DURABLE EFFICACY OF DOLUTEGRAVIR (DTG) PLUS LAMIVUDINE (3TC) IN ANTIRETROVIRAL TREATMENT–NAIVE ADULTS WITH HIV-1 INFECTION— 3-YEAR RESULTS FROM THE GEMINI STUDIES

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HIV Drug Therapy Glasgow 2020; October 5-8, 2020; Virtual

PM-GB-DLL-PPT-200010 – October 2020

Introduction

- Two-drug regimens (2DRs) have been investigated as a means for reducing the number of ARV agents taken by individuals who need lifelong ART[1,2]
- In the primary analysis of the GEMINI-1 and GEMINI-2 studies at Week 48, the 2DR DTG + 3TC was non-inferior to the 3-drug regimen DTG + TDF/FTC in the treatment of ART-naive adults with HIV-1[3]
- DTG + 3TC maintained non-inferior efficacy over 96 weeks vs DTG + TDF/FTC in ART-naive adults, with low rates of confirmed virologic withdrawal (CVW), and no resistance development in either treatment group[4]
- DTG + 3TC is recommended as an initial ART regimen for most PLWH, with exceptions for individuals with HIV-1 RNA >500,000 c/mL, HBV co-infection, or in whom therapy is started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available[5,6]
- We present data from the prespecified Week 144 secondary endpoint analyses of GEMINI-1 and GEMINI-2 evaluating durability after 3 years of therapy with DTG + 3TC

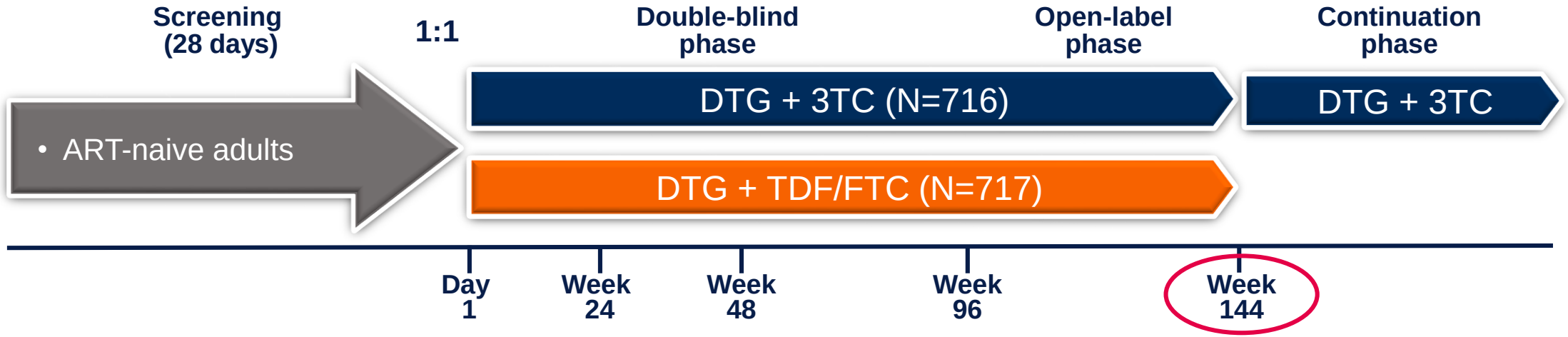
1. Back. *Germs.* 2017;7:113-114. **2.** Kelly et al. *Drugs.* 2016;76:523-531. **3.** Cahn et al. *Lancet.* 2019;393:143-155. **4.** Cahn et al. *J Acquir Immune Defic Syndr.* 2020;83:310-318. **5.** AIDSinfo. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed September 9, 2020. **6.** EACS. https://www.eacsociety.org/files/guidelines-10.0_final_2_2.pdf. Accessed September 9, 2020.

Methods

- GEMINI-1 and GEMINI-2 (ClinicalTrials.gov identifiers, NCT02831673 and NCT02831764, respectively) are identically designed, randomized, double-blind, parallel-group, multicenter, phase III, non-inferiority studies[1]
- Participants with HIV-1 RNA ≤500,000 c/mL at screening were randomized 1:1 (stratified by plasma HIV-1 RNA and CD4+ cell count) to once-daily treatment with DTG + 3TC or DTG + TDF/FTC
- The primary endpoint was proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm in the intention-to-treat–exposed [ITT-E] population)[1]

1. Cahn et al. *Lancet.* 2019;393:143-155.

GEMINI-1 and GEMINI-2 Study Design



Eligibility criteria
- VL 1000-500,000 c/mL at screening
- ≤10 days of prior ART
- No major RT or PI resistance mutations
- No HBV infection or need for HCV therapy

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E Snapshot)[a]

Countries

Argentina	Australia	Belgium
Canada	France	Germany
Italy	Republic of Korea	Mexico
Netherlands	Peru	Poland
Portugal	Romania	Russian Federation
South Africa	Spain	Switzerland
Taiwan	United Kingdom	United States

[a]–10% non-inferiority margin for individual studies.

Cahn et al. HIV Glasgow 2020; Virtual. Poster P018.

Demographic and Baseline Characteristics of the Pooled GEMINI-1 and GEMINI-2 Population[1]

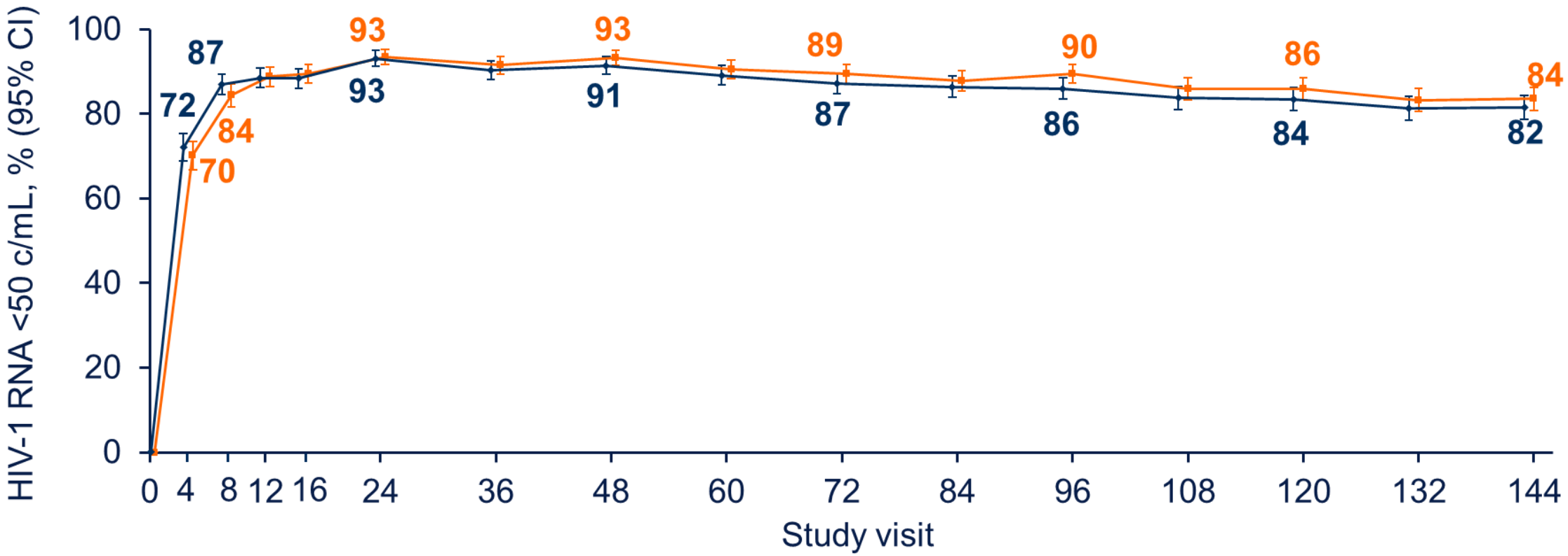
Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32 (18-72)	33 (18-70)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	90 (13)	71 (10)
Asian	71 (10)	72 (10)
White	484 (68)	499 (70)
Other	71 (10)	75 (10)
HIV-1 RNA >100,000 c/mL, n (%)[a]	140 (20)	153 (21)
CD4+ cell count ≤200 cells/mm^3, n (%)	63 (9)	55 (8)

[a]2% of participants in each group had baseline HIV-1 RNA ≥500,000 c/mL and were included in the ITT-E analysis.

- 1433 participants in GEMINI-1 and GEMINI-2 were randomized and received ≥1 dose of study medication (DTG + 3TC, N=716; DTG + TDF/FTC, N=717)
- At baseline, 20% (n=293) of participants had HIV-1 RNA >100,000 c/mL and 8% (n=118) had CD4+ cell count ≤200 cells/mm^3

1. Cahn et al. *J Acquir Immune Defic Syndr.* 2020;83:310-318.

Snapshot Analysis of the Proportion of Participants With Plasma HIV-1 RNA <50 c/mL Through Week 144 by Visit in the Pooled ITT-E Population



- DTG + 3TC was non-inferior to DTG + TDF/FTC in Snapshot HIV-1 RNA <50 c/mL for GEMINI-1, GEMINI-2, and the pooled population at Week 144

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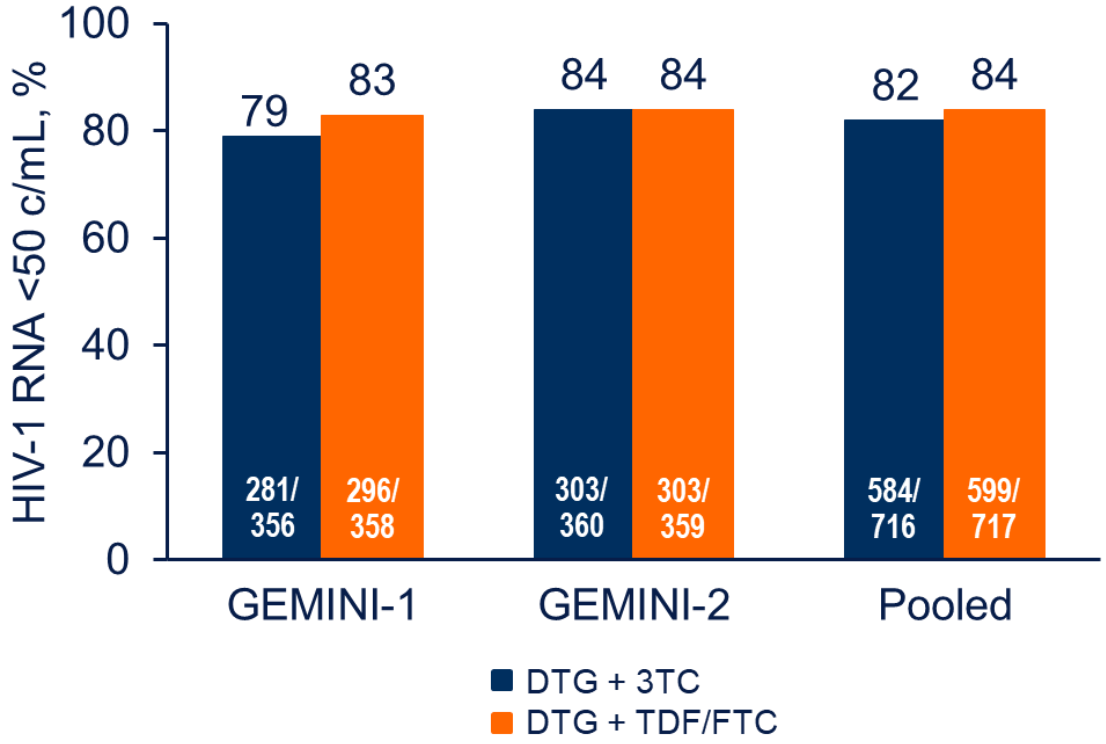
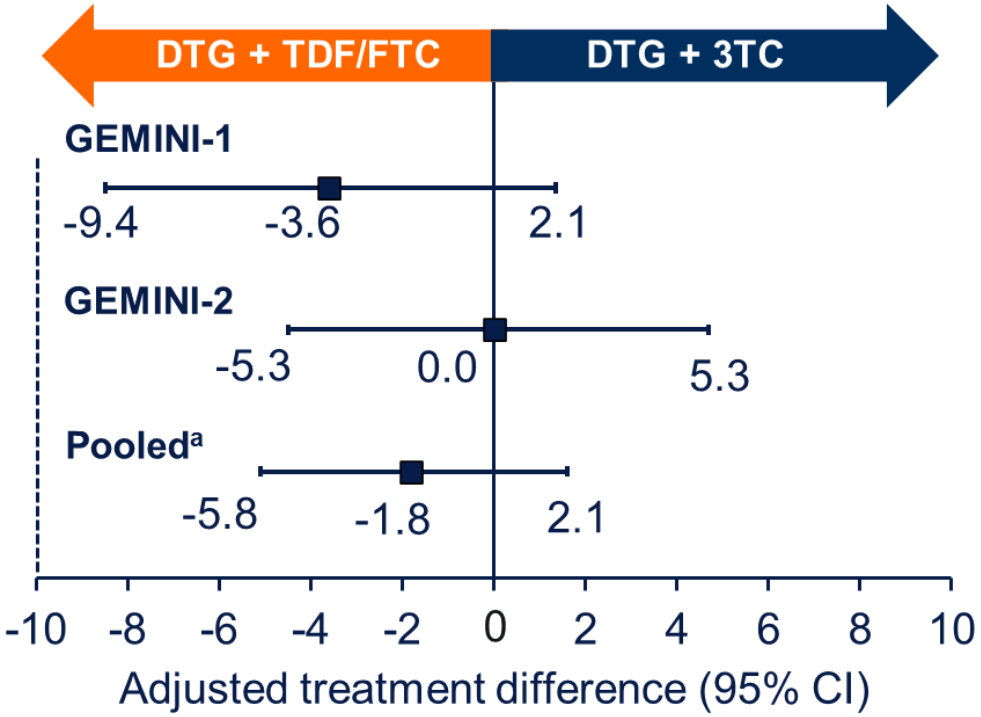
Snapshot Analysis of the Proportion of Participants With Plasma HIV-1 RNA <50 c/mL Through Week 144 in the GEMINI-1, GEMINI-2, and Pooled ITT-E Populations





[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), baseline CD4+ cell count (≤200 vs >200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2).

Summary of Study Outcomes at Week 144: Snapshot Analysis (ITT-E Population)

Snapshot outcome, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA <50 c/mL	**584 (82)**	**599 (84)**
HIV-1 RNA ≥50 c/mL	**23 (3)**	**21 (3)**
Data in window and HIV-1 RNA ≥50 c/mL	4 (<1)	5 (<1)
Discontinued for lack of efficacy	10 (1)	4 (<1)
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	7 (1)	11 (2)
Change in ART	2 (<1)	1 (<1)
No virologic data	**109 (15)**	**97 (14)**
Discontinued study due to AE or death	29 (4)	32 (4)
Discontinued study for other reasons[a]	78 (11)	64 (9)
On study but missing data in window	2 (<1)	1 (<1)

[a]Other reasons for discontinuation at Week 144 included protocol deviation, lost to follow-up, physician decision, withdrawal by participant, and lack of efficacy (in 1 participant in each treatment group in GEMINI-2).

- The proportion of participants with HIV-1 RNA ≥50 c/mL was low and similar between treatment groups (3% in both groups)
- The majority of Snapshot failures were due to non-virologic reasons

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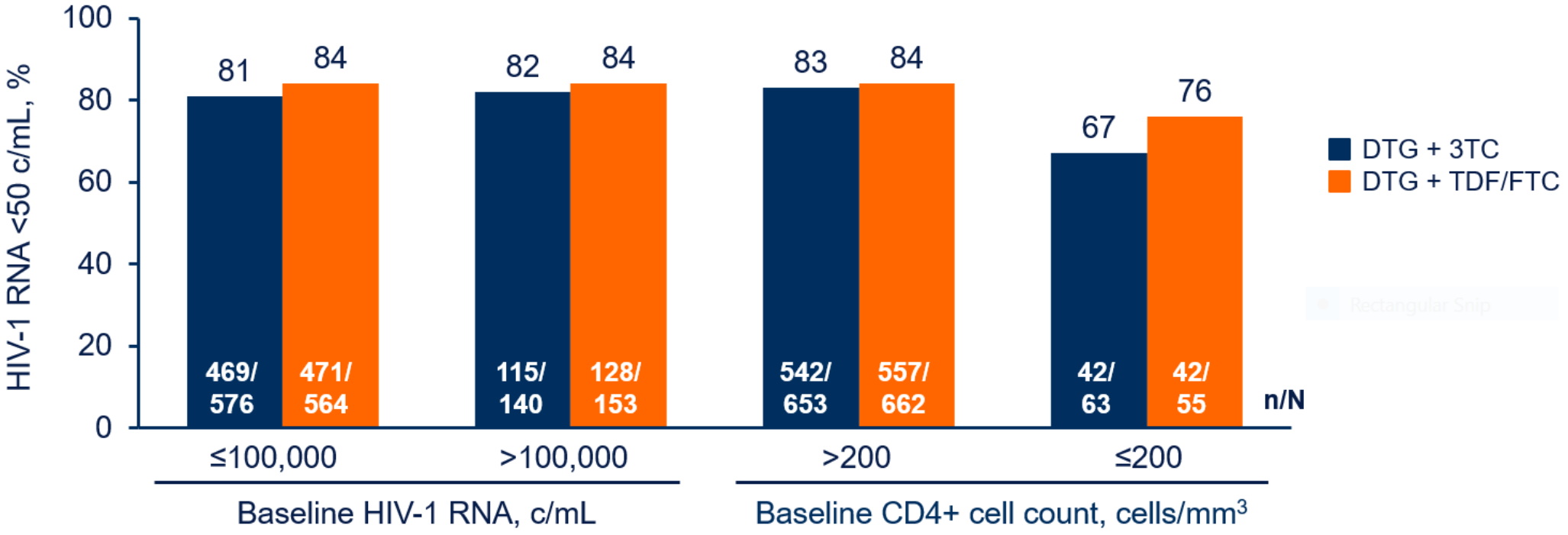
Proportion of Participants With HIV-1 RNA <50 c/mL by Baseline Viral Load and CD4+ Cell Count at Week 144: Snapshot Analysis for the Pooled Population



- At Week 144, in participants with baseline HIV-1 RNA >100,000 c/mL, 82% and 84% in the DTG + 3TC and DTG + TDF/FTC groups, respectively, achieved HIV-1 RNA <50 c/mL; among participants with baseline CD4+ cell count ≤200 cells/mm^3, 67% in the DTG + 3TC group and 76% in the DTG + TDF/FTC group achieved HIV-1 RNA <50 c/mL
- The corresponding proportions were 81% and 84%, respectively, for those with baseline HIV-1 RNA ≤100,000 c/mL and 83% and 84%, respectively, for those with baseline CD4+ cell count >200 cells/mm^3

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Confirmed Virologic Withdrawal

- Across both studies, 12 participants (2%) in the DTG + 3TC group (1 since Week 96) and 9 participants (1%) in the DTG + TDF/FTC group (2 since Week 96) met protocol-defined CVW criteria[1] through Week 144
  - None of these participants had treatment-emergent INSTI or NRTI resistance mutations
- 1 non-CVW participant with reported non-adherence in the DTG + 3TC group developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in susceptibility to DTG
  - Baseline HIV-1 RNA: 93,515 c/mL; CD4+ cell count: 393 cells/mm^3
  - Suppressed to HIV-1 RNA <50 c/mL from Week 4 through Week 120; HIV-1 RNA 61,927 c/mL detected at Week 132, with successive HIV-1 RNA of <50, 135, and 61 c/mL after Week 132
  - Withdrawn due to lack of efficacy after Week 144, switched to DTG once daily + DRV/COBI, and regained virologic suppression

1. Cahn et al. *Lancet.* 2019;393:143-155.

Safety

- Through Week 144, overall AE profiles were similar between treatment groups
- Participants in the DTG + 3TC group had a significantly lower risk of drug-related AEs (20%) compared with the DTG + TDF/FTC group for the pooled population (27%; relative risk, 0.76 [95% CI, 0.63-0.92])
- Overall, 4 deaths occurred (3 in the DTG + 3TC group and 1 in the DTG + TDF/FTC group), all considered unrelated to the study drug regimen
- Overall mean weight change from baseline to Week 144 was 3.7 kg with DTG + 3TC and 2.4 kg with DTG + TDF/FTC

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Summary of AEs in the Pooled Safety Population From GEMINI-1 and GEMINI-2

AE, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Any AE	613 (86)	625 (87)
AEs occurring in ≥10% of participants in either group		
Diarrhea	99 (14)	106 (15)
Nasopharyngitis	93 (13)	127 (18)
Headache	84 (12)	91 (13)
Upper respiratory tract infection	84 (12)	61 (9)
Syphilis	64 (9)	70 (10)
Drug-related AEs	146 (20)	192 (27)
Any grade 2-5 drug-related AE	58 (8)	69 (10)
Grade 2-5 drug-related AEs occurring in ≥1% of participants		
Headache	8 (1)	8 (1)
AEs leading to withdrawal from the study	31 (4)	33 (5)
AEs of interest leading to withdrawal from the study		
Psychiatric disorders	11 (2)	8 (1)
Renal related	2 (<1)	12 (2)
Osteoporosis	0	2 (<1)
Any serious AE	76 (11)	85 (12)

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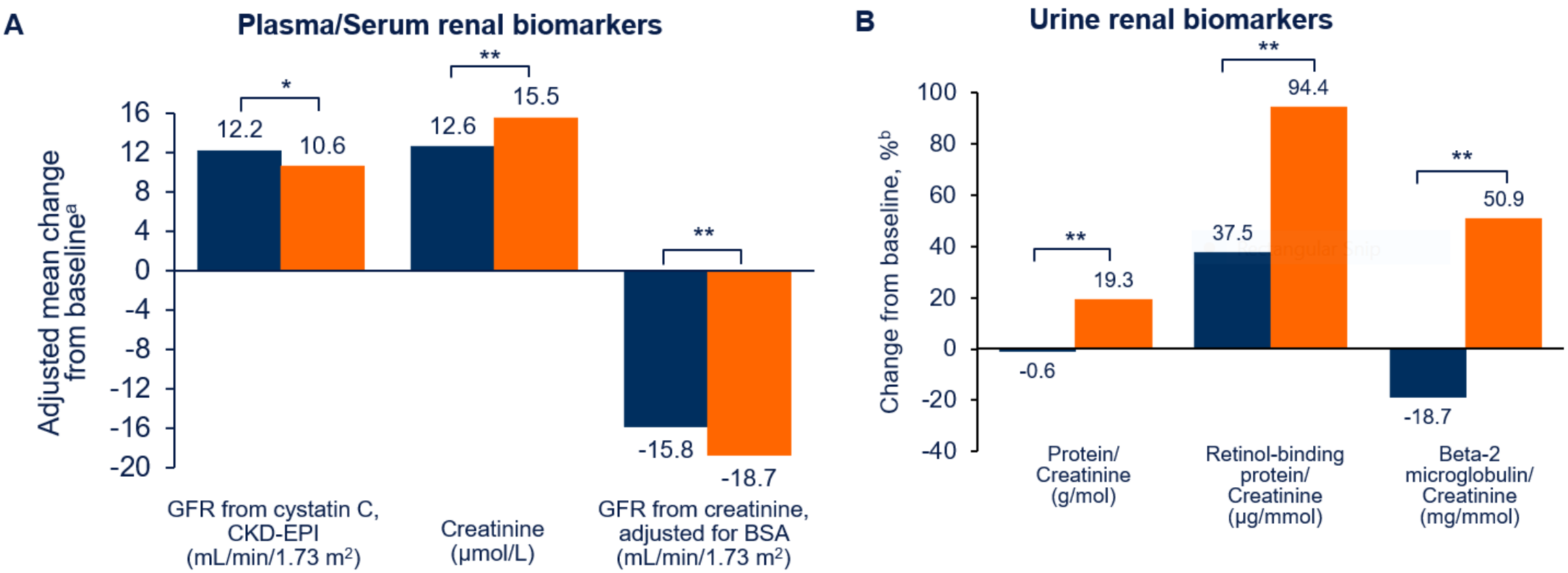
Adjusted Mean Change From Baseline in (A) Serum or Plasma Renal Biomarkers and (B) Ratios of Urine Renal Biomarkers at Week 144



- Changes from baseline in renal biomarkers favored DTG + 3TC vs DTG + TDF/FTC through Week 144

[a]Week 144 analysis used a mixed-effect repeated-measures model. Mean change from baseline adjusted for study, treatment, visit, baseline HIV-1 RNA, baseline CD4+ cell count, age, sex, race, presence of diabetes, presence of hypertension, baseline biomarker value, treatment-by-visit interaction, and baseline biomarker value-by-visit interaction. [b]Estimated from geometric mean ratios for baseline and Week 144. Based on the same model as plasma/serum markers except adjusting for $\log_e$-transformed baseline biomarker. *P<0.01. **P<0.001.

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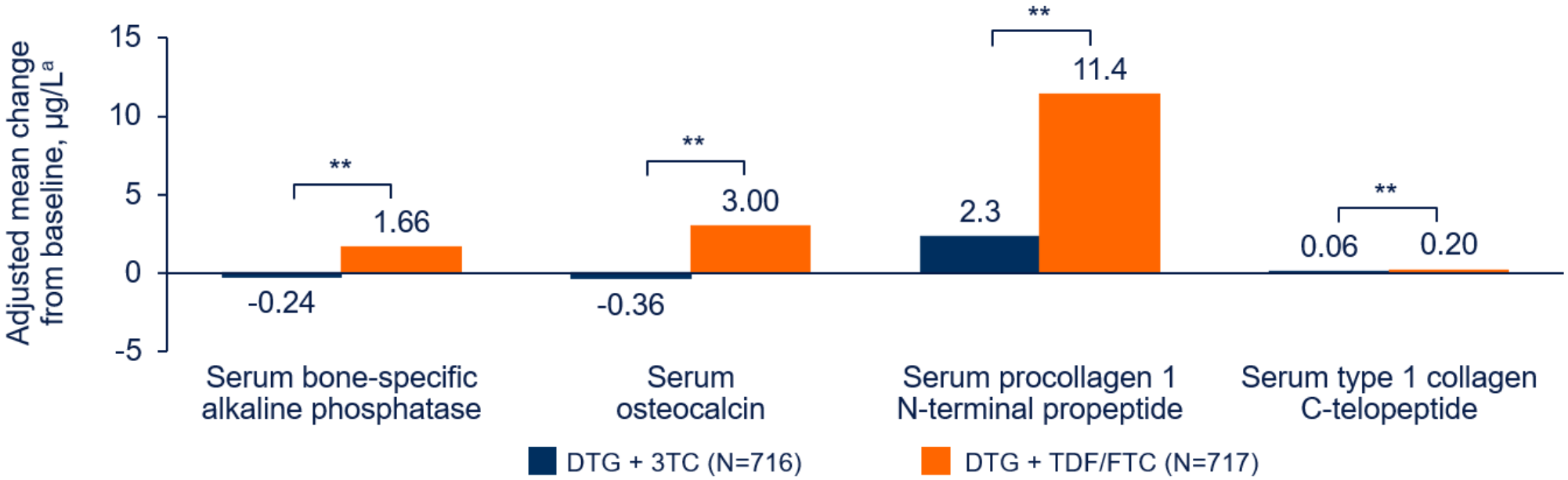
Adjusted Mean Change From Baseline in Serum Bone Turnover Biomarkers at Week 144



- Increase from baseline in bone turnover markers was lower with DTG + 3TC than DTG + TDF/FTC
- Changes in lipid parameters generally favored DTG + TDF/FTC through Week 144
  - Adjusted mean change from baseline at Week 144 in the DTG + 3TC vs DTG + TDF/FTC group: total cholesterol, 0.365 vs −0.027 mmol/L, *P*<0.001; HDL-C, 0.180 vs 0.095 mmol/L, *P*<0.001; LDL-C, 0.158 vs −0.095 mmol/L, *P*<0.001; triglycerides, 0.100 vs −0.079 mmol/L, *P*=0.002; TC/HDL-C ratio, −0.237 vs −0.377, *P*=0.008

[a]Week 144 analysis used a mixed-effect repeated-measures model. Mean change from baseline adjusted for study, treatment, visit, baseline HIV-1 RNA, baseline CD4+ cell count, age, sex, race, BMI, smoking status, current vitamin D use, baseline biomarker value, treatment-by-visit interaction, and baseline biomarker value-by-visit interaction. ***P*<0.001.

Conclusions

- DTG + 3TC maintained non-inferior efficacy vs DTG + TDF/FTC in ART-naive adults and demonstrated a high barrier to resistance, with low rates of CVW through Week 144
  - 1 non-CVW participant in the DTG + 3TC group with reported non-adherence developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in DTG susceptibility; the participant was withdrawn for lack of efficacy after Week 144, switched to DTG once daily + DRV/COBI, and regained virologic suppression
- Overall safety and tolerability were comparable between groups. There was a lower risk of drug-related AEs with DTG + 3TC than with DTG + TDF/FTC
- Changes in renal and bone biomarkers generally favored DTG + 3TC
- These results confirm the durable efficacy, tolerability, and high barrier to resistance of DTG + 3TC, further supporting the 2DR DTG + 3TC as a first-line treatment option for PLWH

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