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BRIEF REPORT

Infectious Diseases Society of America

HIV Medicine Association

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Efficacy and Safety Outcomes in Adults Initiating Dolutegravir/Lamivudine With High Viral Load in the GEMINI-1/-2 and STAT Trials

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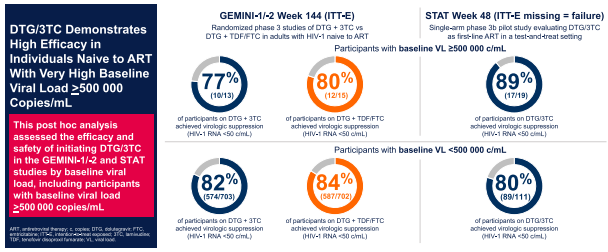
Through 144 weeks in GEMINI-1/-2 and 48 weeks in STAT, dolutegravir/lamivudine demonstrated high rates of virologic efficacy and a good safety profile in individuals naive to antiretroviral therapy across baseline viral load categories, including in those with very high baseline viral load (≥500 000 copies/mL).

Clinical Trials Registration. NCT02831673/NCT02831764; NCT03945981.

Graphical Abstract



Keywords. ART naive; 2-drug regimen; high viral load; test-and-treat setting; virologic suppression.

A key goal of human immunodeficiency virus type 1 (HIV-1) treatment is maximal and durable suppression of plasma viral load (VL), which also reduces the risk of HIV transmission to sexual partners to zero. Baseline plasma VL is a determinant of virologic outcomes, regardless of antiretroviral therapy (ART) [1]. Early diagnosis and treatment with effective ART are important to reduce the clinical impact of elevated VL [2]. However, limited efficacy data are available in adults initiating ART with very high VL (≥500 000 copies/mL) in randomized controlled trials.

Dolutegravir (DTG)/lamivudine (3TC) is a 2-drug regimen approved in multiple countries as first-line therapy for people with HIV-1 who are naive to ART, irrespective of baseline VL [3, 4]. In the phase 3 GEMINI-1 and GEMINI-2 studies, DTG + 3TC demonstrated rapid VL decline, was noninferior to DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in achieving virologic response (HIV-1 RNA <50 copies/mL), and had a favorable safety profile in adults naive to ART at weeks 48, 96, and 144 [5, 6]. In the single-arm STAT study, DTG/3TC fixed-dose combination demonstrated high efficacy and a good safety profile as a first-line regimen for adults naive to ART in a test-and-treat setting through 48 weeks [7, 8]. The GEMINI-1/-2 and STAT studies included participants with baseline VL ≥500 000 copies/mL and provide an opportunity to summarize use of DTG/3TC in this population.

Here we present post hoc efficacy and safety data in participants initiating DTG/3TC through week 144 in the GEMINI-1/-2 studies and through week 48 in the STAT study by baseline VL categories, including those with high VL (≥100 000 copies/mL) and very high VL (≥500 000 copies/mL).

METHODS

Detailed methodologies for the GEMINI-1/-2 (NCT02831673/NCT02831764) and STAT (NCT03945981) studies have been described previously (Supplementary Figure 1) [6, 7]. In this post hoc analysis, 144-week (GEMINI-1/-2) and 48-week (STAT) summaries included proportions of participants with HIV-1 RNA <50 and ≥50 copies/mL (intention-to-treat–exposed [ITT-E] population; GEMINI-1/-2, Snapshot algorithm; STAT, ITT-E missing = failure analysis [treatment modifications were not considered failure if HIV-1 RNA <50 copies/mL]), change from baseline in $CD4^+$ cell count, and safety, assessed by the following baseline VL categories: <100 000, ≥100 000 to <500 000, ≥500 000 to <1 000 000, and ≥1 000 000 copies/mL. Confirmed virologic failure (CVF) criteria are described in the Supplementary Methods.

All study protocols were approved by national, regional, or investigational center ethics committees and institutional

Received 14 January 2025; editorial decision 25 February 2025; accepted 05 March 2025; published online 7 March 2025

Presented in part: HIV Drug Therapy Glasgow, Glasgow, Scotland, 23–26 October 2022. Poster P056.

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https://doi.org/10.1093/ofid/ofaf135

review boards in accordance with the Declaration of Helsinki. All participants provided written informed consent.

In GEMINI-1/-2, the ITT-E population included all randomized participants who received ≥1 dose of study medication and was used for efficacy analyses; the safety population included all participants who received ≥1 dose of study medication and was analyzed according to actual treatment received. In STAT, the ITT-E and safety populations included all enrolled participants who received ≥1 dose of DTG/3TC.

RESULTS

Participants

Participant demographics and baseline characteristics from GEMINI-1/-2 and STAT are shown in Supplementary Table 1. Of 1433 participants in the GEMINI-1/-2 ITT-E population, 20% (n = 293) had baseline VL ≥100 000 copies/mL and 2% (n = 28) had baseline VL ≥500 000 copies/mL. Baseline VL groups were generally evenly distributed across treatments. Of 131 participants in the STAT ITT-E population, 39% (n = 51) had baseline VL ≥100 000 copies/mL and 15% (n = 19) had baseline VL ≥500 000 copies/mL. Participant disposition is summarized in the Supplementary Results.

Virologic and Immunologic Outcomes

Proportions of participants achieving virologic suppression (HIV-1 RNA <50 copies/mL) at week 144 (GEMINI-1/-2) and week 48 (STAT) were high across all studies irrespective of baseline VL, including in those with high and very high baseline VL (Figure 1; Supplementary Table 2). Among participants with baseline VL ≥500 000 copies/mL in GEMINI-1/-2, 85% (11/13) and 77% (10/13) in the DTG + 3TC group and 80% (12/15) and 80% (12/15) in the DTG + TDF/FTC group achieved virologic suppression at weeks 48 and 144, respectively. Among participants with baseline VL ≥500 000 copies/mL in STAT, 89% (17/19) achieved virologic suppression at week 48. Few participants with baseline VL ≥500 000 copies/mL had HIV-1 RNA ≥50 copies/mL at week 48 in GEMINI-1/-2 (DTG + 3TC, 0% [0/13]; DTG + TDF/FTC, 7% [1/15]), week 144 in GEMINI-1/-2 (n = 0 in both groups), and week 48 in STAT (11% [2/19]).

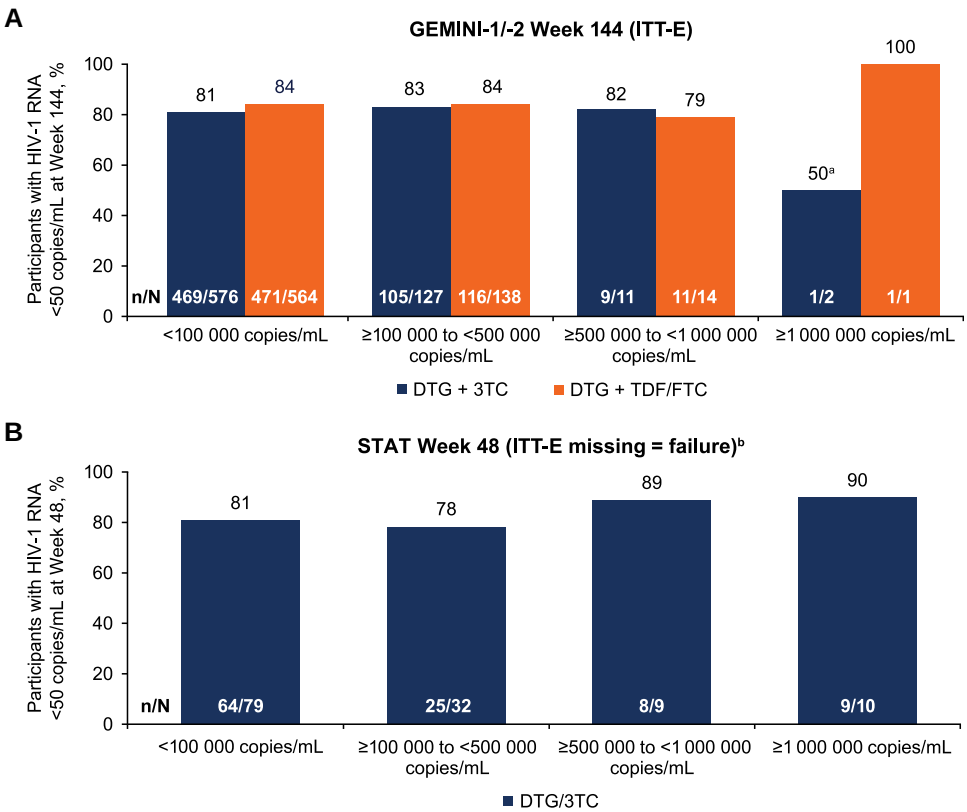

Figure 1. Virologic outcomes in the GEMINI-1/-2 (*A*) and STAT (*B*) trials by baseline viral load. [a]The other participant withdrew from the study due to physician decision and had no virologic data at week 48. [b]ITT-E missing = failure analysis included all participants. Missing data for any reason at week 48 was considered HIV-1 RNA ≥50 copies/mL. Treatment modifications were not considered failure if HIV-1 RNA <50 copies/mL. In STAT, 1 (<1%) participant had missing viral load results at baseline. Abbreviations: 3TC, lamivudine; DTG, dolutegravir; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; ITT-E, intention-to-treat–exposed; TDF, tenofovir disoproxil fumarate.

No treatment-emergent resistance was detected in participants meeting CVF criteria through week 144 in GEMINI-1/-2 (DTG + 3TC, n = 12, including n = 6 with baseline VL ≥100 000 to <500 000 copies/mL; DTG + TDF/FTC, n = 9, including n = 2 with baseline VL ≥100 000 to <500 000 copies/mL and n = 1 with baseline VL ≥500 000 copies/mL) or through week 48 in STAT (n = 2, including n = 1 with baseline VL ≥1 000 000 copies/mL). One participant in the DTG + 3TC group in GEMINI-1 who did not meet CVF criteria had treatment-emergent M184V at week 132 and R263R/K at week 144; this participant had a baseline VL <100 000 copies/mL. Mean increase in $CD4^+$ cell count was generally similar across baseline VL categories and treatment groups from baseline to week 144 in GEMINI-1/-2 (range: DTG + 3TC, 289.7–346.3 cells/μL; DTG + TDF/FTC, 285.3–345.0 cells/μL) and similar across baseline VL categories from baseline to week 48 in STAT (range: 239.4–539.5 cells/μL; Supplementary Table 3).

Safety

Few participants with baseline VL ≥500 000 copies/mL reported drug-related adverse events (AEs) at week 144 in GEMINI-1/-2 (DTG + 3TC, n = 3; DTG + TDF/FTC, n = 2) and at week 48 in STAT (n = 4; Supplementary Table 4). Across all studies, most drug-related AEs were grade 1 or 2, and only 1 participant with baseline VL ≥500 000 copies/mL (in STAT) reported an AE leading to study withdrawal (grade 1 rash).

DISCUSSION

Through 144 weeks in GEMINI-1/-2 and 48 weeks in STAT, DTG/3TC demonstrated high efficacy and a favorable safety profile across baseline VL categories, including in participants with very high baseline VL. Virologic suppression rates were generally high among participants with baseline VL ≥500 000 copies/mL who received DTG + 3TC at 48 and 144 weeks in GEMINI-1/-2 (85% and 77%, respectively) and through 48 weeks in STAT (89%) and generally comparable to those with baseline VL <500 000 copies/mL. With DTG + 3TC in GEMINI-1/-2, 6 participants with baseline VL ≥100 000 to <500 000 copies/mL met CVF criteria. In STAT, 1 participant with baseline VL ≥100 000 copies/mL and 1 participant with baseline VL ≥1 000 000 copies/mL met CVF criteria at week 24, and both remained on DTG/3TC. No participants with CVF developed treatment-emergent resistance in GEMINI-1/-2 or STAT.

Results with DTG/3TC in this analysis were similar to those observed in individuals with baseline VL >400 000 copies/mL enrolled in the registrational bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) studies GS1489 and GS1490 [9]. Consistent with these clinical trial data, a systematic literature review of real-world studies of people living with HIV-1 naive to ART initiating DTG + 3TC reported that 97% (208/215) of individuals with high baseline VL (≥100 000 copies/mL) and 95% (21/22) with very high baseline VL (≥500 000 copies/mL) achieved virologic suppression at week 48 [10].

While the definition of high VL is standardized in HIV-1 studies using a threshold of 100 000 copies/mL, the definition of very high VL varies by study [8–12]. For example, while the GS1489 and GS1490 trials used a threshold of 400 000 copies/mL to define very high VL, the GEMINI-1/-2, STAT, and BIC/FTC/TAF FAST studies used a threshold of 500 000 copies/mL [6, 8–12]. Regardless of the threshold used and treatment evaluated, efficacy data for participants with very high VL are limited in randomized clinical trials since the frequency with which these VLs are found in clinical practice is low [10]. In GS1489 and GS1490, 3% of participants had very high VL (>400 000 copies/mL) [9], which is comparable to the 3% of participants in GEMINI-1/-2 with baseline VL >400 000 copies/mL [11]. In a test-and-treat setting, 19% and 15% of participants had very high VL using a threshold of 500 000 copies/mL in the FAST and STAT clinical trials, respectively [8, 12].

This study has some limitations. The number of participants with very high baseline VL was small, which is common across randomized clinical trials and other post hoc analyses evaluating this topic [9]. Interpretation of results from the STAT study may also be limited by its single-arm noncomparative design. Additionally, short follow-up due to the STAT study design may limit our understanding of the longer-term effects of very high baseline VL. However, GEMINI-1/-2 efficacy and safety results were consistent between weeks 48 and 144 among participants with baseline VL ≥500 000 copies/mL.

In this post hoc analysis, DTG/3TC demonstrated high efficacy and a favorable safety profile in participants across baseline VL categories at week 144 in the GEMINI-1/-2 studies and at week 48 in the STAT study, including in participants with baseline VL ≥500 000 copies/mL. Similar outcomes have been observed with 3-drug regimens such as BIC/FTC/TAF in participants with very high baseline VL [9, 12]. These data reinforce the efficacy and safety of DTG/3TC as a first-line regimen and in a test-and-treat setting in adults naive to ART, including in individuals with high and very high baseline VL.

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.

Notes

Acknowledgments. Editorial assistance was provided under the direction of the authors by Lana Pollock, PhD, and Jennifer Rossi, MA, ELS, MedThink SciCom, and funded by ViiV Healthcare.

Author contributions. M. U., C. M. P., R. G., B. J., and M. K. contributed to the conception and design of the study. C.-P. R., J. R. A., and

R. O. contributed to the acquisition of data. All authors contributed to the analysis and interpretation of data, drafting the manuscript, and critically revising the manuscript for important intellectual content, and all authors approved the manuscript for publication.

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

Disclaimer. The study sponsor had a role in the study design, data collection and analysis, and preparation of the manuscript. The decision to publish was made by the authors.

Financial support. This work was supported by ViiV Healthcare.

Potential conflicts of interest. C.-P. R. has participated in speaker's bureaus for Gilead Sciences and ViiV Healthcare; served as an advisor to ViiV Healthcare; and received research grants (paid to institution) from Gilead Sciences, MSD, and ViiV Healthcare. J. R. A. has received advisory fees, speaker's fees, and research grants from Aelix, Gilead Sciences, GSK, Janssen, MSD, and ViiV Healthcare. M. U., C. M. P., R. G., V. P. D., B. J., and M. K. are employees of ViiV Healthcare or GSK and may own stock in GSK. R. O. has no conflicts to disclose.

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