sex, and Regional Subgroups

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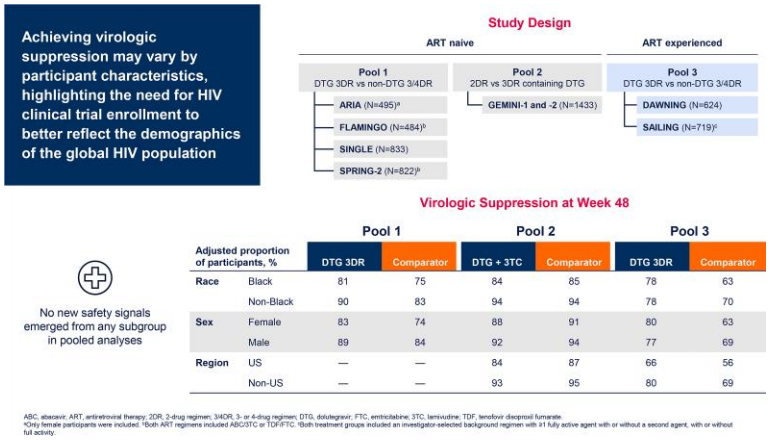
Background. In HIV clinical trials, proportions of Black and female participants achieving virologic suppression (VS) are often lower compared with White and male participants. As the antiretroviral therapy (ART) landscape continues to evolve, addressing existing challenges in clinical trial diversity will be critical to effectively translate results into clinical practice. Here, we pooled data to evaluate the efficacy and safety of dolutegravir (DTG)-containing regimens by race, sex, and regional subgroups.

Methods. Three pooled analyses were conducted using 48-week results from phase 3/3b trials: DTG 3-drug vs non-DTG-containing 3- or 4-drug regimens in ART-naive participants (ARIA, FLAMINGO, SINGLE, SPRING-2), DTG-containing 2-drug vs 3-drug regimens in ART-naive participants (GEMINI-1, GEMINI-2), and DTG 3-drug vs non-DTG-containing 3- or 4-drug regimens in ART-experienced participants (SAILING, DAWNING). Proportions of participants with VS, safety, and change from baseline in CD4+ cell count were analyzed.

Results. Proportions of participants achieving VS were high among those receiving DTG vs comparator regimens. Proportions of participants achieving VS were generally lower in Black (vs non-Black), female (vs male), and US (vs non-US) subgroups. No new safety signals emerged from any subgroup in pooled analyses.

Conclusions. These analyses confirm that, across subgroups, DTG has robust efficacy and a good safety profile at week 48 relative to comparator regimens. Achieving VS may vary by participant characteristics, highlighting the urgent need for enrollment to reflect the demographics of global HIV populations more accurately. Future studies should strive to support participants throughout the trial to ensure optimal representation, inclusion, and retention.

Graphical Abstract



Keywords. dolutegravir; pooled analysis; integrase strand transfer inhibitor; demographics; regional analysis.

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Throughout the highly active antiretroviral therapy era, racial and sexual disparities in suppressing HIV-1 infection have been reported. A 2014 analysis of National HIV Surveillance System data from >650 000 people with HIV (PWH) in the United States found that a lower proportion of Black PWH (41%) sustained virologic suppression (VS) compared with Hispanic (50%) and White PWH (56%); of PWH who did not achieve sustained VS, Black PWH experienced longer periods (52% during the 1-year follow-up) with a viral load >1500 copies/mL compared with Hispanic (47%) and White PWH (41%) [1]. A pooled analysis of the AIDS Clinical Trials Group studies showed that Black PWH had a 40% greater risk of virologic failure compared with White PWH, even after adjusting for a higher prevalence of risk factors [2]. In a military cohort study in which postulated factors for differential virologic response, such as access to care and duration of HIV-1 infection, were minimized, Black PWH were still less likely to attain VS than White PWH in the United States [3]. Lower rates of VS and higher rates of virologic rebound after antiretroviral therapy (ART) have also been observed among women relative to men, particularly among Black and Hispanic/Latina women in the United States and Canada [4, 5].

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) with potent antiviral activity and a high barrier to resistance [6]. In international treatment guidelines for HIV, DTG is recommended as a 2-drug regimen (2DR) combined with a nucleoside reverse transcriptase inhibitor (NRTI) or as a 3-drug regimen (3DR) containing 2 NRTIs for most PWH initiating ART [7, 8]. For ART-experienced PWH experiencing first-line virologic failure, DTG-containing regimens are recommended, including regimens with 2 fully active agents if 1 has a high barrier to resistance [7, 8]. Noninferior efficacy of DTG-containing regimens and high proportions of participants with VS compared with non-DTG-containing regimens have been demonstrated at week 48 across randomized clinical trials (RCTs) in ART-naive and ART-experienced PWH [9–15]. Previously published results by race and sex subgroups were consistent with overall findings but were limited by small subgroup numbers in individual trials [9, 10, 13, 15–17]. Over 5000 participants have been included in DTG clinical trials, which allows for a more in-depth analysis of outcomes across subgroups, particularly among Black participants and women. The data presented here are from 3 pooled analyses of 8 DTG clinical trials in ART-naive and ART-experienced PWH examining efficacy and safety outcomes across subgroups stratified by race (Black vs non-Black), sex (female vs male), and region (US vs non-US).

METHODS

Study Design

Three separate pooled analyses were conducted using participant-level data from 8 phase 3/3b trials of DTG in ART-naive and ART-experienced participants with HIV-1 to evaluate efficacy and safety in subgroups based on race (Black vs non-Black), sex (female vs male), and region (US vs non-US): Pool 1 compared DTG-containing 3DR vs non-DTG-containing 3/4DRs in ART-naive participants from the ARIA, FLAMINGO, SINGLE, and SPRING-2 trials; Pool 2 compared 2DR DTG + lamivudine (3TC) vs 3DR DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in ART-naive participants from the GEMINI-1 and GEMINI-2 trials; and Pool 3 compared DTG-containing 3DR vs non-DTG-containing 3/4DRs in ART-experienced, viremic participants with no previous INSTI experience from the DAWNING and SAILING trials (Figure 1). For all RCTs, ethics committee approval was obtained at all participating centers, in accordance with the principles of the 2008 Declaration of Helsinki, and each participant provided written informed consent before initiation of any study procedures [9–15].

Study Selection

The study protocol was approved in late 2018, and ViiV Healthcare–sponsored phase 3 RCTs that assessed the proportion of participants with VS (HIV-1 RNA <50 copies/mL) at week 48 who were treated with a once-daily 3DR containing DTG 50 mg or a 2DR with DTG 50 mg and 3TC 300 mg were included. Studies with ART-naive or ART-experienced participants with previous virologic failure on a non-INSTI regimen were included.

End Points and Data Extraction

The primary end point of the included trials was the proportion of participants achieving VS (HIV-1 RNA <50 copies/mL) at week 48 using the US Food and Drug Administration Snapshot algorithm (missing, switch, or discontinuation = failure). Change from baseline to week 48 in CD4+ cell count was a secondary end point. Safety end points included study withdrawal by week 48 as well as incidence of any adverse event (AE), AEs leading to withdrawal, adverse drug reactions, and grade 3 or 4 AEs. For all trials, study withdrawals were defined as participants who permanently discontinued study treatment and withdrew from the study before week 48 on the basis of their own request or investigator decision.

Data were analyzed based on the upper limit for the week 48 data assessment window (previously published week 48 assessments included only those up to the week 48 data cutoff).

Statistical Analysis

Efficacy and safety end points were assessed using original study reporting with final study data sets used where appropriate and available. Demographic and efficacy analyses were performed using the intention to treat–exposed (ITT-E) population for all studies, with the exception of FLAMINGO and SAILING, which used a modified ITT-E population [11, 12]. A logistic regression model was fitted to VS at 48 weeks of treatment for each study. The pooled data included ART regimen, race, sex, and country as fixed effects and ART regimen-by-subgroup interaction,

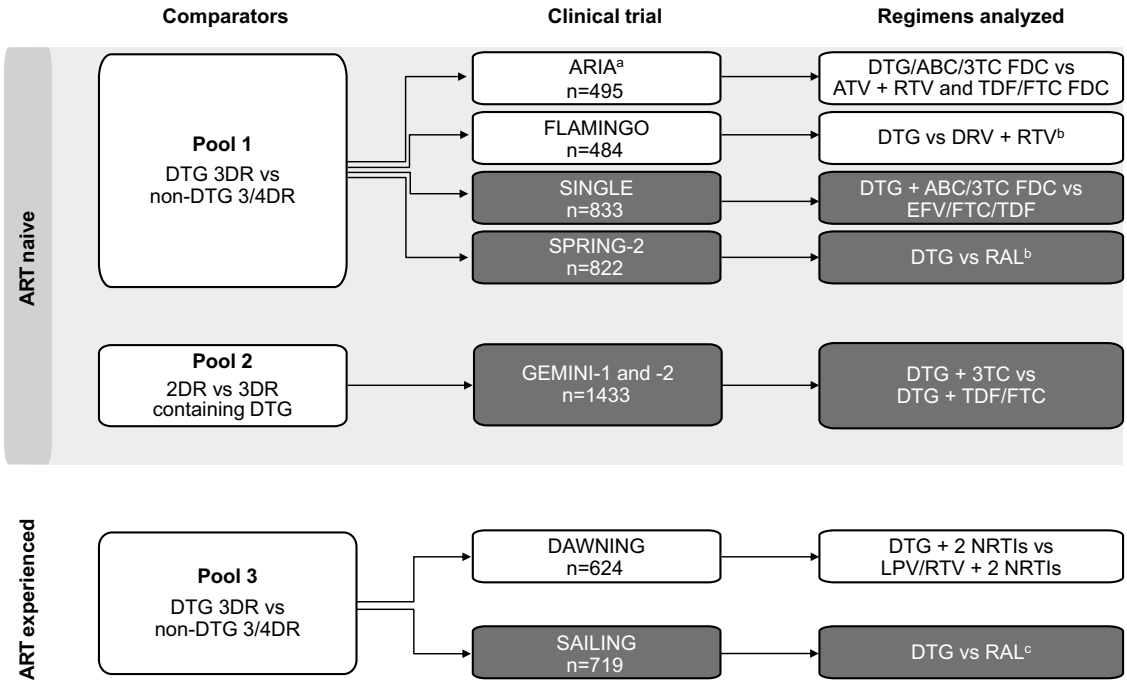


Figure 1. Summary of pools, comparisons, and included studies. Dark gray boxes indicate double-blind through week 48; white boxes indicate open-label through week 48. [a]Only female participants were included. [b]Both ART regimens included ABC/3TC or TDF/FTC. [c]Both treatment groups included an investigator-selected background regimen with ≥1 fully active agent with or without a second agent, with or without full activity. Abbreviations: 2DR, 2-drug regimen; 3DR, 3-drug regimen; 3/4DR, 3/4-drug regimen; 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

baseline plasma HIV-1 RNA, baseline CD4+ cell count, and age as covariates. There was an additional fixed-effect term in the combined trial analysis for study. Bayesian posterior probabilities of VS at week 48 for DTG relative to non-DTG were estimated using an independent noninformative prior [~N (0, 10 000)] and estimated using Markov Chain Monte Carlo simulations using the Gamerman method. Proportions of participants with VS were estimated using a fixed-effects meta-analysis inverse-variance weighted combination of individual study estimates; proportions were not calculated for the US and non-US subgroups of Pool 1, per pooled analysis protocol. A frequentist mixed-effect repeated-measures model was fitted to the change from baseline in CD4+ cell count to each study visit until week 48 for each study and for the pooled data with ART regimen (DTG vs non-DTG), visit, country (US vs non-US), race (Black vs non-Black), and sex (with the exception of ARIA, which included only female participants) as fixed effects; covariates included ART regimen-by-visit, ART regimen-by-subgroup, sub group-by-visit, and ART regimen-by-subgroup-by-visit interactions and $\log_{10}$ baseline plasma HIV-1 RNA, baseline CD4+ cell count, participant age, and study (combined study analysis only). Change from baseline in CD4+ cell count for the US and non-US subgroups was unavailable for all pooled analyses.

Safety analyses were performed using the safety population from each study: in DAWNING and GEMINI-1/-2, the safety population included all participants who received ≥1 dose of study medication and was analyzed according to actual ART received; in all other studies, participants who received a study treatment that differed from their assigned regimen were analyzed by treatment received for the majority of study participation.

Pooled demographics by race, sex, and region subgroups were summarized; week 48 baseline demographics for individual studies have been previously published [9–15]. Treatment comparisons were made within each study pool and limited to DTG vs non-DTG or 2DR DTG + 3TC vs 3DR DTG + TDF/FTC (Figure 1).

RESULTS

Participants

Of the 5406 unique participants included, 25% were Black, 27% were female, and 24% were based in the United States (Table 1).

Analysis by Antiretroviral Therapy

Antiretroviral therapy–naive participants were analyzed in Pool 1 (3DR DTG, n = 1315; 3/4DR non-DTG, n = 1319) and Pool 2 (2DR DTG + 3TC, n = 716; 3DR DTG + TDF/FTC, n = 717). Antiretroviral therapy–experienced participants with no prior INSTI use, including participants who failed first-line ART (DAWNING), were analyzed in the Pool 3 efficacy (3DR

Table 1. Baseline Demographics in Each Pooled Analysis

	Pool 1[a]			Pool 2[b]			Pool 3[c]		
	DTG n = 1315	Non-DTG n = 1319	Total n = 2634	DTG + 3TC n = 716	DTG + TDF/FTC n = 717	Total n = 1433	DTG n = 666	Non-DTG n = 673	Total n = 1339
Race									
Black	311 (24)	299 (23)	610 (23)	101 (14)	79 (11)	180 (13)	273 (41)	272 (40)	545 (41)
Non-Black	1004 (76)	1019 (77)	2023 (77)	615 (86)	638 (89)	1253 (87)	392 (59)	400 (59)	792 (59)
Sex									
Female	409 (31)	407 (31)	816 (31)	113 (16)	98 (14)	211 (15)	223 (33)	226 (34)	449 (34)
Male	906 (69)	912 (69)	1818 (69)	603 (84)	619 (86)	1222 (85)	443 (67)	447 (66)	890 (66)
Region									
US	398 (30)	406 (31)	804 (31)	129 (18)	119 (17)	248 (17)	109 (16)	118 (18)	227 (17)
Non-US	917 (70)	913 (69)	1830 (69)	587 (82)	598 (83)	1185 (83)	557 (84)	555 (82)	1112 (83)
Race/sex									
Black female	155 (12)	160 (12)	315 (12)	20 (3)	18 (3)	38 (3)	133 (20)	141 (21)	274 (20)
Non-Black female	254 (19)	247 (19)	501 (19)	93 (13)	80 (11)	173 (12)	89 (13)	85 (13)	174 (13)
Black male	156 (12)	139 (11)	295 (11)	81 (11)	61 (9)	142 (10)	140 (21)	131 (19)	271 (20)
Non-Black male	750 (57)	772 (59)	1522 (58)	522 (73)	558 (78)	1080 (75)	303 (45)	315 (47)	618 (46)
Race/region									
Black US	184 (14)	192 (15)	376 (14)	64 (9)	54 (8)	118 (8)	58 (9)	71 (11)	129 (10)
Non-Black US	214 (16)	213 (16)	427 (16)	65 (9)	65 (9)	130 (9)	51 (8)	47 (7)	98 (7)
Black non-US	127 (10)	107 (8)	234 (9)	37 (5)	25 (3)	62 (4)	215 (32)	201 (30)	416 (31)
Non-Black non-US	790 (60)	806 (61)	1596 (61)	550 (77)	573 (80)	1123 (78)	341 (51)	353 (52)	694 (52)
Sex/region									
Female US	102 (8)	116 (9)	218 (8)	17 (2)	14 (2)	31 (2)	30 (5)	33 (5)	63 (5)
Male US	296 (23)	290 (22)	586 (22)	112 (16)	105 (15)	217 (15)	97 (15)	85 (13)	182 (14)
Female non-US	307 (23)	291 (22)	598 (23)	96 (13)	84 (12)	180 (13)	193 (29)	193 (29)	386 (29)
Male non-US	610 (46)	622 (47)	1232 (47)	491 (69)	514 (72)	1005 (70)	364 (55)	362 (54)	726 (54)

Abbreviations: 3TC, lamivudine; DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

[a]Pool 1: Data are pooled from 4 studies: ARIA, FLAMINGO, SINGLE, and SPRING-2.

[b]Pool 2: Data are pooled from the GEMINI-1 and GEMINI-2 studies.

[c]Pool 3: Data are pooled from the DAWNING and SAILING studies; table lists efficacy population demographics, which are the same for the safety population, with the following exceptions (No. [%]): overall safety (DTG, n = 671; non-DTG, n = 672; total, n = 1343), Black (DTG, n = 273 [41]; non-DTG, n = 272 [40]; total, n = 545 [41]), non-Black (DTG, n = 397 [59]; non-DTG, n = 399 [59]; total, n = 796 [59]), male (DTG, n = 445 [66]; non-DTG, n = 447 [67]; total, n = 892 [66]), female (DTG, n = 226 [34]; non-DTG, n = 225 [33]; total, n = 451 [34]), non-US region (DTG, n = 562 [84]; non-DTG, n = 554 [82]; total, n = 1116 [83]).

DTG, n = 666; 3/4DR non-DTG, n = 673) and safety populations (3DR DTG, n = 671; 3/4DR non-DTG, n = 672).

In the overall analyses across study pools, high proportions of participants receiving 3DR DTG-based regimens or the 2DR DTG + 3TC achieved VS, consistent with previously published individual studies (Supplementary Figure 1A).

Adverse drug reactions were generally less frequent with DTG-based regimens or the 2DR DTG + 3TC compared with non-DTG-based regimens or the 3DR DTG + TDF/FTC, respectively (Supplementary Figure 1B). Overall safety was otherwise generally similar between treatment groups.

In each study pool, comparable increases from baseline to week 48 in CD4+ cell count were observed between treatment groups (Supplementary Figure 1C).

Analysis by Race: Black vs Non-Black Participants

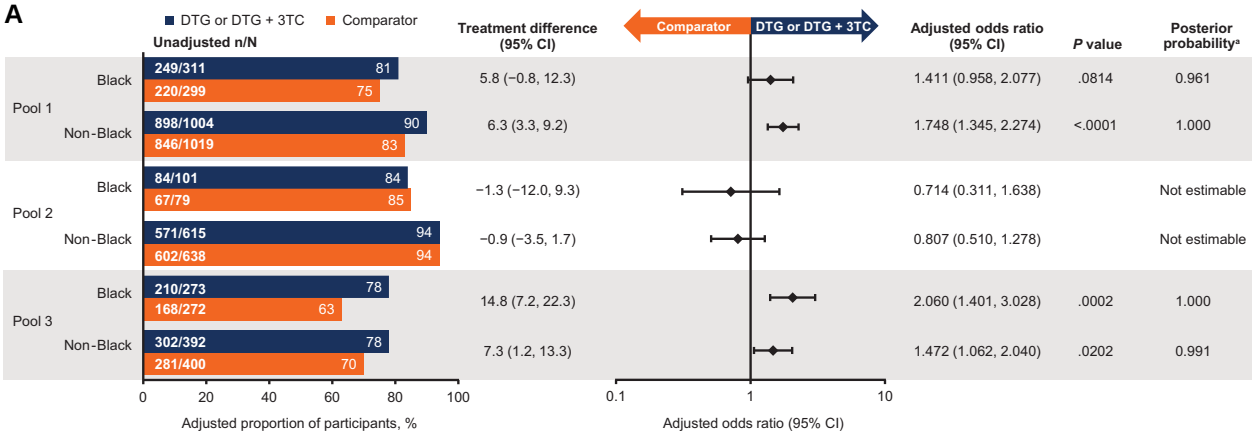
Among the ART-naive PWH in Pools 1 and 2, Black participants represented 23% and 13% of the population, respectively, and 41% of ART-experienced PWH in Pool 3 (efficacy and safety populations). Across pooled analyses, the adjusted proportions of participants with VS were lower for Black vs non-Black participants in both treatment groups in the ART-naive studies (Pools 1 and 2; Figure 2*A*).

Incidence of study withdrawals was higher in Black vs non-Black participants in ART-naive studies (Pools 1 and 2) and similar between race subgroups in the ART-experienced studies (Pool 3) (Figure 2*B*). Incidence of AEs leading to withdrawal and grade 3 or 4 AEs was similar between Black and non-Black participants.

Increases in CD4+ cell count from baseline were observed across all study pools and were similar by race subgroups (Figure 2*C*).

Analysis by Sex: Female vs Male Participants

Proportions of female participants varied across the 3 study pools, with 31% of ART-naive PWH in Pool 1 (ARIA exclusively enrolled female participants), 15% of ART-naive PWH in Pool 2, and 34% of ART-experienced PWH in Pool 3 (efficacy and safety populations). The proportion with VS at week 48 was generally lower or similar in female vs male participants across study pools (Figure 3*A*).



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	Study withdrawals		AEs leading to withdrawal		Adverse drug reactions		Grade 3 or 4 AEs	
Adjusted %[b]	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator
Pool 1								
Black	17	19	3	6	37	43	14	15
Non-Black	10	15	2	7	35	50	8	12
Pool 2								
Black	15	11	4	1	22	22	9	4
Non-Black	6	5	2	2	17	24	6	7
Pool 3								
Black	12	22	1	3	21	26	9	14
Non-Black	14	19	3	5	17	33	10	10

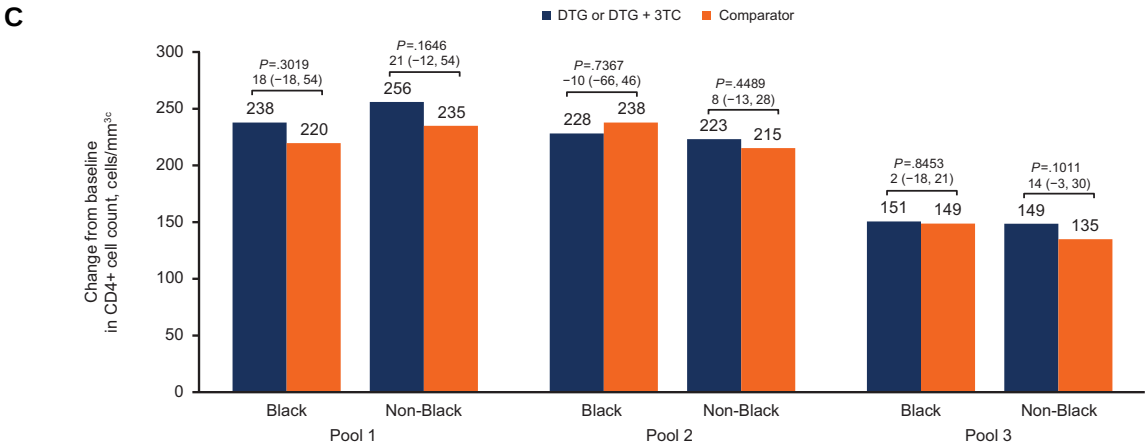
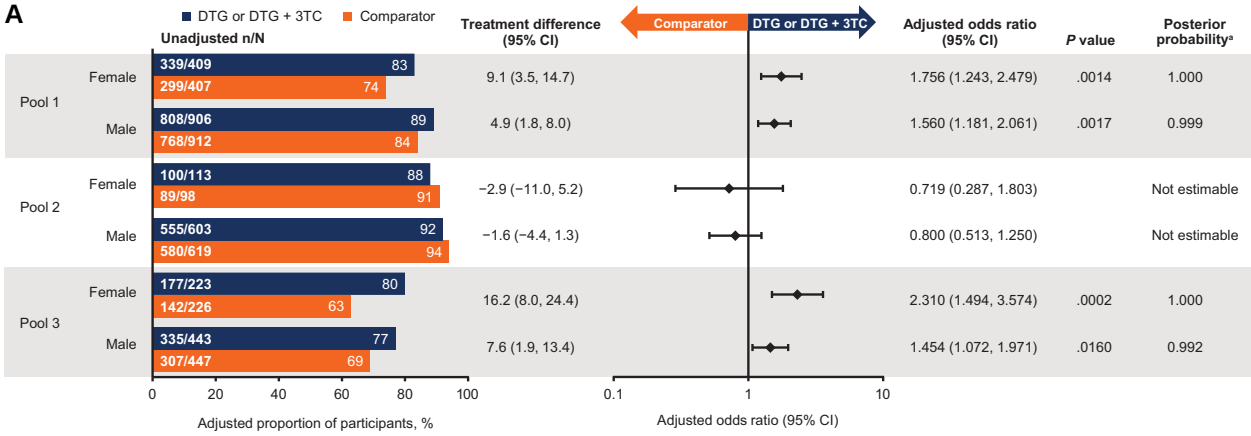


Figure 2. *A*, Proportion of participants with HIV-1 RNA <50 copies/mL, (*B*) safety summary, and (*C*) change from baseline in CD4+ cell count (cells/mm^3) by race across 3 study pools at week 48. Pools 1 and 3 compared DTG 3DR vs non-DTG 3/4DR regimens; Pool 2 compared the 2DR DTG + 3TC vs the 3DR DTG + TDF/FTC. [a]Posterior probability of HIV-1 RNA <50 copies/mL for DTG relative to non-DTG. Not estimable for Pool 2 as both treatment groups contained DTG. [b]Cochran-Mantel-Haenszel-corrected percentages are presented. [c]Treatment difference (95% CI) is shown above each subgroup. The study-level models included ART regimen (DTG vs non-DTG), visit, country (US vs non-US), race (Black vs non-Black), and sex (with the exception of ARIA, which included only female participants) as fixed effects; covariates included ART regimen-by-visit, ART regimen-by-subgroup, subgroup-by-visit, ART regimen-by-subgroup-by-visit interactions and $\log_{10}$ baseline plasma HIV-1 RNA, baseline CD4+ cell count, and participant age. Abbreviations: 2DR, 2-drug regimen; 3DR, 3-drug regimen; 3TC, lamivudine; AE, adverse event; ART, antiretroviral therapy; DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

The incidence of study withdrawals was generally higher in female vs male participants across study pools (Figure 3*B*). Safety profiles of female and male participants were comparable between treatment groups for AEs leading to withdrawal and grade 3 or 4 AEs, with frequency of adverse drug reactions generally being lower with 3DR DTG-based regimens or the 2DR DTG + 3TC compared with 3/4DR non-DTG-based regimens or 3DR DTG + TDF/FTC, respectively.

Similar increases from baseline in CD4+ cell count were observed between female and male subgroups in each pooled analysis (Figure 3*C*).



B

	Study withdrawals		AEs leading to withdrawal		Adverse drug reactions		Grade 3 or 4 AEs	
Adjusted %[b]	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator
Pool 1								
Female	16	24	4	7	36	47	11	17
Male	10	15	2	6	35	50	9	11
Pool 2								
Female	10	9	2	2	15	16	8	3
Male	7	6	2	2	18	25	6	7
Pool 3								
Female	11	24	1	5	20	27	7	11
Male	15	19	3	4	18	32	11	12

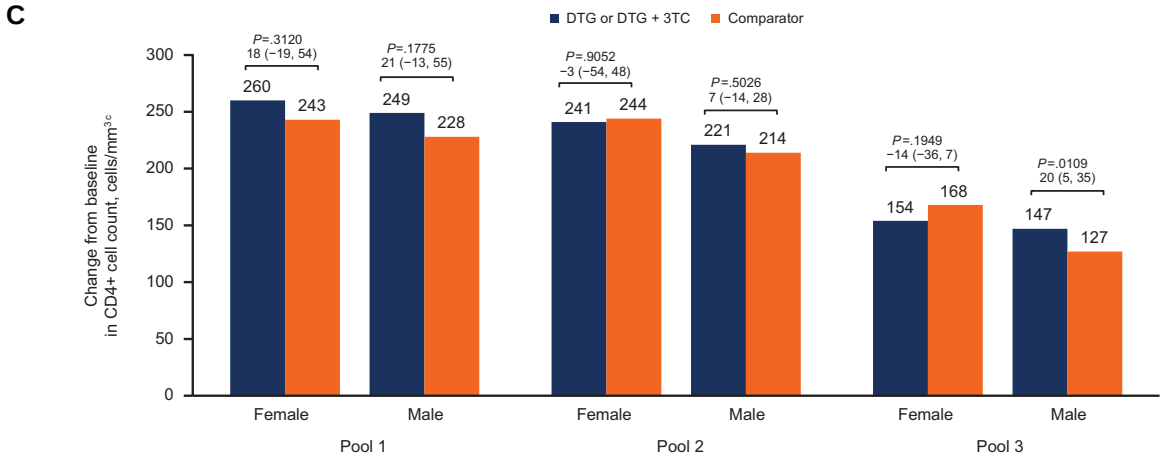
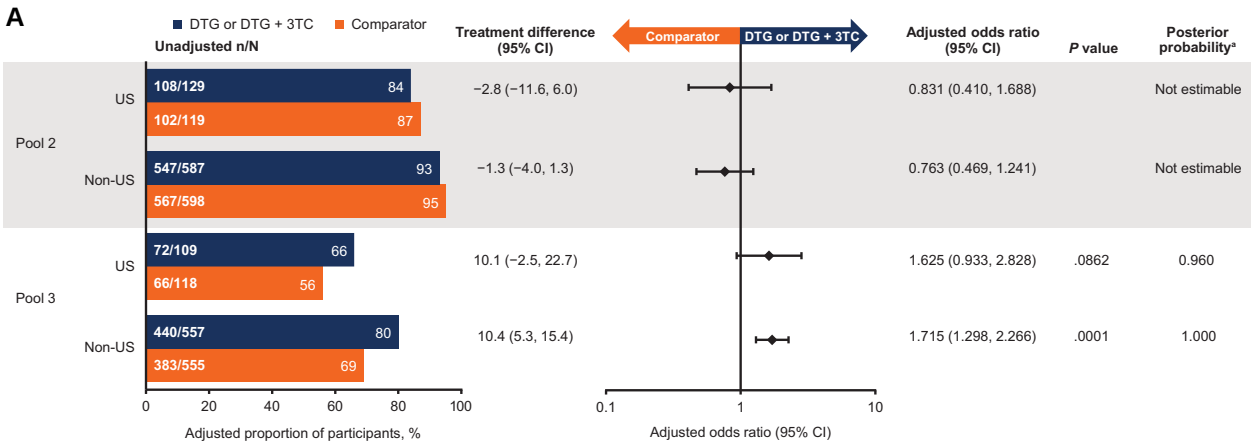


Figure 3. *A*, Proportion of participants with HIV-1 RNA <50 copies/mL, (*B*) safety summary, and (*C*) change from baseline in CD4+ cell count (cells/mm^3) by sex across 3 study pools at week 48. Pools 1 and 3 compared DTG 3DR vs non-DTG 3/4DR regimens; Pool 2 compared the 2DR DTG + 3TC vs the 3DR DTG + TDF/FTC; Pool 1 included 1 study with female participants only (ARIA). [a]Posterior probability of HIV-1 RNA <50 copies/mL for DTG relative to non-DTG. Not estimable for Pool 2 as both treatment groups contained DTG. [b]Cochran-Mantel-Haenszel-corrected percentages are presented. [c]Treatment difference (95% CI) is shown above each subgroup. The study-level models included ART regimen (DTG vs non-DTG), visit, country (US vs non-US), race (Black vs non-Black), and sex (with the exception of ARIA, which included only female participants) as fixed effects; covariates included ART regimen-by-visit, ART regimen-by-subgroup, subgroup-by-visit, ART regimen-by-subgroup-by-visit interactions and $\log_{10}$ baseline plasma HIV-1 RNA, baseline CD4+ cell count, and participant age. Abbreviations: 2DR, 2-drug regimen; 3DR, 3-drug regimen; 3TC, lamivudine; AE, adverse event; ART, antiretroviral therapy; DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

Analysis by Region: US vs Non-US Participants

Participants residing in the United States represented 31% and 17% of ART-naive PWH in Pools 1 and 2, respectively, and 17% of ART-experienced PWH in Pool 3 (DAWNING did not include US participants). Proportions of participants with VS at week 48 were lower in US vs non-US participants in Pools 2 and 3 (Figure 4*A*). Among US participants, VS was achieved in the DTG groups of Pools 1, 2, and 3 in 78.3%



B

	Study withdrawals		AEs leading to withdrawal		Adverse drug reactions		Grade 3 or 4 AEs	
Adjusted %[b]	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator	DTG or DTG + 3TC	Comparator
Pool 1								
US	16	19	4	5	42	54	15	15
Non-US	10	17	2	7	33	47	7	11
Pool 2								
US	13	12	<1	2	9	18	7	5
Non-US	6	5	2	2	19	24	6	7
Pool 3								
US	18	25	3	4	21	20	17	24
Non-US	12	19	2	5	18	32	8	9

Figure 4. *A*, Proportion of participants with HIV-1 RNA <50 copies/mL by region across 2 study pools and (*B*) safety summary by region across 3 study pools at week 48. Pools 1 and 3 compared DTG 3DR vs non-DTG 3/4DR regimens; Pool 2 compared the 2DR DTG + 3TC vs the 3DR DTG + TDF/FTC; Pool 3 included 1 study with no US participants (DAWNING). [a]Posterior probability of HIV-1 RNA <50 copies/mL for DTG relative to non-DTG. Not estimable for Pool 2 as both treatment groups contained DTG. [b]Cochran-Mantel-Haenszel-corrected percentages are presented. Abbreviations: 2DR, 2-drug regimen; 3DR, 3-drug regimen; 3TC, lamivudine; AE, adverse event; DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

(125/161), 86.1% (55/64), and 67.2% (39/58) of Black participants and in 89.2% (153/172), 83.1% (53/65), and 64.7% (33/51) of non-Black participants, respectively. In the non-DTG or 3-drug DTG groups of Pools 1, 2, and 3, VS was achieved in 75.5% (122/166), 79.9% (43/54), and 47.9% (34/71) of Black participants and in 83.5% (138/165), 92.2% (59/65), and 68.1% (32/47) of non-Black participants, respectively.

Incidence of study withdrawals was higher in the US vs non-US subgroups across all study pools (Figure 4*B*). Adverse event profiles were generally similar by regional subgroup, with more adverse drug reactions in the US vs non-US subgroups of Pool 1 and more grade 3 or 4 AEs in the US vs non-US subgroups of Pools 1 and 3.

DISCUSSION

Previously published data from individual RCTs evaluating DTG-containing regimens demonstrated noninferior or superior efficacy relative to comparator regimens in ART-naive and ART-experienced PWH, with similar efficacy results in subgroups based on race and sex [9–15]. Using multiple pooled analyses of RCT data, the present analysis confirmed the robust efficacy of DTG-based vs comparator regimens. However, unlike the individual studies, this pooled analysis revealed that the proportions of participants with Snapshot VS at week 48 were generally lower in Black (vs non-Black) participants and US (vs non-US) participants. Because all the analyzed clinical trials involved a DTG-containing regimen, this analysis is relevant to showing that the disparities in efficacy among these subpopulations persist even when using an ART regimen with a high barrier to resistance.

Across pooled analyses, there was an underrepresentation of Black (vs non-Black) and female (vs male) participants in the ITT-E populations. For RCT data to be applicable to clinical practice, site enrollment needs to better reflect the regional demographics and epidemiology of the intended populations. In the United States in 2019, 64% of HIV diagnoses among adults and adolescents were in 10 states, with the South accounting for nearly half of new HIV diagnoses [18, 19]. In 2019, Black people accounted for more people with HIV than any other racial group, with an estimated 479 300 (40%) of the 1.2 million PWH in the United States [19]. Black people also have the

highest rate of new HIV diagnosis, followed by Latinx people: in 2019, the rate of new HIV diagnoses per 100 000 for Black people (45.0) was ~8 times the rate in White people (5.3), and the rate for Hispanic/Latinx people (21.5) was ~4 times the rate in White people [19, 20]. Underrepresentation in US-based clinical trials can also negatively affect various aspects of patient care and outcomes [21]. This disparity in representation is not limited to the United States. Globally, Sub-Saharan Africa accounts for 60% of new HIV infections [22]. It should be noted that this pooled analysis did not analyze enrollment by geographic region. While the present analysis demonstrates that the United States has a clear disparity of enrollment to the country epidemic, in-country demography could be better aligned to trial enrollment in non-US regions, although analysis by individual country to geographic region was outside the scope of the study.

Regarding female vs male participants, this analysis suggests variability in VS based on ART exposure among participants who were viremic at baseline. The results in women were not convincingly worse than those in men beyond the ART-naive studies in Pool 1. Women represent 53% of all PWH worldwide [23], and complications of HIV or childbirth are the leading causes of death among women of reproductive age with HIV [23, 24]. Accurate representation of women can vary by geographic region. Women accounted for 63% of new HIV diagnoses in Sub-Saharan Africa in 2020, compared with 19% of new HIV diagnoses in the United States in 2018. However, Black women accounted for 55% of new HIV diagnoses among women with HIV in the United States, followed by White women (22%) and Hispanic/Latina women (18%) [19]. Multiregional studies enrolling women from different countries, like the ARIA study [13], are likely to be critical for addressing the shortage of data from women [25].

Another finding was a slightly higher proportion of study withdrawals among subgroups. However, the differences observed appear to be based more on DTG regimen vs comparator than between demographic groups. While the analysis shows that withdrawals due to AEs were low across subgroups, it did not assess withdrawals unrelated to study treatment or due to lack of efficacy or resistance. Moreover, rates of AEs leading to withdrawal were consistently low and similar across subgroups, minimizing the likelihood that safety contributed to study withdrawals. Although Black and female participants tended to have a higher incidence of study withdrawals, this was only seen consistently between US and non-US participants. Immune reconstitution was also consistently observed across treatment groups in the pooled analyses. These data support the efficacy and safety of DTG across race, sex, and regional subgroups in ART-naive and ART-experienced participants. Together, these data emphasize the need for expansion of site selection and the importance of recruitment to better our understanding of retention challenges within and between populations and to provide more accurate assessments of key therapeutic outcomes.

Fewer participants were included from clinical trial sites based in vs outside the United States. Of the ~37.7 million PWH estimated worldwide in 2020, 1.2 million were living in the United States, 3.7 million were living in Southeast Asia, and 25.4 million were living in African countries [20, 26]. Proportions of participants with VS were lower in US subgroups compared with non-US subgroups. Higher proportions of study withdrawals were observed in US vs non-US subgroups. In the future, it will be important to better identify and address the individual and structural barriers that contribute to clinical trial recruitment, participation, and withdrawal.

Due to greater US representation of participants relative to the global pandemic and more participant withdrawals from US sites, it will be important for future studies to better understand why VS, even within RCTs, is lower in the United States. A systematic review assessing minority participation in HIV medication or vaccine clinical trials in the United States found that while research efforts to understand the unique and important barriers to racial and ethnic minority participant enrollment (eg, HIV-related stigma) have been undertaken, few interventions have translated this knowledge into practice [27]. Several studies investigating barriers to minority participation in clinical trials have found that not being asked to participate in research by their health care providers was one of the primary reasons for not participating [21, 28–31], yet many were willing to participate if asked [28, 30, 32]. Having the research recommended by their primary health care provider or having the study visits at the same site as their medical care could facilitate clinical trial participation for PWH from racial and ethnic minority groups [32]. Potentially beneficial interventions could include training on the value of recruiting diverse populations, diversity in creating research teams, and designing culturally competent trials. Future clinical trials that involve community stakeholders throughout the research process and encourage culturally and linguistically appropriate recruitment and retention of populations disproportionately impacted by HIV could improve diversity in US trial enrollment [27]. Additionally, real-world studies in specific regions and demographic subgroups could help improve understanding of HIV outcomes in these populations. Together with diversifying enrollment in RCTs, research efforts could then help provide a more comprehensive understanding of broader populations of PWH.

There are several limitations to this analysis. Race and ethnicity data were not documented consistently across studies. For the Black subgroup, distinctions were not made between African American participants and those of African heritage, who may experience different sociocultural factors influencing RCT enrollment and retention. While a strength of this analysis (pooling of similar data from several phase 3 trials) was that it identified disparities by sex and race, it was not intended to

understand the cause of the disparities observed. Although it is important to consider social determinants of health to identify a root cause of lower efficacy, it is challenging to conduct such an analysis in a global study where the standard of living and quality of health care vary. However, future studies that explore the association between factors such as social vulnerability index and virologic suppression could help health care providers improve HIV treatment in underserved populations. Individual studies were not designed to detect statistical differences between subgroups of Black vs non-Black participants, or within Black female vs Black male participants, limiting our ability to draw comparisons in the pooled analysis as well. Another potential limitation is that this pooled analysis used data reported at week 48 because some studies were not followed beyond the primary end point (eg, ARIA, DAWNING), whereas other trials (eg, GEMINI studies) have published long-term results at weeks 96 and 144 [10, 33]. Week 48 represented the latest common time point for all analyses, and inclusion of a later time point would have potentially biased the results by excluding studies. Nonetheless, a pooled analysis allowed for a more precise analysis of efficacy by race, sex, and regional subgroups relative to individual longer-term studies with small subgroups, with subgroup differences observed within 1 year of treatment.

In conclusion, these pooled analyses confirm that DTG has robust efficacy and good safety at week 48 across diverse subgroups relative to comparator regimens. In addition, the present pooled analysis suggests that the proportion of participants achieving VS may vary by demographic characteristics, highlighting the urgent need to diversify RCT enrollment to reflect the populations of the study sites more accurately and those of their local or regional jurisdictions. As the ART landscape continues to evolve with INSTI-based ART being the guideline-recommended treatment option, addressing the existing challenges in clinical trial diversity will be critical to effectively translate results into clinical practice [8]. Future studies should strive to recruit participants from diverse racial, ethnic, sexual, regional, and cultural backgrounds and to support participants throughout the trial to ensure optimal representation, inclusion, and retention.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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