

Initial Viral Load Decline and Response Rates by Baseline Viral Load Strata With Dolutegravir Plus Lamivudine Versus Dolutegravir Plus Tenofovir Disoproxil Fumarate/Emtricitabine: Pooled Results From the GEMINI Studies

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Disclosures: Michael Aboud, MD

- Michael Aboud is an employee of ViiV Healthcare and owns stock in GlaxoSmithKline

Introduction

- The requirement for lifelong antiretroviral therapy (ART) for HIV infection has heightened interest in 2-drug regimens (2DRs) to minimize cumulative drug exposure¹
- Lower ART exposure may translate to less long-term drug toxicity
- GEMINI-1 and -2 demonstrated non-inferior virologic efficacy for the 2DR DTG + 3TC vs the 3DR DTG + TDF/FTC at Week 48 for treatment-naïve participants with HIV-1 viral load (VL) $\leq 500,000$ c/mL at screening²
- Response rate in participants with high baseline (BL) VL is a key test of potency of ART regimens
- We describe the initial VL decline, time to suppression, and week 48 efficacy outcomes by baseline VL strata

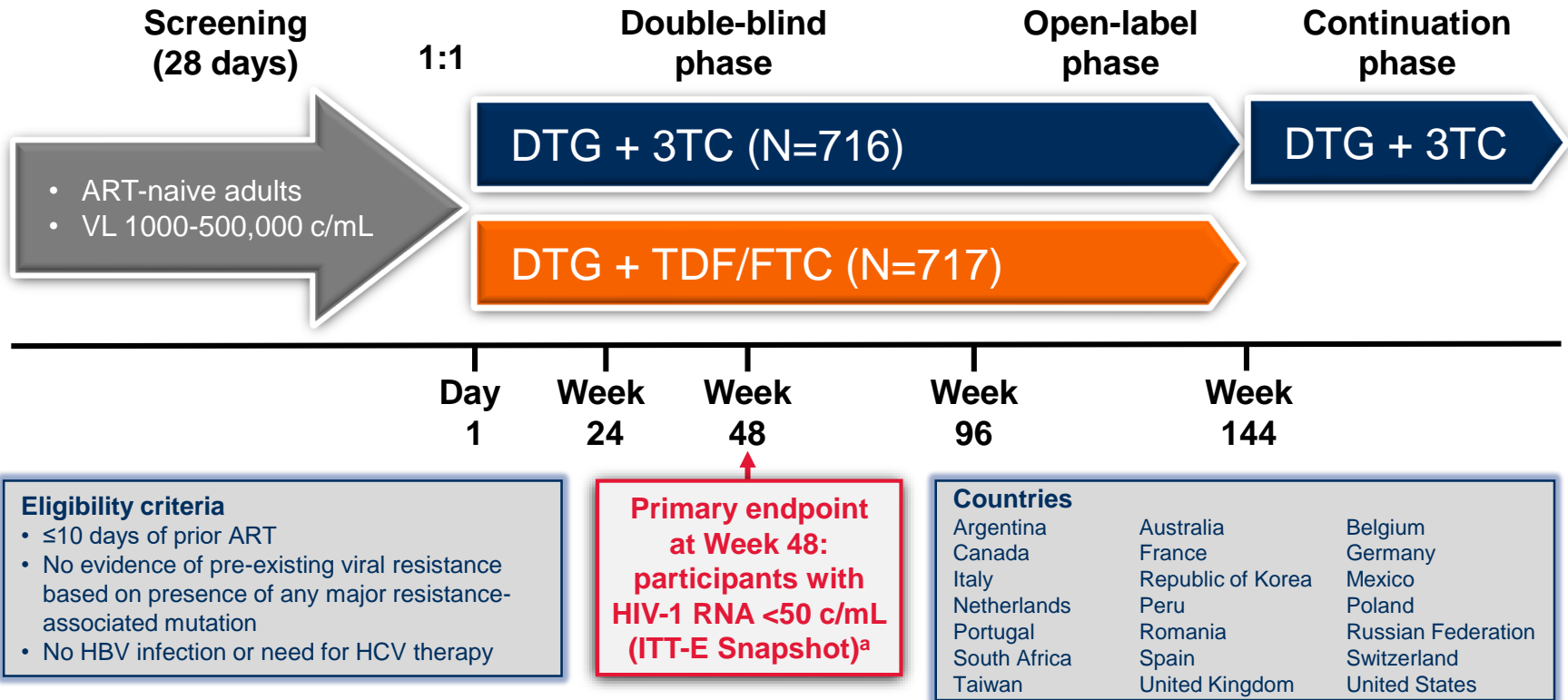
1. Kelly et al. *Drugs*. 2016;76:523-531. 2. Cahn et al. *Lancet*. 2018 [Epub ahead of print].

Why DTG +3TC

- Historic data from naïve 2DR studies support efficacy of regimens comprising 3TC and a core agent with a high barrier to resistance
- DTG has demonstrated a high barrier to resistance both in clinical trials and in real world use
- DTG and 3TC have complementary PK profiles, with matched 24 hour PK and PK tails (intracellular for 3TC)
- Dual target blockade of HIV life cycle, including RT
- Pilot data (PADDLE, A5353) suggest high combined potency and efficacy for DTG + 3TC

GEMINI-1 and -2 Phase III Study Designs

Identically designed, randomized, double-blind, parallel-group, multicenter, non-inferiority studies



Baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm³).

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

Cahn et al. *Lancet*. 2018 [Epub ahead of print].

Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Oral Presentation #7.

Demographic and Baseline Characteristics for the Pooled GEMINI-1 and -2 Population



Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
White	480 (67)	497 (69)
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log₁₀ c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000	140 (20)	153 (21)
>250,000	51 (7)	46 (6)
>400,000	18 (3)	24 (3)
>500,000 ^a	13 (2)	15 (2)
CD4+ cell count, median (range), cells/mm³	427.0 (19-1399)	438.0 (19-1497)
≤200	63 (9)	55 (8)
>200	653 (91)	662 (92)

^aParticipants were required to have HIV-1 RNA ≤500,000 c/mL at screening. Other than 1 participant enrolled without meeting study entry criteria, these participants had an observed increase in HIV-1 RNA between screening and baseline.

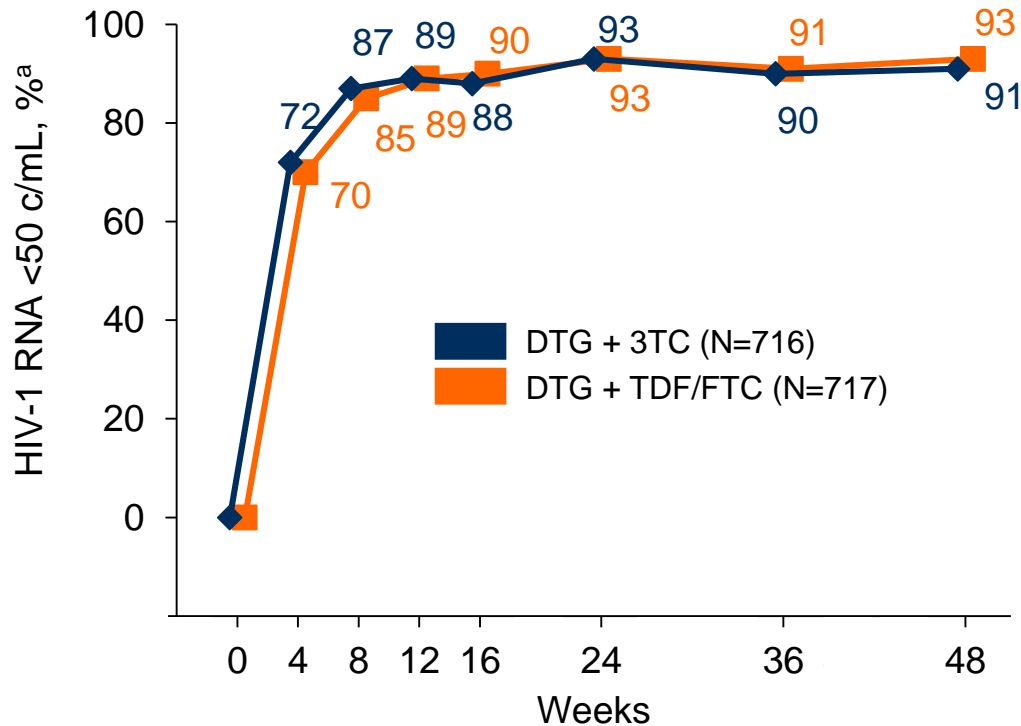
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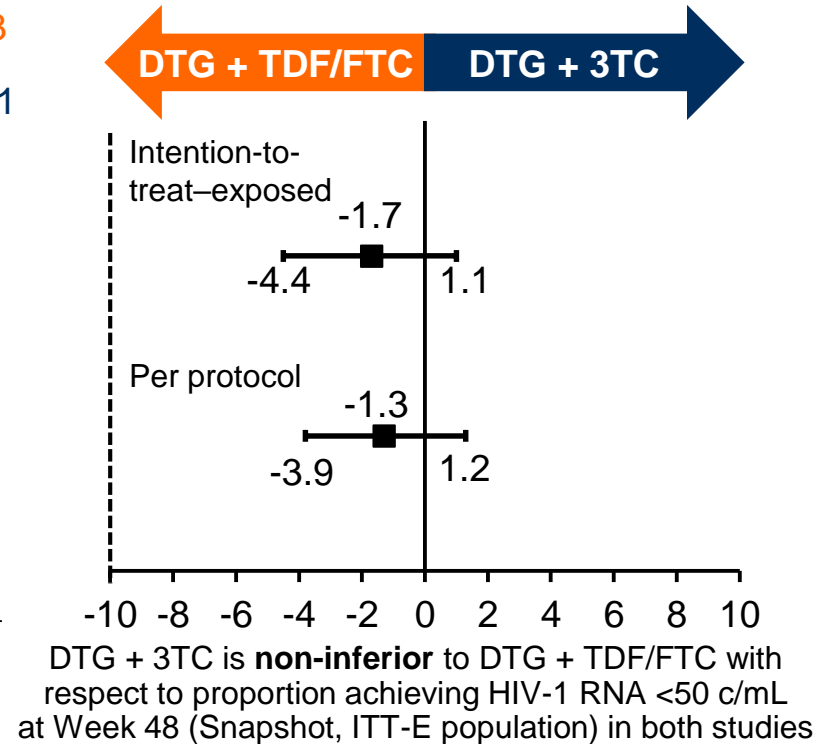
Snapshot Analysis by Visit: Pooled ITT-E Population



Snapshot analysis



Adjusted treatment difference (95% CI) at Week 48^b



^aCalculated from a repeated-measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction. ^bBased on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA ($\leq 100,000$ vs $> 100,000$ c/mL) and CD4+ cell count (≤ 200 vs > 200 cells/mm³).

Figures adapted from Cahn et al. *Lancet*. 2018 [Epub ahead of print].

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Potency Analysis

- Initial viral load decline by BL VL >100,000 c/mL
- Time to suppression by BL VL >100,000 c/mL
- Efficacy by BL VL strata >100,000, >250,000, >400,000, and >500,000 c/mL

Viral Load Decline Through 48 Weeks in All Participants: Pooled ITT-E Population

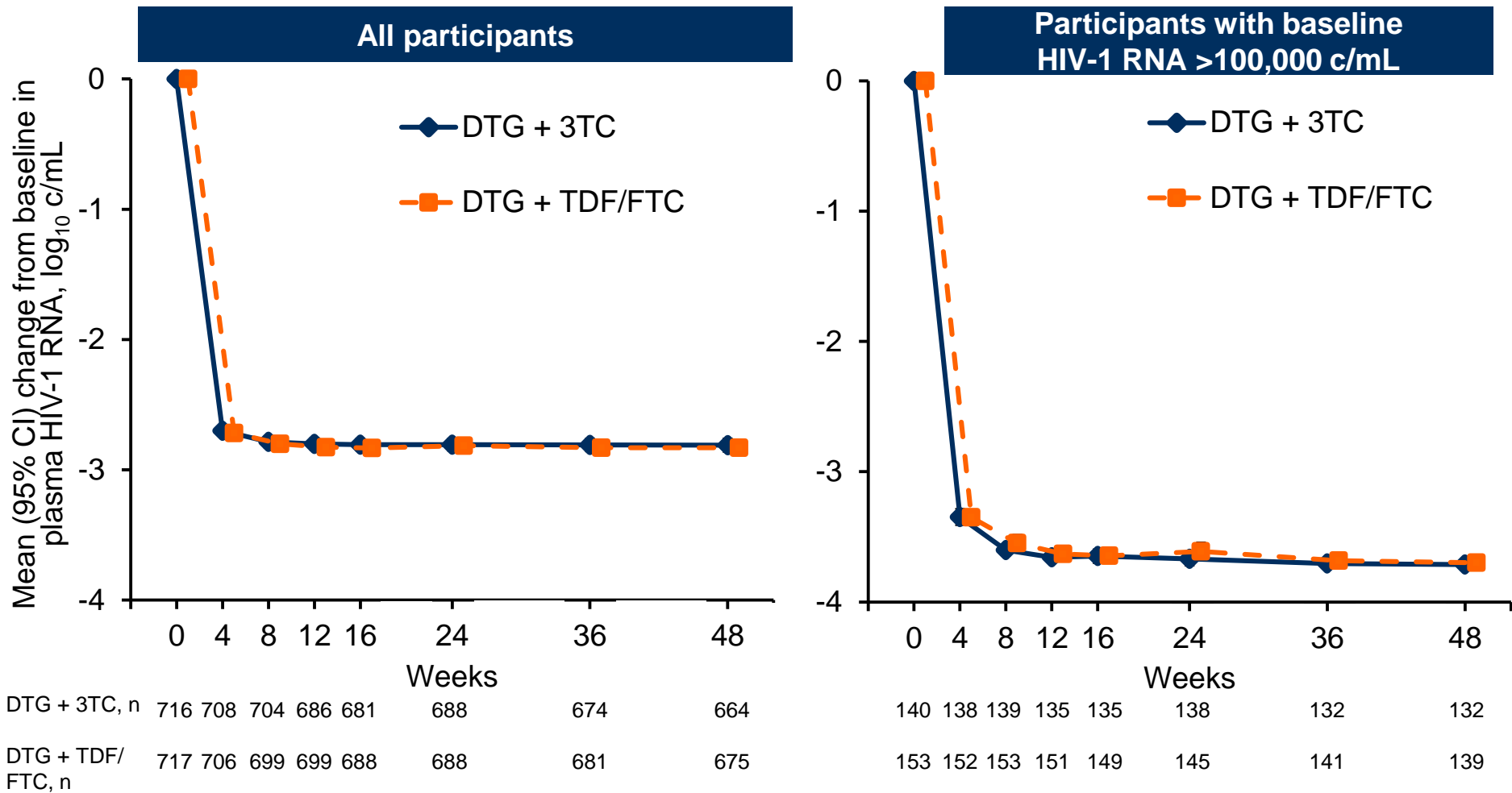


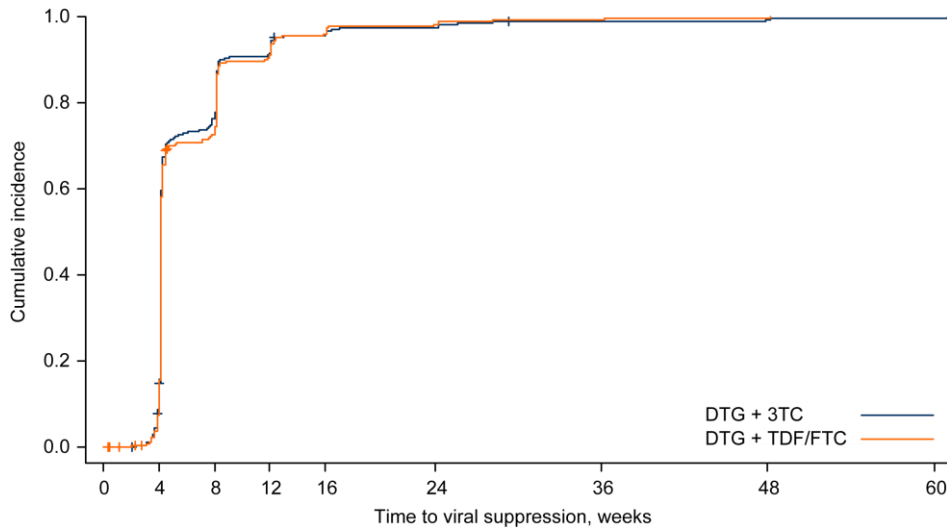
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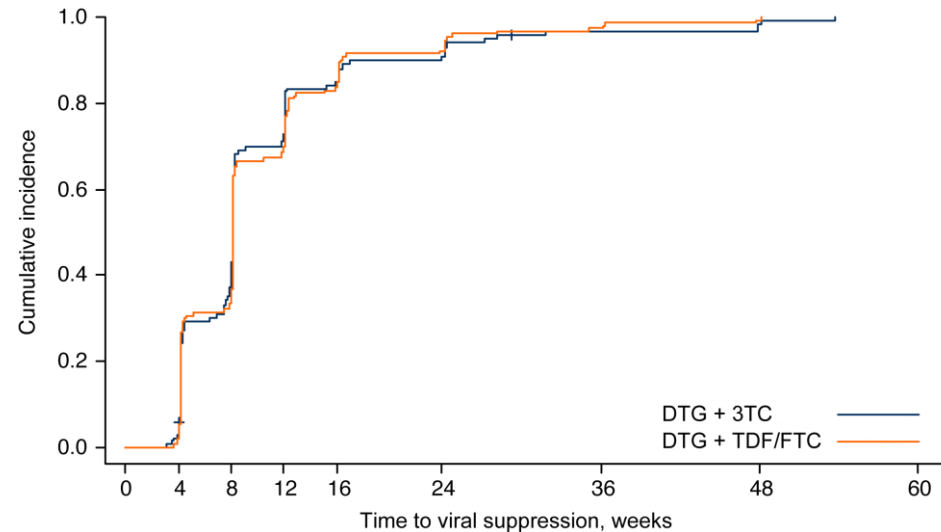
Time to Viral Suppression: Pooled ITT-E Population



All participants



Participants with baseline HIV-1 RNA >100,000 c/mL

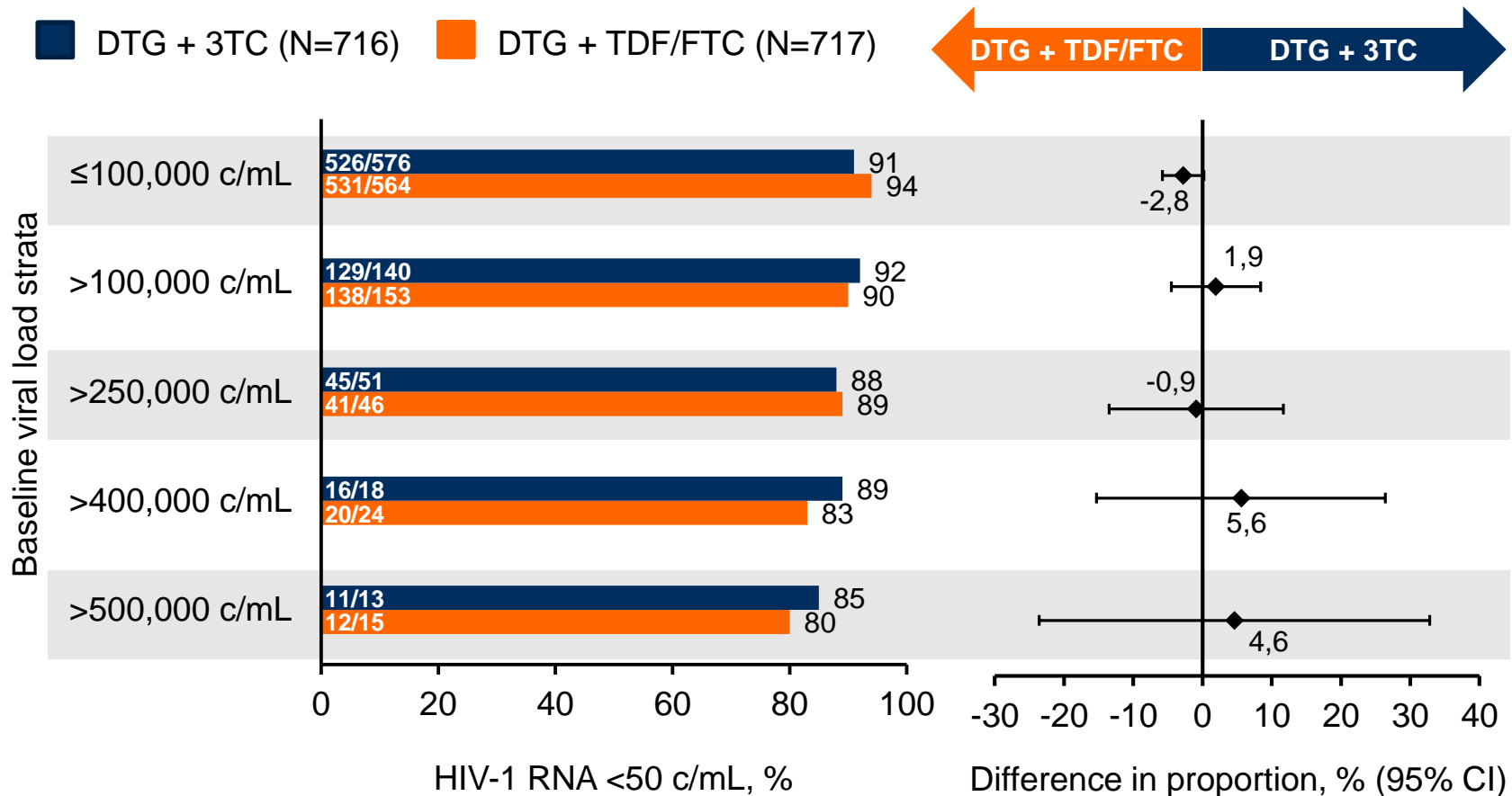


Time to viral suppression	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Median (95% CI), days	29.0 (NE-NE)	29.0 (NE-NE)
Hazard ratio (95% CI)	1.01 (0.91-1.12)	

Time to viral suppression	DTG + 3TC (N=140)	DTG + TDF/FTC (N=153)
Median (95% CI), days	57.0 (56.0-57.0)	57.0 (NE-NE)
Hazard ratio (95% CI)	1.00 (0.79-1.26)	

NE = Not Estimable. 95% CI for the quartile cannot be estimated

Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA: Pooled ITT-E Population



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Participants With Viral Load >500,000 c/mL at Baseline



DTG + 3TC			DTG + TDF/FTC		
Baseline VL, c/mL	Time to viral suppression	Snapshot outcome <50 c/mL at Week 48	Baseline VL, c/mL	Time to viral suppression	Snapshot outcome <50 c/mL at Week 48
500-750K	48 weeks	✓	500-750K	8 weeks	✓
	8 weeks	✓		36 weeks	✓
	12 weeks	✓		16 weeks	✓
	16 weeks	No virologic data ^a		36 weeks	✓
	8 weeks	✓		12 weeks	✓
	36 weeks	✓		12 weeks	✓
	16 weeks	✓		4 weeks	≥50 c/mL ^c
	8 weeks	✓		16 weeks	No virologic data ^a
750-1,000K	8 weeks	✓	750-1,000K	8 weeks	✓
	8 weeks	✓		4 weeks	✓
	48 weeks	✓		12 weeks	✓
1,000-2,500K	24 weeks	✓		4 weeks	No virologic data ^a
	Not reached	No virologic data ^b		36 weeks	✓
			1,000-2,500K	12 weeks	✓

- Of participants with baseline VL >500,000 c/mL, only 3/13 in the DTG + 3TC group and 5/15 in the DTG + TDF/FTC group had baseline CD4+ cell count ≤200 cells/mm³
- No participants met confirmed virologic withdrawal criteria^d

^aParticipant discontinued study for other reason. ^bParticipant discontinued shortly after baseline for not meeting entry criteria (screening viral load >500,000 c/mL). ^cParticipant reached HIV-1 RNA <40 c/mL at Week 4, had 205 c/mL at Week 24, and again reached <40 c/mL at Week 36. ^dDefined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound. Virologic non-response is defined as either a decrease in plasma HIV-1 RNA of <1 log₁₀ c/mL by Week 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL or confirmed plasma HIV-1 RNA ≥200 c/mL on or after Week 24. Virologic rebound is defined as confirmed rebound in plasma HIV-1 RNA to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

Conclusions

- The magnitude and speed of viral load decline with DTG + 3TC were comparable to those with DTG + TDF/FTC, irrespective of baseline VL
- Time to viral suppression with DTG + 3TC was comparable to that with DTG + TDF/FTC, irrespective of baseline VL
- Response rates in participants with baseline VL >100,000 c/mL (including those with baseline VL >500,000 c/mL) were high with DTG + 3TC and similar to those with DTG + TDF/FTC
- These data further demonstrate the high potency of DTG + 3TC and support the efficacy of this 2-drug regimen for the treatment of HIV-1 infection

Acknowledgments

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Cahn	Angel	Antinori	Den Hollander	Arbune	Antela Lopez	Calmy	Eron	Clarke
Cassetti	Baril	Barchi	Rijnders	Jianu	Arribas Lopez	Hauser	Fife	Gazzard
David	Conway	Caramello		Oprea	Casado Osorio	Fehr	Fichtenbaum	Fox
Figueras	de Pokomandy	Castelli	<u>Peru</u>	Preotescu	Castaño Carracedo		Flamm	Johnson
Losso	Szabo	Cattelan	Hidalgo	Prisacariu	De Los Santos Gil	<u>Taiwan</u>	Goldstein	Kegg
Lopardo	Walmsley	D'Arminio Montforte	Hercilla Vasquez		Estrada Perez	Cheng	Gupta	Khoo
Lupo		Di Biagio	Illescas	<u>Russia</u>	Falco Ferrer	Ko	Hagins	Mazhude
Porteiro	<u>France</u>	Di Perri		Belonosova	Force	Lin	Hoffman-Terry	Orkin
Sánchez	Bouchaud	Gori	<u>Poland</u>	Borodkina	Galinda Puerto	Lu	Jayaweera	Schembri
	Chidiac	Gulminetti	Olczak	Chernova	Garcia Deltoro	Hung	Kinder	Ustianowski
<u>Australia</u>	Delobel	Maggiolo		Gankina	Gatell	Tseng	Klein	
Bloch	Girard	Menzaghi	<u>Portugal</u>	Kizhlo	Goenaga Sanchez	Wang	McDonald	
Cooper	Goujard	Migliorino	Mansinho	Kulagin	González Cordón	Wong	Mills	
Finlayson	Katlama	Mussini	Correia Pacheco	Kurina	Knobel	Yang	Nahass	
Kelleher	Molina	Penco	Teófilo	Nagimova	Lopez Bernaldo de Quiros		Ortiz	
Koh	Pialoux	Puoti	Saraiva da Cunha	Pokrovsky	Losa Garcia	<u>USA</u>	Osiyemi	
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McMahon	Philibert	Lazzarin	Serrão	Voronin	Montero-Alonso	Benson	Parks	
Moore	<u>Germany</u>	Quirino		Yakovlev	Ocampo Hermida	Berhe	Prelutsky	
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