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MAJOR ARTICLE

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Background: Antiretroviral therapy (ART) that achieves virologic suppression using fewer antiretroviral agents is an optimized approach to HIV treatment initiation. VOGUE is the first randomized, head-to-head study comparing the 2-drug regimen dolutegravir/lamivudine (DTG/3TC) with the 3-drug regimen bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) as initial ART, including among individuals with high viral loads (VLs) and/or low CD4+ cell counts.

Methods: This phase 3b, randomized (1:1), open-label, non-inferiority study compared DTG/3TC vs BIC/FTC/TAF as first-line ART in adults with HIV-1. Participants were enrolled without baseline VL or CD4+ cell count restrictions and initiated treatment before availability of resistance testing results. The primary endpoint was the proportion of participants with HIV-1 RNA <50 copies/mL at Week 48 (Snapshot; -10% non-inferiority margin).

Results: Among 509 randomized participants (DTG/3TC, n=254; BIC/FTC/TAF, n=255), 47% had baseline VL ≥100,000 copies/mL and 16% had CD4+ cell count <200 cells/mm^3. At Week 48, DTG/3TC demonstrated non-inferior efficacy to BIC/FTC/TAF, with HIV-1 RNA <50 copies/mL achieved in 89% and 92% of participants, respectively (adjusted difference, -3% [95% CI, -8%, 2%]). Median time to virologic suppression was rapid (4.1 weeks) in both groups. Confirmed virologic withdrawals were similar between groups (n=7 each), with no treatment-emergent resistance identified. Safety outcomes were comparable.

Conclusions: Dolutegravir/Lamivudine demonstrated non-inferior efficacy to BIC/FTC/TAF as initial ART, with no treatment-emergent resistance through Week 48. These findings establish DTG/3TC as an effective and simplified initial ART regimen across a broad clinical spectrum.

Clinical trial registration: ClinicalTrials.gov identification number, NCT05979311; URL, https://clinicaltrials.gov/study/NCT05979311

Keywords: antiretroviral therapy; baseline viral load; BIC/FTC/TAF; DTG/3TC; HIV-1; non-inferiority trial; treatment naive; virologic suppression

INTRODUCTION

Treatment guidelines recommend second-generation integrase strand transfer inhibitor (INSTI)-based regimens as the foundation of first-line antiretroviral therapy (ART) because of their demonstrated efficacy, potency, tolerability, and high barrier to resistance [1-4]. Widespread use

of INSTI-based therapy has transformed HIV management, enabling rapid and durable virologic suppression in most individuals initiating treatment [2,5-7]. As a result, treatment decisions at ART initiation increasingly extend beyond virologic efficacy and incorporate considerations such as cumulative antiretroviral exposure, long-term tolerability, drug–drug interaction profiles, and regimen simplicity [8]. Recent advances in HIV treatment have focused on approaches that reduce antiretroviral exposure while achieving or maintaining virologic efficacy [8-14]. Current and emerging therapies reflect a shift toward 2-drug regimens (2DRs) from historical 3- or 4-drug regimens (3DRs/4DRs) [10-15].

As the first and only 2DR indicated for HIV treatment initiation [10], dolutegravir/lamivudine (DTG/3TC) is a guideline-recommended oral 2DR supported by randomized clinical trials and real-world evidence [2-5,16-28]. These data demonstrate that DTG/3TC provides durable virologic suppression, has a high barrier to resistance, and is generally well tolerated [5,16-28], with comparable efficacy to 3DRs or 4DRs consistently shown in randomized trials [5,16-24]. This substantial evidence base from clinical trials, supplemented by data from studies conducted in real-world settings cumulatively including >75,000 people with HIV [29-34], establishes DTG/3TC as the most extensively studied oral 2DR, including in adults initiating ART [5,16-19,35,36].

People with HIV initiating ART present with substantial heterogeneity at diagnosis, including variations in viral load (VL), immune status, and disease stage [37,38]. This variability underscores the need to evaluate ART regimens across the range of clinical presentations encountered at treatment initiation. Pharmacologic robustness and regimen durability are essential at treatment initiation, including in a test-and-treat approach in which treatment may be started as soon as possible after diagnosis, before complete baseline resistance or laboratory data are available [3,39]. Despite the established efficacy of INSTI-based regimens, direct comparative data between INSTI-based therapies to inform regimen selection at ART initiation remain limited. In particular, no randomized controlled trial has directly compared the 2DR DTG/3TC with the 3DR bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) as first-line therapy. The phase 3b VOGUE study was therefore designed as the first randomized, head-to-head trial comparing the efficacy and safety of DTG/3TC with BIC/FTC/TAF as initial ART in adults with HIV-1. By enrolling a clinically diverse population without baseline VL or CD4+ cell count restrictions and who initiated treatment before availability of genotypic resistance results, VOGUE provides a robust comparative evaluation of 2-drug DTG/3TC vs 3-drug BIC/FTC/TAF in a setting representative of routine HIV care.

METHODS

Study design and participants

VOGUE (ClinicalTrials.gov, NCT05979311) is an ongoing phase 3b, randomized, open-label, multicenter, non-inferiority study evaluating the efficacy and safety of DTG/3TC compared with BIC/FTC/TAF as first-line ART in adults with HIV-1 (Supplemental Figure 1). This study was conducted in 17 countries across 4 continents.

People with HIV-1 aged ≥18 years who were naive to ART were eligible for enrollment. After a screening period of up to 14 days, participants were randomized 1:1 to initiate once-daily oral, single-tablet DTG/3TC or BIC/FTC/TAF at Day 1 (baseline). Genotypic resistance testing was performed at screening, but randomization and treatment initiation occurred before resistance results were available. Resistance-associated mutations (RAMs) at screening were reviewed once results became available (approximately Week 4). Participants with major RAMs to INSTIs, 3TC, FTC, or TAF as defined by the International Antiviral Society–USA were required to discontinue study treatment (Supplemental Methods) [40].

Participants with immunity to hepatitis B virus (HBV), including those with isolated hepatitis B core antibody (HBcAb) positivity without detectable HBV DNA, were not excluded. Key exclusion criteria included active HBV infection and Centers for Disease Control and Prevention stage 3 HIV disease (except cutaneous Kaposi's sarcoma not requiring systemic therapy and CD4+ cell count <200 cells/mm^3). Participants of childbearing potential were counseled on the benefits and risks of contraception. Individuals who became pregnant during the study could continue study treatment if virologic suppression was maintained.

Randomization was stratified by plasma HIV-1 RNA (<100,000 vs ≥100,000 copies/mL) and CD4+ cell count (<200 vs ≥200 cells/mm^3) at screening. Plasma HIV-1 RNA and CD4+ cell count were assessed at screening, baseline, every 4 weeks through Week 12, and every 12 weeks thereafter through Week 96.

Study outcomes

The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 per the US Food and Drug Administration Snapshot algorithm. Secondary endpoints included time to virologic suppression (first HIV-1 RNA measurement <50 copies/mL), the proportion of participants with HIV-1 RNA ≥50 copies/mL (Snapshot) at Week 48, and change from baseline in CD4+ cell count through Week 48. Additional secondary endpoints included the proportion of participants meeting confirmed virologic withdrawal (CVW) criteria and assessment of treatment-emergent resistance in participants meeting CVW criteria. Exploratory endpoints at Week 48 included the proportion of participants with HIV-1 RNA <200 copies/mL (Snapshot) and proportions of participants with HIV-1 RNA <50 copies/mL (Snapshot) by baseline VL strata (<100,000 vs ≥100,000 copies/mL) and CD4+ cell count strata (<200 vs ≥200 cells/mm^3).

Confirmed virologic withdrawal was defined as 2 consecutive plasma HIV-1 RNA measurements meeting protocol-defined criteria for either virologic non-response or virologic rebound. Virologic non-response was defined as any of the following: (1) confirmed HIV-1 RNA decrease of <2.0 $\log_{10}$ copies/mL at Week 8, unless HIV-1 RNA was <200 copies/mL; (2) confirmed HIV-1 RNA ≥1000 copies/mL at Week 12; or (3) HIV-1 RNA ≥200 copies/mL on or after Week 24. Virologic rebound was defined as confirmed HIV-1 RNA ≥200 copies/mL after prior suppression to <200 copies/mL. Participants meeting CVW criteria were required to discontinue the study. Baseline and virologic withdrawal samples (including available suspected virologic withdrawal and/or confirmatory samples meeting HIV-1 RNA thresholds ≥200 copies/mL) were analyzed for resistance using next-generation sequencing by Cerba Laboratory (Frépillon, France; 3% detection threshold) for participants in the European Union or Monogram Biosciences (South San Francisco, CA, USA; 10% detection threshold) for participants outside of the European Union. The numbers of samples tested, successfully analyzed, and not evaluable due to low VL or assay constraints are reported.

Safety endpoints included the incidence and severity of adverse events (AEs), including drug-related AEs, serious AEs (SAEs), and AEs leading to study treatment discontinuation or withdrawal. A key secondary anthropometric endpoint included change from baseline in weight at Week 48.

HIV-1 RNA quantification

Plasma HIV-1 RNA for participant management during the study, including assessment of CVW, was measured using the Roche cobas 6800 HIV-1 assay (Roche Diagnostics, Indianapolis, IN, USA), reflecting its increasing adoption in clinical practice and research settings for VL monitoring. Given known assay-related variability at low VL thresholds [41], primary efficacy analyses, including Week 48 Snapshot outcomes and time to virologic suppression, were conducted on stored plasma samples at the central laboratory using the Abbott RealTi*m*e HIV-1 assay (Abbott Molecular Diagnostics, Des Plaines, IL, USA). Use of the Abbott RealTi*m*e assay was aligned with prior DTG/3TC clinical trials [5,20,22] and ensured consistency in efficacy assessment across the clinical development program. If an Abbott RealTi*m*e result was not available within the analysis window, the corresponding Roche cobas 6800 result was used. All analyses were conducted according to the prespecified statistical analysis plan.

Statistical analyses

A sample size of 254 participants per treatment group was estimated to provide 90% power to detect non-inferiority using a -10% non-inferiority margin and 2.5% 1-sided significance level, assuming an 86% response rate for both treatment groups.

All randomized participants who received ≥1 dose of study treatment were included in efficacy and safety analyses. The adjusted difference in Week 48 response rate between treatment groups (DTG/3TC − BIC/FTC/TAF) and associated 95% CIs were estimated using a Cochran-Mantel-

Haenszel method across 4 strata defined by baseline plasma HIV-1 RNA (<100,000 vs ≥100,000 copies/mL) and baseline CD4+ cell count (<200 vs ≥200 cells/mm^3).

Time to virologic suppression, defined as the first plasma HIV-1 RNA measurement <50 copies/mL, was analyzed using Kaplan-Meier methods, with 2-sided 95% CIs calculated using the Brookmeyer-Crowley method. Treatment differences in achieving virologic suppression were evaluated using an adjusted Cox proportional-hazards model, with treatment as a covariate and stratification across 4 strata defined by baseline plasma HIV-1 RNA (<100,000 vs ≥100,000 copies/mL) and baseline CD4+ cell count (<200 vs ≥200 cells/mm^3); an adjusted hazard ratio, 2-sided 95% CI, and *P* value were estimated. Week 48 response rate by baseline VL and CD4+ cell count strata was analyzed using Bayesian shrinkage estimates and 2-sided 95% credible intervals to assess treatment differences [42]. Analyses for change from baseline in CD4+ cell count and weight are described in the Supplemental Methods.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 29.0) and graded according to the Division of AIDS table (version 2.1). Adverse events were summarized descriptively from baseline to the Week 48 analysis data cutoff (May 11, 2026).

Ethics and patient consent statement

The study was conducted in accordance with International Council for Harmonisation Good Clinical Practice guidelines, applicable laws and regulations, and the ethical principles outlined in the Declaration of Helsinki. The protocol design was reviewed by volunteer representatives from the European AIDS Treatment Group. Feedback received and incorporated into the protocol included expansion of preventative measure examples in the Sexual Health section; encouragement of sites to consider gender in screening strategies to achieve women and transgender enrollment targets; and modifications to metabolic health, health outcomes, and implementation science assessments. The protocol and amendments were approved by institutional review boards or ethics committees at each participating site. All participants provided written informed consent before any study-specific procedures were performed.

RESULTS

Participants

Between February 9, 2024, and April 3, 2025, 548 individuals were screened and 509 were randomized to receive DTG/3TC (n=254) or BIC/FTC/TAF (n=255; Supplemental Figure 2). Demographics and baseline characteristics were balanced between treatment groups (Table 1). Overall, median (range) age was 33 (18, 84) years, 16% of participants were assigned female sex at birth, 16% identified as non-White, and 39% were of Hispanic or Latino ethnicity. At baseline, 47% of participants had HIV-1 RNA ≥100,000 copies/mL and 16% had CD4+ cell count <200 cells/mm^3.

RAMs were present in 1% (5/548) of screened individuals based on resistance testing results available at approximately Week 4. Among these, 2 individuals failed screening for other reasons (Supplemental Figure 2) and 3 were randomized and initiated treatment. Two participants (1 per treatment group) with baseline M184V achieved HIV-1 RNA <50 copies/mL at Week 4 and discontinued study treatment per protocol. One participant in the BIC/FTC/TAF group with isolated V75I at very low frequency (5.1%) at baseline achieved HIV-1 RNA <50 copies/mL at Week 4 and continued on study. Overall, 0.4% (2/548) of individuals were excluded due to active HBV infection at screening. Among individuals screened, 3% (14/548) had isolated HBcAb positivity (without detectable HBV DNA) and 13% (71/548) had resolved HBV infection (positive for HBcAb and hepatitis B surface antibody and negative for hepatitis B surface antigen). The median (IQR) time from screening to treatment initiation was 10 (8, 14) days.

Efficacy

For the primary analysis at Week 48, DTG/3TC demonstrated non-inferior efficacy to BIC/FTC/TAF, with HIV-1 RNA <50 copies/mL achieved in 89% of participants receiving DTG/3TC and 92% receiving BIC/FTC/TAF (adjusted difference, -3% [95% CI, -8%, 2%]; Figure 1A; Supplemental Table). Most participants with HIV-1 RNA ≥50 copies/mL at Week 48 had previously achieved virologic suppression <50 copies/mL and had a transient VL elevation between 50 and 200 copies/mL. Among participants with HIV-1 RNA ≥50 copies/mL at Week 48, in-window HIV-1 RNA values were <200 copies/mL in most (13/16) participants receiving DTG/3TC and 3 of 8 participants receiving BIC/FTC/TAF. Most (14/16) participants receiving DTG/3TC and 3 of 8 participants receiving BIC/FTC/TAF continued on study after Week 48. Rates of HIV-1 RNA <200 copies/mL were high and comparable between treatment groups at Week 48 (DTG/3TC, 94%; BIC/FTC/TAF, 93%), meeting the non-inferior efficacy threshold (adjusted difference, 1% [95% CI, -4%, 5%]; Figure 1B; Supplemental Table). At Week 48, DTG/3TC demonstrated non-inferior efficacy to BIC/FTC/TAF regardless of the assay used (Abbott RealTi*m*e or Roche cobas 6800; Supplemental Figure 3).

Median time to virologic suppression was rapid in both treatment groups (DTG/3TC, 4.1 [95% CI, 4.1, 4.1] weeks; BIC/FTC/TAF, 4.1 [95% CI, 4.1, 4.3] weeks; Figure 2). The adjusted hazard ratio was 1.23 (95% CI, 1.03, 1.47; *P*=0.0357), indicating participants receiving DTG/3TC had a 23% higher hazard of achieving virologic suppression than those receiving BIC/FTC/TAF. Increases in CD4+ cell count at Week 48 were comparable, with adjusted mean (SE) change from baseline values of 232 (13) cells/mm^3 for DTG/3TC and 236 (13) cells/mm^3 for BIC/FTC/TAF.

Week 48 Snapshot response rates were similar between treatment groups within baseline VL strata (Figure 3). Among participants with baseline VL <100,000 copies/mL, 93% (119/128) receiving DTG/3TC and 94% (134/142) receiving BIC/FTC/TAF achieved HIV-1 RNA <50 copies/mL (shrinkage estimate of difference, -1.9% [95% credible interval, -7.7%, 4.0%]). Virologic suppression rates among participants with baseline VL ≥100,000 copies/mL were also comparable in both treatment groups, with 85% (107/126) of participants receiving DTG/3TC and 89%

(101/113) receiving BIC/FTC/TAF achieving HIV-1 RNA <50 copies/mL (shrinkage estimate of difference, -3.5% [95% credible interval, -11.2%, 3.6%]). Week 48 Snapshot response rates were also generally similar between treatment groups across baseline VL and CD4+ cell count strata regardless of the assay used (Figure 3; Supplemental Figure 4).

By Week 48, the frequency of CVW was similar between treatment groups, with 3% (n=7) of participants receiving DTG/3TC and 3% (n=7) receiving BIC/FTC/TAF meeting protocol-defined CVW criteria. Among 14 participants meeting CVW criteria, resistance data were obtained for 6 individuals (DTG/3TC, n=2; BIC/FTC/TAF, n=4), and no treatment-emergent resistance to INSTIs or nucleoside reverse transcriptase inhibitors (NRTIs) was identified. For the remaining 8 participants (DTG/3TC, n=5; BIC/FTC/TAF, n=3), resistance testing at virologic withdrawal failed due to VL of samples being below the assay cutoff.

Safety

Safety outcomes through the Week 48 data cutoff were comparable between treatment groups (Table 2). The overall incidence of AEs was similar between DTG/3TC and BIC/FTC/TAF, including drug-related AEs, SAEs, and AEs leading to study treatment discontinuation or withdrawal. Serious AEs were reported in 9% of participants receiving DTG/3TC and 8% receiving BIC/FTC/TAF; none were considered drug related, and no fatal SAEs were reported. Adverse events leading to study treatment discontinuation or withdrawal were uncommon, with drug-related treatment discontinuations reported in no participants in the DTG/3TC group and 2 participants in the BIC/FTC/TAF group. Six participants became pregnant during the study (DTG/3TC, n=5; BIC/FTC/TAF, n=1); 5 of those continued on study and 1 receiving DTG/3TC withdrew after Week 48 with HIV-1 RNA <200 copies/mL. No new HBV infections or reactivations were observed. No new safety signals were identified.

At Week 48, adjusted mean (SE) change in weight from baseline was +3.6 (0.5) kg for DTG/3TC and +4.0 (0.5) kg for BIC/FTC/TAF. Proportions of participants with a ≥10% increase in weight from baseline were 19% (45/240) for DTG/3TC and 21% (50/238) for BIC/FTC/TAF.

DISCUSSION

Dolutegravir/Lamivudine offers a simplified approach to initial ART that reduces third-agent exposure while preserving virologic efficacy [5,8,23]. VOGUE is the first randomized, head-to-head study comparing the 2DR DTG/3TC and the 3DR BIC/FTC/TAF in individuals initiating ART. In a broad population with no baseline VL or CD4+ cell count restrictions who initiated therapy before availability of genotypic resistance results, DTG/3TC demonstrated non-inferior efficacy at Week 48 compared with BIC/FTC/TAF and was associated with rapid virologic suppression. Rates of CVW were comparable between treatment groups, with no treatment-emergent resistance identified in participants with available resistance data. Together, these

findings provide direct comparative evidence for 2 guideline-recommended, INSTI-based therapies at treatment initiation.

The non-restrictive enrollment criteria in VOGUE enabled inclusion of populations frequently encountered in routine clinical practice, with nearly half of enrolled participants having high baseline VL ≥100,000 copies/mL. Rapid virologic suppression was achieved in VOGUE, with a median time to suppression of 4.1 weeks in both treatment groups. The adjusted Cox proportional-hazards analysis indicated that participants receiving DTG/3TC had a 23% higher hazard of achieving virologic suppression than those receiving BIC/FTC/TAF (adjusted hazard ratio, 1.23 [95% CI, 1.03, 1.47]; *P*=0.0357). Rapid virologic suppression was also achieved in a comparable population in the STAT test-and-treat study (median of 5 weeks) [35], demonstrating the potency of DTG/3TC, including in participants with high VLs. Among participants with high baseline VL ≥100,000 copies/mL, DTG/3TC demonstrated high virologic response rates that were comparable to those observed with BIC/FTC/TAF. These results from VOGUE reinforce those from the DOLCE study and a meta-analysis of 5 DTG/3TC clinical trials showing high and comparable virologic response rates in individuals with high baseline VL and low CD4+ cell count receiving DTG/3TC as first-line ART [19,43]. These findings support the consistency of DTG/3TC efficacy across clinically relevant baseline characteristics commonly encountered in routine care.

In VOGUE, DTG/3TC was initiated before the availability of resistance testing results, a clinical setting in which some major treatment guidelines have recommended a more conservative approach [2,3]. A low prevalence of RAMs to INSTIs and NRTIs was observed in screening resistance testing samples (0.9%), consistent with the reported rates of transmitted drug resistance to INSTIs and NRTIs in regions where VOGUE was primarily conducted [44,45]. Of note, M184V was also infrequent (0.7%), reflecting the generally low prevalence of transmitted M184V [44]. The participant who initiated DTG/3TC treatment before baseline M184V was identified achieved virologic suppression without development of additional RAMs to INSTIs or NRTIs prior to discontinuation. Screening failure due to active HBV infection was uncommon (0.4%), although HBV prevalence varies considerably by region and population [46]. Active HBV infection was an exclusion criterion in VOGUE, whereas participants with isolated HBcAb positivity without detectable HBV DNA were eligible for enrollment. No new HBV infections or reactivations were observed through Week 48, consistent with prior DTG/3TC studies that included participants with isolated reactive HBcAb [47]; ongoing follow-up will continue through Week 96 in the VOGUE study. Although DTG/3TC is not recommended for individuals with known HIV/HBV coinfection without an additional HBV-active agent [2-4,10], the STAT study allowed DTG/3TC initiation before availability of HBV serology results [36]. In STAT, therapy modification after interpreting HBV serology results did not impact maintenance of virologic suppression or compromise future HBV therapy options.

Safety outcomes through Week 48 were comparable between DTG/3TC and BIC/FTC/TAF and were consistent with the established safety profiles of each regimen [5-7]. No new safety signals were identified. Increases from baseline in weight were observed in both treatment groups at Week

48, most likely representing a "return to health" in this population of people with HIV naive to ART [48]. Ongoing follow-up through Week 96 will further characterize long-term weight changes, as well as durability and safety of DTG/3TC in this setting.

Some limitations should be considered when interpreting these findings. The open-label study design could potentially influence AE reporting. The study population included relatively low proportions of participants who were assigned female sex at birth or identified as non-White; however, the findings are supported by an extensive body of randomized clinical trial and real-world evidence evaluating DTG/3TC across broad and diverse populations of people with HIV. In addition, the study was not powered to demonstrate non-inferiority within baseline VL and CD4+ cell count strata. However, the inclusion of participants with high baseline VLs and/or low CD4+ cell counts, populations often underrepresented in or excluded from clinical trials [49], represents a key strength and enhances the clinical relevance of the results. A further consideration is that participant management and primary efficacy analyses relied on different VL assays, with Roche cobas 6800 used for on-study monitoring and Abbott RealTi*m*e prioritized for efficacy analyses. Although this dual-assay strategy introduced some variability, particularly in the setting of low-level viremia where assay-related differences are most likely to occur [41,50], it did not alter interpretation of the efficacy results. Clinicians should consider these assay-specific characteristics when interpreting low-level VL measurements in the context of adherence and clinical history.

CONCLUSIONS

In VOGUE, once-daily oral DTG/3TC demonstrated non-inferior efficacy to BIC/FTC/TAF as initial ART in adults with HIV-1. Dolutegravir/Lamivudine was associated with rapid virologic suppression, was generally well tolerated, and demonstrated a high barrier to resistance, with no treatment-emergent resistance identified through Week 48. VOGUE enrolled a broad population of adults initiating ART with no baseline VL or CD4+ cell count restrictions. These findings provide the first randomized, head-to-head evidence comparing DTG/3TC with BIC/FTC/TAF in the initial treatment setting and support DTG/3TC as a simplified, extensively studied, guideline-recommended, 2-drug, INSTI-based option for adults starting ART, for whom durable virologic suppression, regimen simplicity, and cumulative antiretroviral exposure are important considerations.

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Data availability: Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Patient consent statement: All participants provided written informed consent before study initiation.

Potential conflicts of interest: JG has received honoraria from Gilead Sciences, GSK, MSD, and ViiV Healthcare outside of this work. FP has served as a consultant to and received speakers' fees from Gilead Sciences, Janssen Pharmaceutica, MSD, and ViiV Healthcare. GDL has served as a consultant to, received honoraria from, and participated in data safety monitoring/advisory boards for Gilead Sciences and GSK and has received travel/meeting support from Gilead Sciences. AO has received honoraria and travel/meeting support from Gilead Sciences, GSK, and MSD and has participated in data safety monitoring/advisory boards for Gilead Sciences and GSK. DR has received consulting fees and travel/meeting support from Gilead Sciences, Merck, and ViiV Healthcare; has received honoraria from Gilead Sciences and ViiV Healthcare; and has participated in data safety monitoring/advisory boards for Gilead Sciences. CM has received research grants, honoraria, and travel/meeting support from and has participated in advisory boards for Gilead Sciences and ViiV Healthcare and has served as principal investigator for and received institutional fees from GSK for this work. OPC, MJMV, SM, and DE have no conflicts of interest to disclose. HS has received research grants, consulting fees, or honoraria from and has participated in advisory boards for Dr. Reddy's Laboratories, Gilead Sciences, MSD, and ViiV Healthcare; has served as CEO of EPIMED; and has served as a member of the Akademie für Infektionsmedizin, DAGNÄ, and Deutsche Gesellschaft für Infektiologie. HG has received honoraria from Gilead Sciences, MSD, and ViiV Healthcare. GW has received travel and research grants from and has served as an advisor/speaker for Gilead Sciences, GSK, and ViiV Healthcare. JIMG has received consulting fees, honoraria, payment for expert testimony, and travel/meeting support from and has participated in data safety monitoring/advisory boards for Gilead Sciences and ViiV Healthcare. PM, KW, RG, RW, AJ, KS, EE, RM, RB, BJ, MK, PB, and JvW are employees of ViiV Healthcare or GSK and may own stock in GSK.

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Table 1. Demographics and Baseline Characteristics

Parameter	DTG/3TC (n=254)	BIC/FTC/TAF (n=255)	Total (N=509)
Sex assigned at birth, n (%)			
Female	41 (16)	38 (15)	79 (16)
Male	213 (84)	217 (85)	430 (84)
Gender (self-identified), n (%)			
Cisgender man	207 (81)	211 (83)	418 (82)
Cisgender woman	41 (16)	38 (15)	79 (16)
Transgender woman	5 (2)	6 (2)	11 (2)
Nonbinary	1 (<1)	0	1 (<1)
Age, median (range), y	33 (18, 73)	33 (18, 84)	33 (18, 84)
≥50 y, n (%)	39 (15)	47 (18)	86 (17)
Race (self-reported), n (%)			
White	211 (83)	212 (83)	423 (83)
Black or African American	24 (9)	20 (8)	44 (9)
Asian	14 (6)	12 (5)	26 (5)
Native Hawaiian or other Pacific Islander	3 (1)	5 (2)	8 (2)
American Indian or Alaska Native	1 (<1)	4 (2)	5 (<1)
Unknown[a]	1 (<1)	2 (<1)	3 (<1)
Ethnicity (self-reported), n (%)			
Hispanic or Latino	100 (39)	97 (38)	197 (39)
Not Hispanic or Latino	149 (59)	151 (59)	300 (59)
Not reported/Unknown[a]	5 (2)	7 (3)	12 (2)
Region, n (%)			
Europe	191 (75)	195 (76)	386 (76)

Latin America	43 (17)	42 (16)	85 (17)
Asia	20 (8)	18 (7)	38 (7)
Plasma HIV-1 RNA, median (range), copies/mL	95,250 (13, 3,640,000)	83,200 (13, 6,000,001[b])	87,400 (13, 6,000,001[b])
≥100,000 copies/mL, n (%)	126 (50)	113 (44)	239 (47)
≥500,000 copies/mL, n (%)	45 (18)	38 (15)	83 (16)
≥1,000,000 copies/mL, n (%)	22 (9)	21 (8)	43 (8)
CD4+ cell count, median (range), cells/mm^3	375 (19, 1377)	372 (19, 1296)	373 (19, 1377)
<200 cells/mm^3, n (%)	40 (16)	39 (15)	79 (16)
<100 cells/mm^3, n (%)	17 (7)	16 (6)	33 (6)
CDC HIV-1 classification, n (%)			
Stage 0-2	217 (85)	218 (85)	435 (85)
Stage 3	37 (15)	37 (15)	74 (15)
Weight, median (range), kg	72.0 (42.5, 122.2)	72.0 (41.0, 111.0)	72.0 (41.0, 122.2)
BMI, median (range), kg/m^2	24.0 (16.8, 41.8)	23.9 (16.0, 44.1)	24.0 (16.0, 44.1)

BIC, bictegravir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine.
[a]Unknown to the participant. [b]Values above the maximum reportable range of the Roche cobas 6800 HIV-1 assay (6,000,000 copies/mL) were imputed.

Table 2. Summary of AEs

Parameter, n (%)	DTG/3TC (n=254)	BIC/FTC/TAF (n=255)
Any AE	224 (88)	237 (93)
AEs occurring in ≥5% of participants in either treatment group		
Nasopharyngitis	26 (10)	29 (11)
Headache	23 (9)	18 (7)
Increased weight	23 (9)	21 (8)
Diarrhea	19 (7)	26 (10)
Insomnia	19 (7)	14 (5)
Osteopenia	19 (7)	23 (9)
Influenza-like illness	16 (6)	16 (6)
Upper respiratory tract infection	16 (6)	18 (7)
Influenza	12 (5)	16 (6)
Osteoporosis	7 (3)	12 (5)
Drug-related AEs	44 (17)	49 (19)
Grade 2-5 AEs	141 (56)	120 (47)
Drug-related grade 2-5 AEs[a]	13 (5)	16 (6)
AEs leading to study treatment discontinuation or withdrawal	3 (1)	3 (1)

Drug-related AEs leading to study treatment discontinuation	0	2 (<1)[b]
Any SAE[c]	23 (9)	20 (8)
Drug-related SAEs	0	0
Fatal SAEs	0	0

AE, adverse event; BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; SAE, serious AE; TAF, tenofovir alafenamide; 3TC, lamivudine.

[a]Any drug-related grade 3 AE: DTG/3TC, n=1 (increased weight); BIC/FTC/TAF, n=1 (diarrhea). There were no grade ≥4 drug-related AEs. [b]Drug-related AEs leading to study treatment discontinuation included alopecia and increased weight (n=1 each). [c]Serious AEs reported in >1 participant in either treatment group included anal abscess (DTG/3TC, n=2; BIC/FTC/TAF, n=0), hepatitis A virus infection (DTG/3TC, n=0; BIC/FTC/TAF, n=2), and diffuse large B cell lymphoma (DTC/3TC, n=1; BIC/FTC/TAF, n=2).

Figure 1. Week 48 virologic outcomes using HIV-1 RNA thresholds of **(A)** <50 copies/mL (primary endpoint) and **(B)** <200 copies/mL (US Food and Drug Administration Snapshot algorithm). BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine. [a]For the primary endpoint analysis, Roche cobas 6800 results were used for 1 participant with HIV-1 RNA <50 copies/mL at Week 48 (BIC/FTC/TAF group) and 5 participants who had early withdrawal and no virologic data in the Week 48 window (DTG/3TC, n=3; BIC/FTC/TAF, n=2).

Alt text: Bar graphs in 2 panels showing virologic outcomes with DTG/3TC vs BIC/FTC/TAF at Week 48 per the US Food and Administration Snapshot algorithm. Panel A presents the proportion of participants with HIV-1 RNA <50 copies/mL, HIV-1 RNA ≥50 copies/mL, and no virologic data. Panel B presents the proportion of participants with HIV-1 RNA <200 copies/mL, HIV-1 RNA ≥200 copies/mL, and no virologic data.

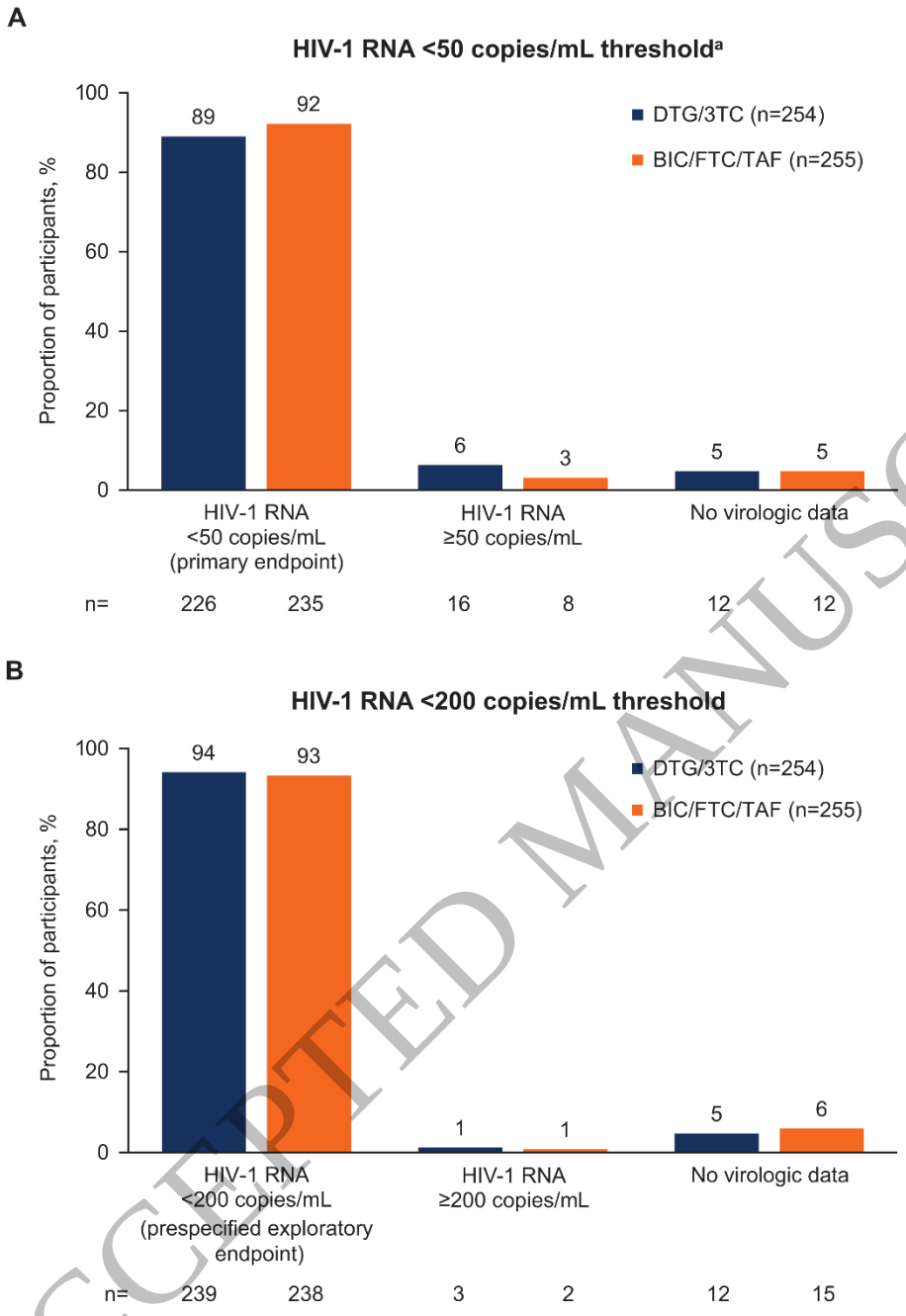

Figure 2. Kaplan-Meier plot of time to virologic suppression. BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine. [a]Number of participants at risk and remaining on study at the start of each study visit window. Participants who withdrew from the study without achieving virologic suppression were censored.

Alt text: A Kaplan-Meier plot showing the probability of virologic suppression with DTG/3TC vs BIC/FTC/TAF and the number of participants at risk per treatment group at each time point through Week 48.

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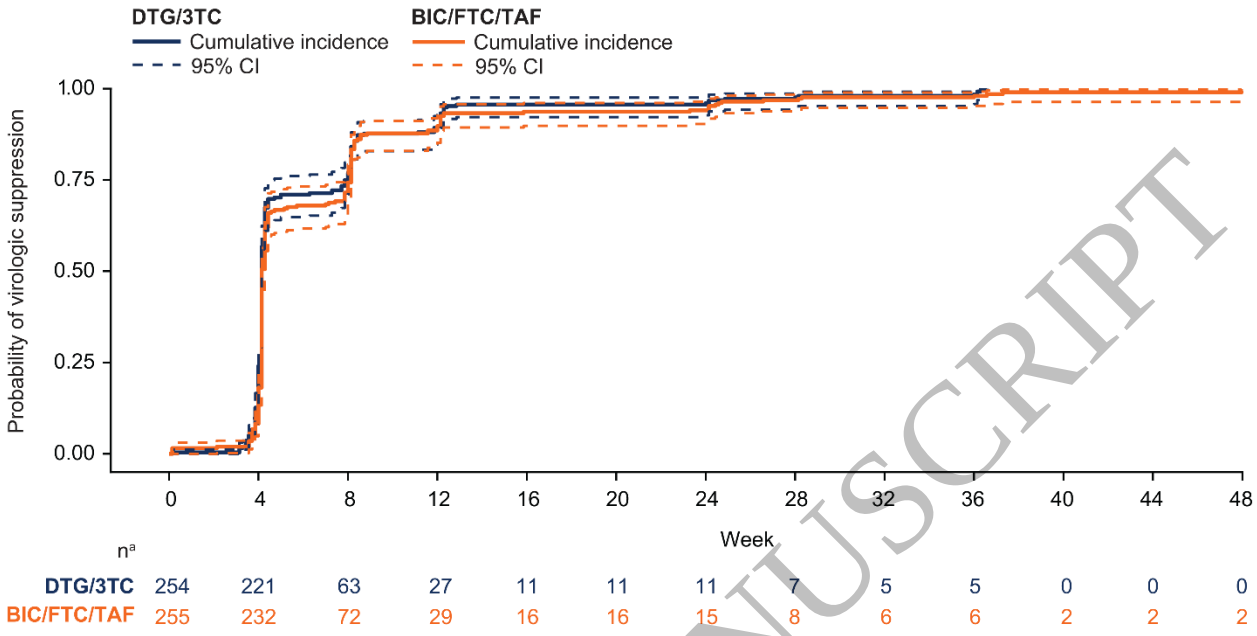

Figure 3. Virologic suppression at Week 48 by baseline VL and CD4+ cell count strata (US Food and Drug Administration Snapshot algorithm; primary efficacy analysis). BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine; VL, viral load.

Alt text: Figure showing virologic suppression with DTG/3TC vs BIC/FTC/TAF at Week 48 per the US Food and Drug Administration Snapshot algorithm in strata defined by baseline VL of <100,000 or ≥100,000 copies/mL and baseline CD4+ cell count of <200 or ≥200 cells/mm^3. The bar graph on the left shows the proportion of participants with HIV-1 RNA <50 copies/mL, and the forest plot on the right shows the shrinkage estimate of difference in proportion with 95% credible intervals.

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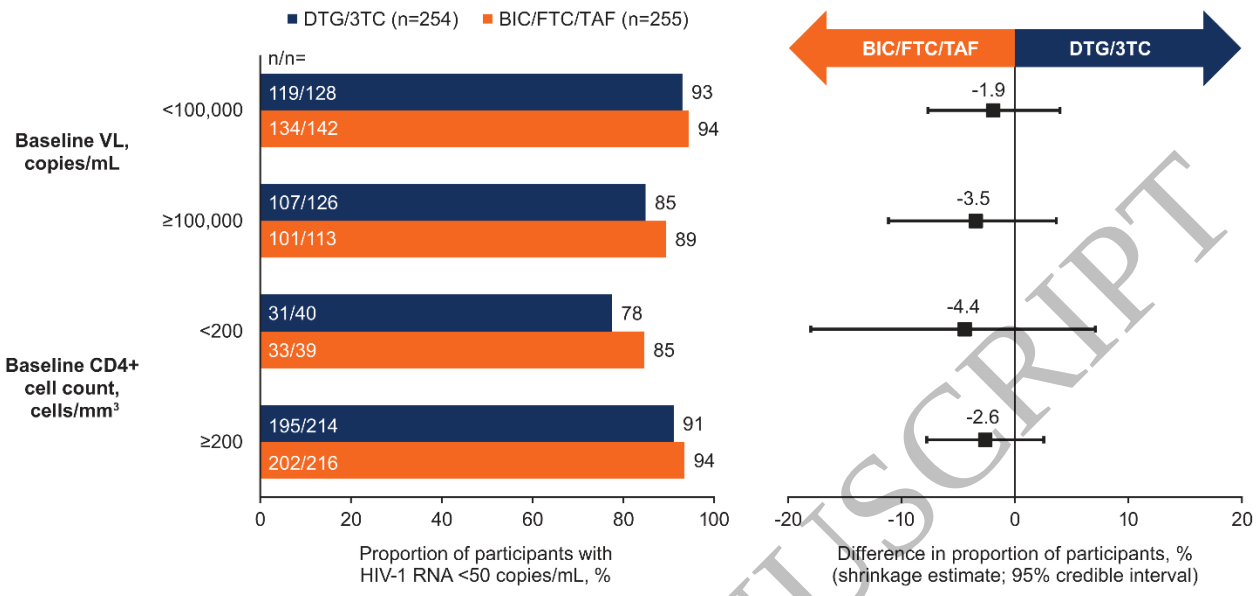

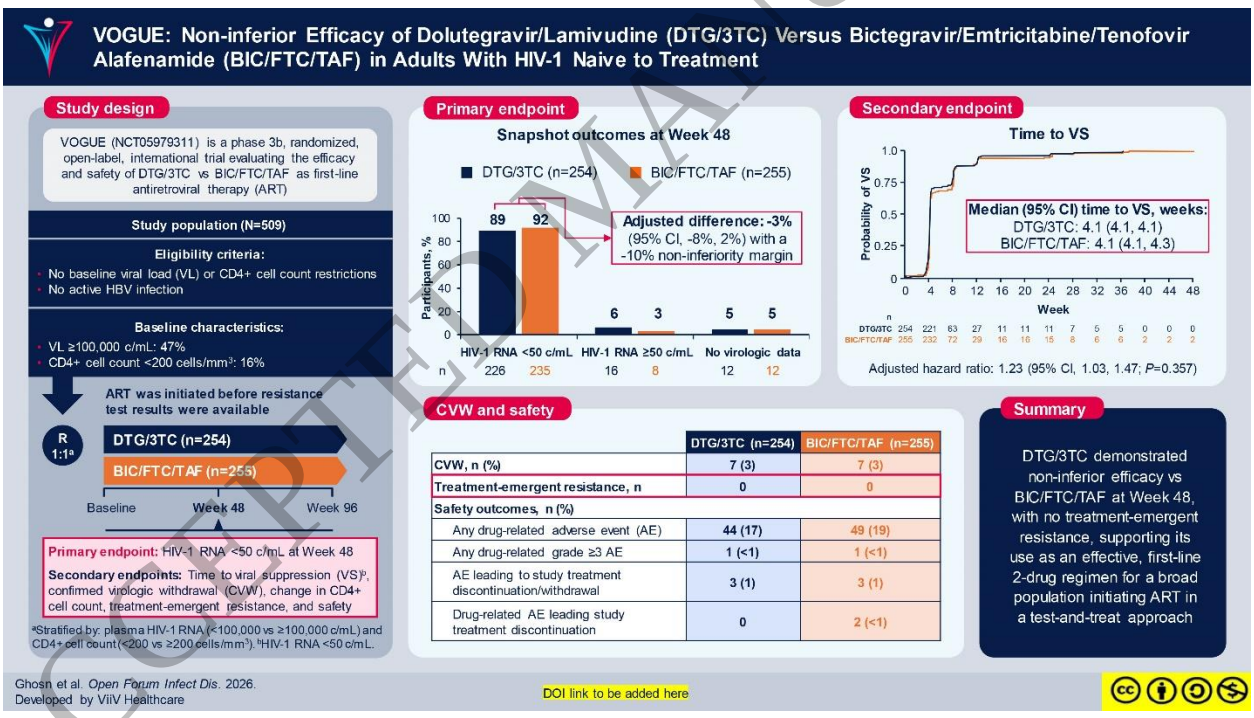

Graphical Abstract