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Efficacy and Safety of Dual Therapy With Dolutegravir/Lamivudine in Treatment-naive Persons With CD4 Counts <200/mm^3: 48-Week Results of the DOLCE Study

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Background. Dolutegravir (DTG)/lamivudine dual therapy (DT) has demonstrated noninferiority to triple therapy (TT) in the GEMINI trials. Although the population with ≤200 CD4 cells/mm^3 had a lower response rate, this was unrelated to virological failure. This trial evaluated the antiviral of dolutegravir/lamivudine among antiretroviral therapy (ART)-naive patients with human immunodeficiency virus (HIV) with a CD4 count ≤200 cells/mm^3.

Methods. DOLCE is a randomized, hypothesis-based, open-label, multicenter study l, assessing the antiviral efficacy of DTG/3TC at week 48 in treatment-naive people with HIV (PWH) with CD4 counts ≤200 cells/mm^3. Participants were randomly assigned in a 2:1 ratio to receive DTG/3TC as a single tablet regimen or DTG plus Tenofovir disoproxil fumarate (TDF)/XTC: Emtricitabine or lamivudine (FTC or 3TC). The primary endpoint was the proportion of participants with pVL <50 copies/mL at week 48 (Food and Drug Administration snapshot analysis intent-to-treat exposed population). This report presents results at week 48.

Results. Baseline characteristics were similar in both arms. In the DT arm, median CD4 cell count was 109 cells/mm (interquartile range [IQR]: 49–177) and median pVL was 180,000 copies/mL (IQR: 53 309–468 691); 45.4% had CD4 <100 cells/mm^3, and 61.4% had pVL >100 000 copies/mL. CDC (Centers for Disease Control and Prevention) stage C: 31.4%. At week 48, virological suppression (pVL <50 copies/mL) was achieved 82.2% in the DT (125/152), and the CD4 count increased by +200 cells/mm^3. Per-protocol analysis showed a response rate of 91.9%. Severe adverse events ($n = 17$) were reported in 15 of 152 participants (11.1%).

Conclusions. Dolutegravir/3TC demonstrated high efficacy in a population with low CD4 counts and high viral load. This study adds information regarding the efficacy and safety of DTG/3TC, regardless of baseline CD4 counts and viral load.

Clinical Trials Registration. NCT04880395.

Keywords. HIV; dual therapy; naive; advanced disease.

Dolutegravir (DTG)–based antiretroviral regimens emerged as a potent and well-tolerated antiretroviral therapy (ART) option. When combined with lamivudine (3TC), DTG offers a simplified, once-daily regimen with a favorable safety profile. Dolutegravir plus 3TC is the only recommended 2-drug regimen for initial human immunodeficiency virus (HIV) treatment in international guidelines, except for individuals with HIV-1 RNA >500 000 copies/mL, hepatitis B virus coinfection, or after preexposure prophylaxis failure [1–3].

While the efficacy and safety of DTG plus 3TC have been established in treatment-naive individuals with higher CD4 cell counts [4, 5] as well as a simplification strategy among virally suppressed patients [6, 7], data on its performance in individuals with advanced HIV remain limited. Most available data come from retrospective cohorts [5, 8–10]. The GEMINI trials suggested a lower treatment response among participants with baseline CD4 count ≤200 cells/mm^3 in the dual-therapy (DT) arm, but the number of participants in this subgroup was small, and nonresponse was unrelated to efficacy [4].

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Dolutegravir plus 3TC DT has many potential benefits, including reduced cumulative toxicity, lower costs [11, 12], and preservation of NRTI activity after failure. However, limited data exist among people with advanced HIV disease. Given that a substantial proportion of people with HIV (PWH) present to care with advanced disease, particularly in lower-income settings, further investigation is critical [13, 14].

The primary objective of the DOLCE trial was to assess the antiviral activity of DTG + 3TC among ART-naive adults with HIV and a CD4 count ≤200 cells/mm^3.

METHODS

Study Design

The DOLCE study was a Phase IV, randomized (for secondary objectives comparison purposes), open-label, hypothesis-based, multicenter trial conducted in 11 sites in Argentina and Brazil between 17 May 2021 and 7 May 2024. Study protocols were approved by investigational ethics committees following the Helsinki Declaration and the International Conference on Harmonisation Guidelines for Good Clinical Practices. Written informed consent was provided by each participant before enrollment. DOLCE was registered on Clinical Trials.gov (NCT04880395).

Participants

Eligible participants were nonpregnant, not breastfeeding adults (18 years or older) with HIV-1, ART naive, having plasma HIV-1 (pVL) RNA ≥1000 copies/mL at screening, CD4 cell counts ≤200 cells/mm^3, and be able to consent to participation. Key exclusion criteria included a positive hepatitis B coinfection, preexisting major viral resistance mutations to DTG, 3TC, or Tenofovir disoproxil fumarate (TDF), active opportunistic infections, and liver or kidney disease. Eligibility criteria are listed in the Supplementary Appendix.

Randomization and Masking

Participants were randomly assigned (2:1) to either DTG/3TC (DT) or DTG plus TDF/XTC (triple therapy [TT]) for 48 weeks using a computer-generated randomization scheme, through REDCap. Randomization was stratified by country and viral load (VL, ≥100 000 or <100 000 copies/mL) and served secondary treatment comparison objectives.

Procedures

Participants received either a single tablet regimen of DTG (50 mg) coformulated with 3TC (300 mg) or 2 tablets of a 3-drug regimen of DTG (50 mg) plus a fixed-dose combination of TDF (300 mg)/emtricitabine (FTC, 200 mg) or 3TC (300 mg) (XTC). Both treatments were administered orally, once daily.

The screening period was limited to 10 days, followed by a 48-week treatment period and a 4-week posttreatment follow-up period to document adverse events (AEs). Study visits occurred at screening, baseline, weeks 4, 12, 24, 36, 48, and end-of-study. Assessments included medical history, physical examination, vital signs, laboratory tests, AEs, adherence monitoring (self-administered ACTG [AIDS Clinical Trials Group] questionnaires), health-related quality of life EQ-5D-5L (EuroQOL five dimensions), and depression PHQ-9 (Patient health questionnaire) assessments. Details are shown in Supplementary Table 1.

All laboratory tests in Argentina were performed at a central laboratory, while those in Brazil were conducted at local site laboratories. The Laboratories were required to meet CLIA (Clinical Laboratory Improvement Ammendments) or country-equivalent standards. Plasma HIV-1 RNA levels were determined using the Abbott Real-time HIV-1 assay (Abbott Molecular, Inc., Des Plaines, IL, USA). Genotypic resistance testing was performed at screening, but participants were randomized and initiated treatment before results were available, due to the urgency of treatment and low risk of primary resistance. Genotypic assays utilized included the following: nested PCR followed by Sanger sequencing (ViroSeq, Thermo Fisher) in Brazilian samples and MagnaPure 96 DNA and Viral NA Small Volume Kit (Roche) followed by Nextera® XT DNA Library Preparation Kit and MiSeq reagent kit (Illumina, USA) in Argentinian samples. Those participants whose resistance test showed evidence of resistance to DTG (mutations: G118R, Q148 H/K/R, N155H, or R263K), lamivudine (M184V/I), or tenofovir (K65R or more than 3 TAMs [Thymidne analogue mutations]) were discussed with the study medical monitor.

Participants were discontinued from the study if they met virological failure criteria, required dose modifications, met toxicity stopping rules, or experienced an AE Grade 4 considered related to treatment. Virological withdrawal criteria were as follows: a confirmed virological rebound (ie, rebound in plasma HIV-1 RNA levels ≥200 copies/mL after prior virological suppression to ≤200 copies/mL) or virological nonresponse (ie, decrease from baseline in HIV-1 RNA of <1 log10 copies/mL unless HIV-1 RNA <200 copies/mL, by week 12 or confirmed plasma HIV-1 RNA of 200 copies/mL or more at or after week 24). In case of virological failure, a genotyping resistance test was performed.

Outcomes

The primary objective of DOLCE study was to assess the antiviral activity at week 48 of DTG/3TC among ART-naive patients with HIV with a CD4 count ≤200 cells/mm^3, with the primary endpoint being the proportion of patients with VL <50 copies/mL at week 48 using the Food and Drug Administration (FDA) snapshot algorithm [15] intent-to-treat exposed (ITT-E) population. Secondary endpoints included: the proportion of participants in each arm with VL <50 copies/mL at week 24 as well as the proportion of those with baseline VL >100 000 copies/mL that achieved virological suppression at week 48; change from baseline in CD4 cell count

at week 24 and 48; HIV disease progression; and the emergence of resistance mutations in participants with confirmed virological non response. Safety was evaluated by the incidence and severity of AEs and the proportion of participants who discontinued due to AEs.

Statistical Analysis

As a hypothesis-based study, the sample size was estimated to detect a response rate >70% in the DT arm. Based on GEMINI studies results [5], we anticipated an 80% response rate in the DT arm. A sample size of 230 participants, 153 in the DTG/3TC arm and 77 in the DTG plus TDF/XTC, would provide 85% power to detect a response >70% in the DT arm. The primary efficacy analysis of DTG/3TC was conducted in the ITT-e population—participants who were randomized and received ≥1 dose—excluding those with major protocol violations or virological failures occurring after Week 24, using the FDA Snapshot algorithm. Per-protocol (PP) analysis was also performed excluding participants with major protocol violations and/or virological failures after week 24. Efficacy endpoints were reported as frequencies, percentages, and 95% CIs. A posthoc efficacy comparison was calculated as the risk difference with 95% CI (for both ITT-E and PP populations), adjusted for VL at screening (HIV-1 RNA >100 000 vs ≤100 000 c/mL) and country, using the Cochran–Mantel–Haenszel test. This secondary noninferiority analysis (significance level 0.05) used a 10% margin for the difference in the proportion of participants with <50 copies/mL at week 48. Safety assessment was described as number of AEs and serious AEs (SAEs). The incidence of EAs and SAEs was also calculated (multiple occurrences of the same event in one individual were counted only once). To assess the changes in VL and CD4 count over time and between arms, mixed effects linear models were fitted, with subjects as random term, the treatment group and time as factors, and the stratification variables as covariables. The time to viral suppression was

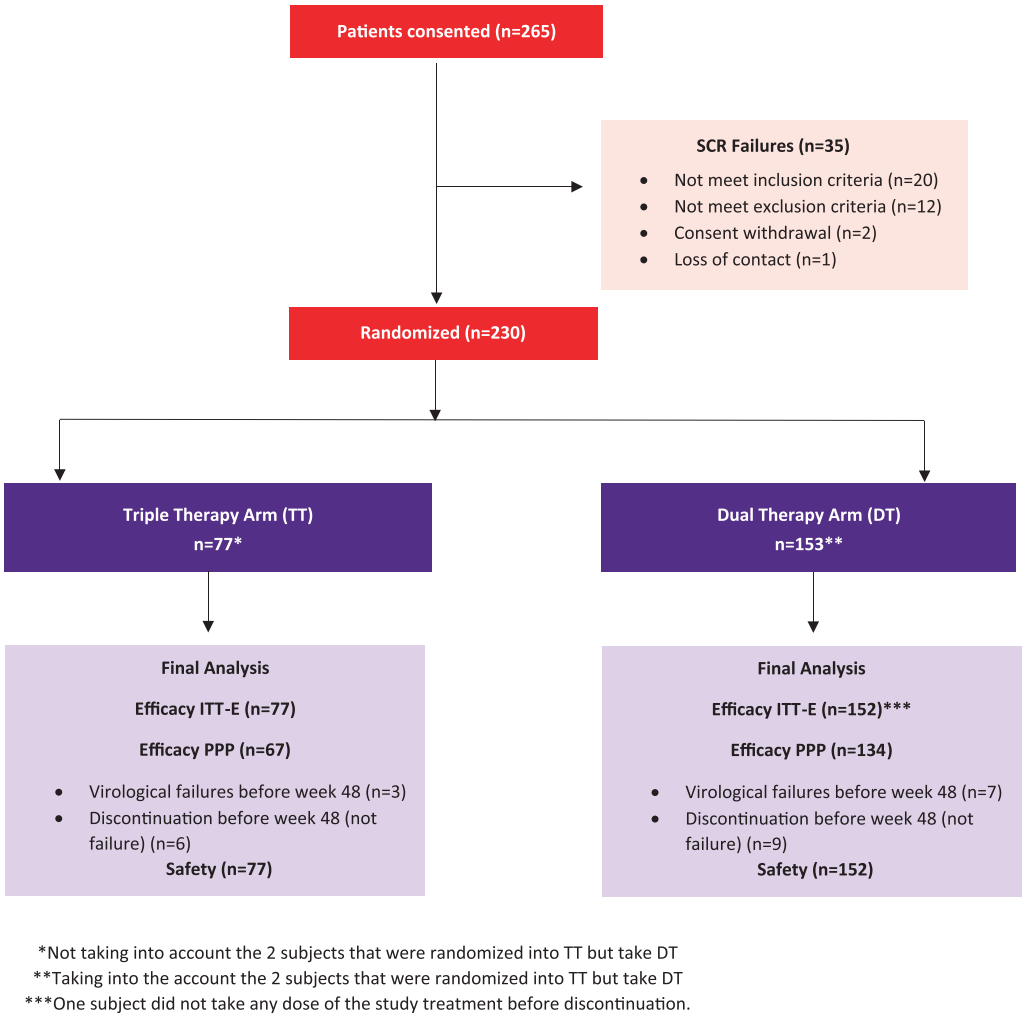

Figure 1. Flow diagram illustrating participants' progression through each study stage.

estimated using the Kaplan–Meier method. All analyses were conducted using R: A Language and Environment for Statistical Computing version 4.4.1 (Foundation for Statistical Computing, Vienna, Austria). The study was registered with ClinicalTrials.gov NCT04880395.

RESULTS

Between 17 May 2021, and 3 May 2023, 265 participants were screened, of whom 230 were eligible and randomized: 151 to the DTG/3TC arm and 79 to the DTG plus TDF/XTC arm. However, 2 participants randomized to the TT arm received

Table 1. Participant Demographics and Baseline Characteristics

	Total $n = 230$	TT $n = 77$	DT $n = 153$
Sex at birth, *n* (%)			
Female	56 (24.3%)	21 (27.3%)	35 (22.9%)
Male	174 (75.7%)	56 (72.7%)	118 (77.1%)
Gender, *n* (%)			
Male	167 (72.6%)	53 (68.8%)	114 (74.5%)
Female	57 (24.8%)	22 (28.6%)	35 (22.9%)
Transgender	5 (2.2%)	2 (2.6%)	3 (2.0%)
Other	1 (0.4%)	0 (0.0%)	1 (0.7%)
Age, median (IQR)	35 (28, 47)	34 (28, 47)	36 (29, 48)
Race, *n* (%)			
Black	35 (15.2%)	9 (11.7%)	26 (17.0%)
Native	8 (3.5%)	0 (0.0%)	8 (5.2%)
Other (Hispanic-Latino/mixed)	98 (42.6%)	31 (40.3%)	67 (43.8%)
White	89 (38.7%)	37 (48.1%)	52 (34.0%)
Body mass index, median (IQR)	23 (20.0, 25)	23 (20.1, 25)	22 (19.9, 24)
Sexual risk behaviors, *n* (%)			
Heterosexual contact	111 (48.3%)	41 (53.2%)	70 (45.8%)
MSM contact	104 (45.2%)	29 (37.7%)	75 (49.0%)
Other	6 (2.6%)	2 (2.6%)	4 (2.6%)
Unknown	9 (3.9%)	5 (6.5%)	4 (2.6%)
CDC stage, *n* (%)			
Category A	80 (34.8%)	27 (35.1%)	53 (34.6%)
Category B	75 (32.6%)	23 (29.9%)	52 (34.0%)
Category C	75 (32.6%)	27 (35.1%)	48 (31.4%)
CD4 cell count (cell/mL), median (IQR)	116 (53.3, 188)	128 (58.5, 200)	109 (48.8, 177)
CD4%, median (IQR)	8 (4, 13)	10 (4.1, 13)	8 (4, 12)
CD4 cells count ≤100 cells/mm^3, *n* (%)			
≤100 cells/mL	98 (43.4%)	29 (39.2%)	69 (45.4%)
HIV-1 RNA (copies/mL), median (IQR)	151 000 (49 027.5, 446,947)	137 084 (43 901.5, 419,628)	180 000 (57 309.5, 468,691)
HIV-1 RNA copies ≥100 000 copies/mL, *n* (%)			
≥100 000 copies/mL	141 (61.3%)	47 (61.0%)	94 (61.4%)
HIV-1 RNA copies ≥500 000 copies/mL, *n* (%)			
≥500 000 copies/mL	53 (23.0%)	18 (23.4%)	35 (22.9%)
HIV-1 RNA copies ≥1 000 000 copies/mL, *n* (%)			
≥1 000 000 copies/mL	23 (10.0%)	7 (9.1%)	16 (10.5%)
Log10 HIV-1 viral load, mean (SD)	5 (0.7)	5 (0.7)	5 (0.7)
HIV subtypes, *n* (%)			
B	143 (63.0%)	51 (68.0%)	92 (60.5%)
BF	62 (27.3%)	18 (24.0%)	44 (28.9%)
C	10 (4.4%)	3 (4.0%)	7 (4.6%)
F	7 (3.1%)	1 (1.3%)	6 (3.9%)
Others	5 (2.1%)	2 (2.5%)	3 (1.9%)
Mutations, *n* (%)			
No mutations	145 (63.0%)	51 (66.2%)	94 (61.4%)
RT: NNRT/NRTI	65 (28.3%)	20 (26.0%)	45 (29.4%)
INSTI (secondary mutations and polymorphism)	17 (7.4%)	5 (6.5%)	12 (7.8%)
PI	6 (2.6%)	1 (1.3%)	5 (3.3%)

Not available data for baseline: 4 cases for CD4 cell count and percentage (TT arm: 3; DT arm: 1); 3 HIV subtype (TT arm: 2 DT arm: 1); BMI (DT arm: 1).

Abbreviations: DT, dual therapy; IQR, interquartile range; HIV, human immunodeficiency virus; SD, standard deviation; TT, triple therapy.

Table 2. Efficacy Analysis

	Total	TT	DT	Adjusted Risk Difference (95% CI)
ITT-E (global $n = 229$; TT $n = 77$; DT $n = 152$) n (%) [95% CI]	187 (81.7%) [76%; 86%]	62 (80.5%) [70%; 88%]	125 (82.2%) [75%; 88%]	2.0% (−8.7%;12.8%)
ITT-E, baseline VL >100 000 copies/mL (global $n = 141$; TT $n = 47$; DT $n = 94$) n (%) [95% CI]	112 (79.4%) [72%; 86%]	36 (76.6%) [62%; 87%]	76 (80.9%) [71%; 88%]	5.1% (−10.1%; 20.3%)
Per protocol (global $n = 204$; TT $n = 68$; DT $n = 136$) n (%) [95% CI]	187 (91.7%) [87%; 95%]	62 (91.2%) [81%; 96%]	125 (91.9%) [86%; 96%]	1.8% (−6.3%; 9.9%)

Primary outcome VL<50 copies/mL at week 48.

Abbreviations: DT, dual therapy; ITT-E, intent-to-treat exposed; TT, triple therapy; VL, viral load.

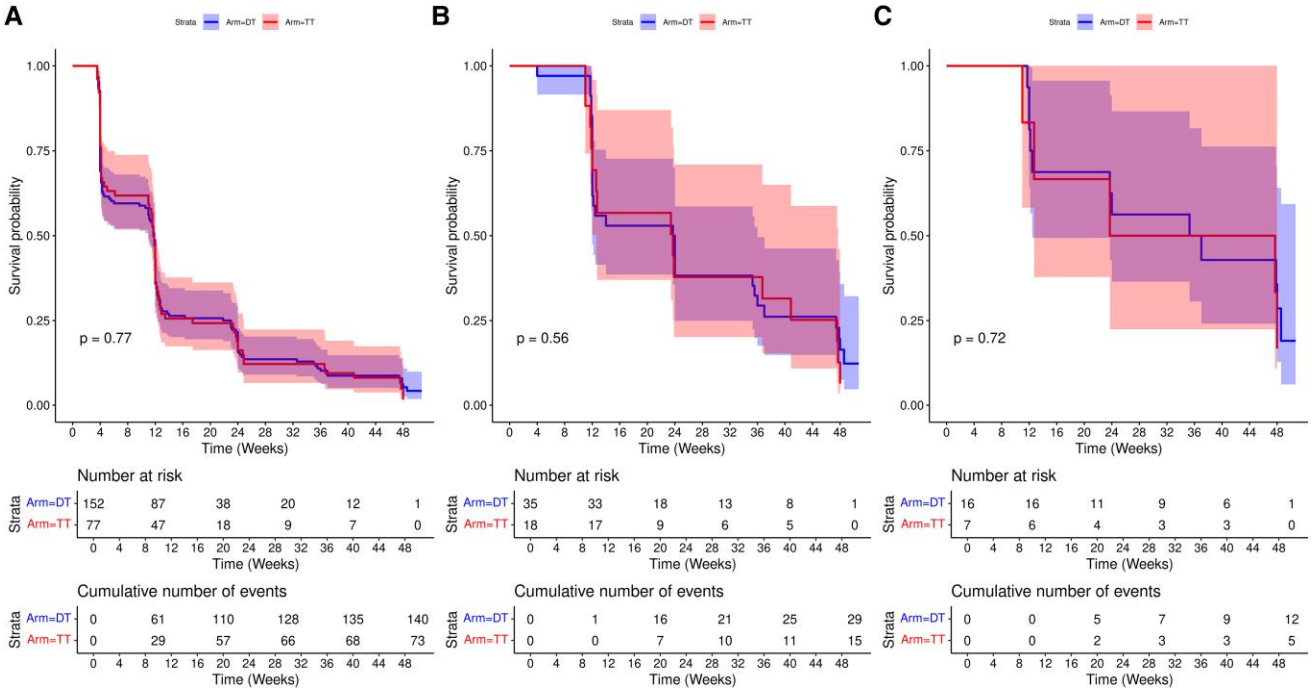

Figure 2. Kaplan–Meier curves showing time-to-viral-load suppression estimates for all subjects and each initial viral load subgroup, stratified by study arm (Fig A: Total population; Fig B: HIV RNA above 500,000 copies/mL; Fig C: HIV RNA above 1,000,000 copies/mL).

DTC/3TC by mistake and were considered in the DT arm for all the analyses. In addition, 1 participant randomized to DT arm was withdrawn before receiving any dose and excluded from all analyses (Figure 1).

Baseline characteristics were similar between the arms (Table 1). In DT arm, median CD4 cell count was 109 (interquartile range [IQR]: 49–177), median pVL 180 000 copies/mL (IQR: 57 309–468 691). At baseline, most participants were symptomatic, including 48 (31.4%) in Centers for Disease Control and Prevention (CDC) category stage C, 69 (45.4%) having a CD4 cell count ≤100 cells/mL, 94 (61.4%) having a VL >100 000 copies/mL and 35 (22.9%) having >500 000 copies/mL. Of note, 10.5% of the participants had a baseline VL >1 000 000 copies/mL. The most frequent HIV viral subtype was B, found in 92 cases (60.5%).

In the ITT-E efficacy analysis, 82.2% (95% CI: 75.0–88.0) of the participants in the DT arm achieved a VL <50 copies/mL. Efficacy among the subpopulation of participants with baseline VL >100 000 copies/mL was 80.9% (95% CI: 71.0–88.0); among participants with baseline VL >500 000 copies/mL was 74.3% (95% CI: 56.0–87.0), and among participants with baseline VL >1 000 000 copies/mL was 62.5% (95% CI: 36.0–84.0). The proportion of participants with virological suppression at week 48 in the PP analysis was 91.9% (95% CI: 86.0–96.0) (Table 2). A secondary posthoc comparative analysis showed an adjusted risk difference of 2.0% (95% CI: −8.7; 12.8) in the ITT-E population ($P = .016$); 5.1% (95% CI: −10.1; 20.3) in the subpopulation with baseline VL >100 000 copies/mL; and 1.8 (95% CI: −6.3; 9.9) in the PP population, suggesting

n(%)	DT (n=152)	TT (n=77)
Virological Success (HIV-1 RNA < 50 copies/mL	125 (82.2%)	62 (80.5%)
Virologic nonresponse	18 (11.8%)	9 (11.7%)
Data in window not < 50 copies/mL	18 (11.8%)	9 (11.7%)
Discontinued for other reasson while not < 50 copies/mL	0	0
Change in ART	0	0
No virologic data	9 (5.9%)	6 (7.8%)
Discontinued because of AE or death	5 (3.3%)	2 (2.6%)
Discontinued for other reassons	4 (2.6%)	4 (5.2%)
Missing data during window but on study	0	0

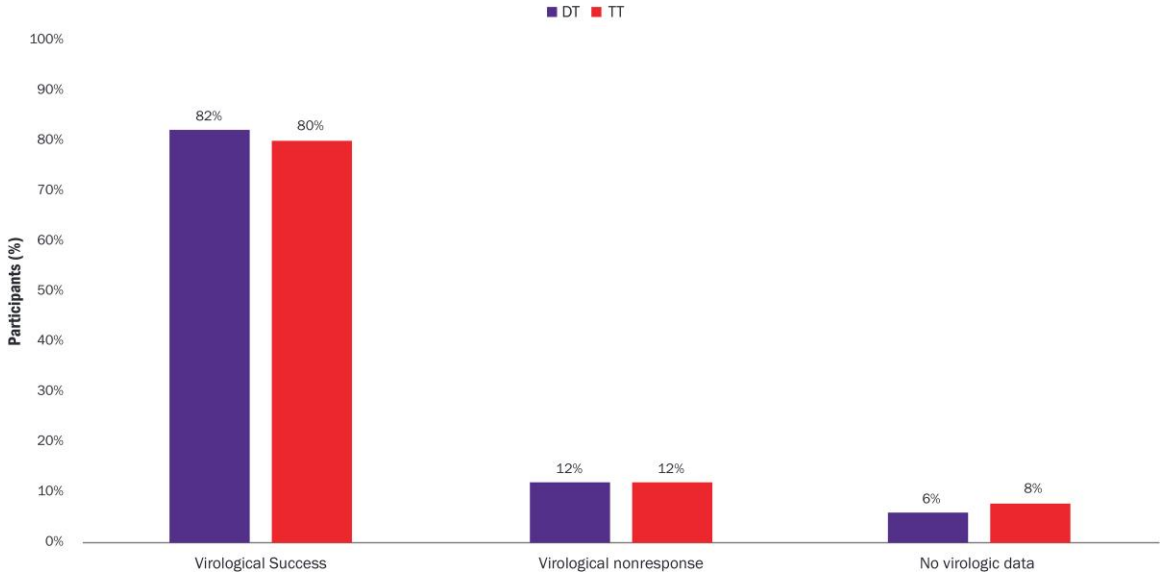

Figure 3. Table and bar plots showing the number of participants who achieved virological suppressions, exhibited nonresponse, or lacked virological data.

that the DT arm was noninferior to TT in the ITT-E population, ITT-E population with baseline VL >100 000 copies/mL ($P = .025$), and PP population ($P = .005$) (Supplementary Table 2). There was no statistically significant difference in time to viral suppression between arms, including the subpopulation with a higher baseline HIV RNA (Figure 2).

In the DT arm, 13 (8.6%) participants discontinued treatment before week 48: 6 due to AE or death, 2 due to virological failure, 2 did not meet the inclusion criteria, and 3 were lost to follow-up. Of the 6 (7.8%) participants who discontinued in the TT, 3 participants were due to loss to follow-up, 2 due to serious AEs or death, and another one due to consent withdrawal.

In the DT arm, 18 (11.8%) met the virological nonresponse criteria through week 48 (7 participants with VL >200 copies/mL at week 24 or 36 and 11 with VL >50 copies/mL at week 48). In the TT arm, 9 (11.7%) met the virological nonresponse criteria through week 48 (3 participants with VL >200 copies/mL at week 24 or 36 and 6 with VL >50 copies/mL at week 48) (Figure 3). The median VL at protocol-defined virological failure at week 48 was 114 copies/mL (IQR 72–167). Of the 27 virological nonresponses, 11 samples were successfully amplified. None had the emergence of mutations conferring resistance to INSTIs (Integrase strand transfer inhibitors) or NRTIs (Nucleoside reverse transcriptase inhibitors).

There was a significant increase in CD4 cell counts between baseline and week 48 in both arms, with a median change from baseline of +200 CD4 cells (IQR 127, 316) in the DT arm and +177 CD4 cells (IQR 128, 267) in the TT arm (Figure 4).

In the DT arm (Table 3), there were 467 AEs (84.9%; 129/152), 50 events were considered treatment related (24.3%; 37/152); 1 participant discontinued due to a treatment-related AE (0.7%; 1/152). The most frequent treatment-related AEs were skin/subcutaneous disorders (10 events, 20.0%) and gastrointestinal disorders (7 events, 14.0%). Twenty-seven events were grade 1 (54.0%), 18 were grade 2 (36.0%). and 5 were grade 3 (10.0%). Nine participants developed IRIS (Immune Reconstitution Inflammatory Syndrome) (5.9%); 2 had increased liver enzymes

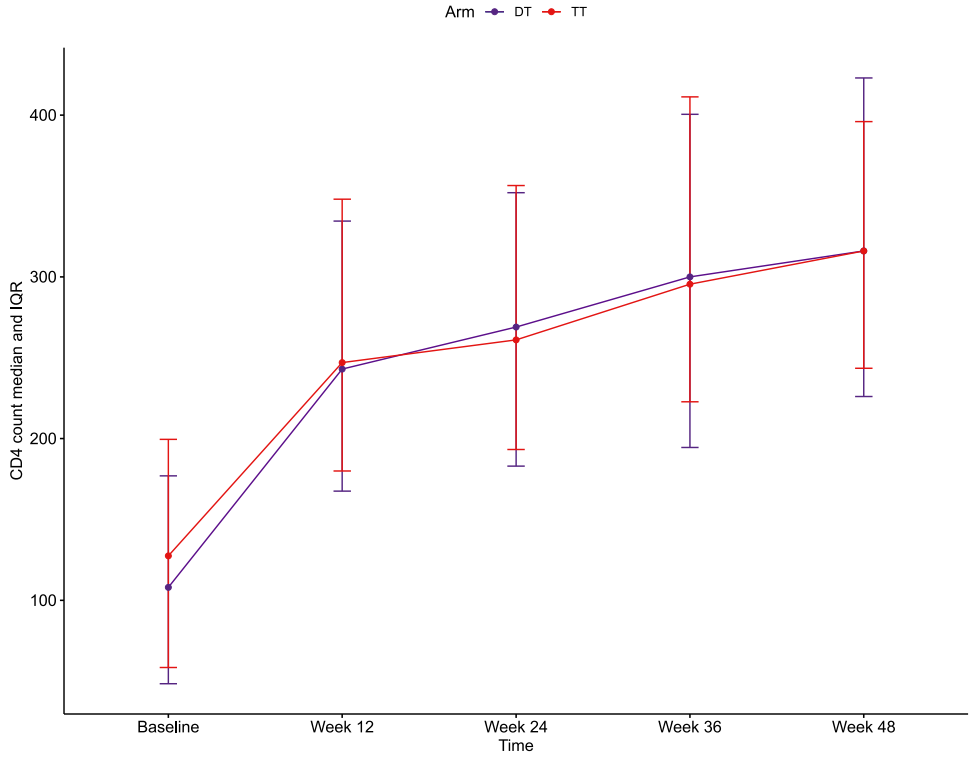

Figure 4. Line plots showing CD4 median values and interquartile ranges at each time point, stratified by study arm.

Table 3. Adverse Events

	Total ($n = 229$)	TT ($n = 77$)	DT ($n = 152$)
Participants with AEs (related to treatment, any grade), *n* (%)	58 (25.3%)	21 (27.3%)	37 (24.3%)
Participants with SAEs, *n* (%)	24 (10.5%)	9 (11.7%)	15 (9.9%)
Participants with SAEs (related to treatment), *n* (%)	3 (1.3%)	1 (1.3%)	2 (1.3%)
Deaths, *n* (%)	6 (2.6%)	2 (2.6%)	4 (2.6%)
Deaths related to treatment, *n* (%)	2 (0.8%)	1 (1.3%)	1 (0.7%)
Participants with IRIS, *n* (%)	15 (6.5%)	6 (7.7%)	9 (5.9%)

Abbreviations: AE, adverse event; DT, dual therapy; SAE, serious AE; TT, triple therapy.

(1.3%), but treatment continued as no severe hepatotoxicity was observed.

In the TT arm, there were 282 AEs (85.7%), and 33 events were considered related to treatment in any grade (27.3%); 1 participant discontinued the study due to a treatment-related AE (1.3%). Six participants developed IRIS (7.7%); 1 participant developed increased liver enzyme, without change in assignment arm as no evidence of related or severe hepatotoxicity was found.

Overall, 24 participants (10.5%) experienced 27 SAEs, 15 (9.9%) in DT and 9 (9.9%) in TT. Three participants (1.3%) experienced SAEs considered by the investigator as possibly or probably related to treatment: 2 (1.3%) in DT (disseminated TB with meningeal involvement and febrile pancytopenia) and 1 (1.3%) in TT (renal tubular acidosis + bronchopneumonia). There were 6 deaths (2.6%) overall, 4 (2.6%) in DT and 2 (2.6%) in TT. One death on each treatment arm: renal tubular acidosis + bronchopneumonia (TT) and febrile pancytopenia (DT) (0.8%) were deemed possibly and unlikely related to treatment, respectively, per site investigators.

Regarding laboratory abnormalities (Table 4), grade 2 or higher abnormalities were observed in alanine aminotransferase (ALT; DT 10.5%, TT 10.4%), hemoglobin (DT 9.2%, TT 9.1%), and low platelet count (DT 5.9%, TT 9.1%). We did not observe changes in renal function measured by creatinine values. Some abnormalities were observed exclusively at baseline. Weight changes and lipid abnormalities were similar in both arms.

One participant in the TT arm became pregnant, reported at week 18 of ART. She remained in the study with informed

Table 4. Incidence of Laboratory Abnormalities

Selected Grade 2–4 Laboratory Abnormalities (From Baseline)		
	Triple Therapy ($n = 77$)	Double Therapy ($n = 152$)
High ALT/TGP	8 (10.4%)	16 (10.5%)
Low hemoglobin	7 (9.1%)	14 (9.2%)
Low platelet count	7 (9.1%)	9 (5.9%)
High total cholesterol	2 (2.6%)	8 (5.3%)
High triglycerides	1 (1.3%)	9 (5.9%)
High LDL-cholesterol	0	5 (3.3%)
High uric acid	1 (1.3%)	3 (2.0%)
High creatinine	1 (1.3%)	2 (1.3%)

Abbreviation: ALT, alanine aminotransferase.

consent and approval from the medical monitor. Her pVL was undetectable (<40 copies) from week 4 until delivery. Pregnancy and delivery were uneventful, and the newborn tested HIV negative.

DISCUSSION

This hypothesis-based study found that DT with DTG-3TC was highly efficacious and safe among a severely immunosuppressed population of PWH with low CD4 counts and high VL. Notably, efficacy remained consistent even in participants with very high baseline VLs (≥500 000 and ≥1 000 000 copies/mL). Also, our posthoc comparative analyses suggested no significant differences between the DT and TT treatment arms in virological efficacy outcomes, CD4 cell count recovery, and treatment-related AEs. Altogether, these findings support DTG/3TC as a safe and effective initial ART option regardless of baseline CD4 counts and VL.

The GEMINI studies demonstrated high and durable efficacy of DT with DTG/3TC up to 144 weeks in a high proportion of ART-naive PWH [5]. However, the GEMINI studies excluded people with baseline VL >500 000 copies/mL, and a lower response rate was documented in a small subset of participants with baseline CD4 cell count ≤200 cells/mm^3. The DOLCE study extends the findings of the GEMINI studies by confirming the efficacy and safety of DT with 3TC-DTG in a severely immunosuppressed population of PWH (ie, 45.4% had a baseline CD4 count ≤100 cells/mm^3, 31.4% were in CDC category C, and 22.9% had a baseline VL >500 000 copies/mL). In ITT-E analysis, 82.2% of the participants achieved plasma HIV-1 RNA of <50 copies per mL at week 48 (as per the FDA snapshot algorithm), which, although lower than the observed rate in the GEMINI studies (90%), was similar to the observed suppression rate in the subgroup with ≤200 cells/mm^3 (79%) in the GEMINI trials, and not significantly different to the TT arm in the DOLCE study (80.5%). Of note, similar to the GEMINI studies, most cases of snapshot failures were related to a lack of virological data (11%) rather than a lack of efficacy (8%). The high efficacy of the DT arm in this population was also confirmed by the PP analysis showing a 91.9% VL suppression rate at week 48.

Another important finding of the DOLCE study is that although values of virological success for the DT arm in the subgroups of participants with very high VL were lower than the overall results (74.4% for VL >500 000 copies/mL and 62.5% for VL >1 000 000 copies/mL), there were no significant differences with the TT arm in the same subgroup of participants.

Although the 48-week success rate of DTG-based DT in the subpopulation of people with baseline VL >500 000 is lower than rates observed in prior studies, results and comparisons should be done with caution, given the small sample in the subgroup of participants with very high baseline VL in all the studies [4, 16, 19]. Regardless, the collective evidence to date, including no significant differences with TT, suggests that DTG-based DT may be considered as a viable treatment option even in ART-naive PWH with very high baseline VL [9, 10, 17–19].

A concern regarding DT regimens is the potential for increased risk of resistance emergence in case of virological failure, particularly in the context of very high baseline VL. In our study, 27 (11.8%) participants had confirmed virological failure. As most virological failures had a VL <400 copies/mL, only a subset of 11 samples could be amplified for genotypic testing, with no evidence of emergence of resistance to either INSTIs or NRTIs. These findings provide additional reassurance regarding the robustness and high genetic barrier of DTG-based regimens, even in severely immunosuppressed PWH with high VL.

Overall, the study regimens were safe and well tolerated. There were 6 deaths, with one of them in each arm considered related to the treatment. This association reported by the investigators (possibly related and unlikely, respectively) was related to the start of treatment in the context of a possible AIDS-defining illness not diagnosed in time, but was not considered as toxicity associated with the treatment. No unexpected AEs were observed.

This study has some limitations, including the relatively small sample size. Although a posthoc analysis suggested the noninferiority of the DT arm versus the triple arm, the sample size precluded us from conducting adequately powered comparative analyses. In particular, the relatively small sample size of the TT arm might affect the direct comparison accuracy.

Additionally, the study population consisted mostly of males younger than 50 years old from 2 South American countries, and thus, extrapolation of our findings to other subgroups of PWH or in other settings should be made with caution. Also, the DT arm was provided as a single tablet regimen, while the TT arm required 2 separate tablets a day, which might have impacted participants' adherence, albeit this was not observed in the adherence reports. Finally, follow-up was limited to 48 weeks; longer follow-up might be needed to confirm our findings.

In conclusion, the results of this study add important information regarding the efficacy and safety of DT with DTG-3TC, regardless of baseline CD4 counts and VL. Real-life cohort studies might add further evidence regarding the efficacy, safety, and durability of DT with DTG-3TC in the population of PWH with advanced immunosuppression.

Supplementary Data

Supplementary materials are available at *Clinical 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

Author contributions. O. S., C. B., M. I. F., and P. C. conceived and designed the study. P. C., O. S., and C. B. procured the funding. M. I. F., D. C., and UEM teams implemented and coordinated the study at all sites. Principal investigators and the research team at each site performed the recruitment, clinical supervision, and data collection. Quality assurance for the entire study was conducted by D. C. and monitors in each country. J. V. M., G. M., MD, and MC designed the electronic case report and performed the data management and statistical analyses. MD and AG performed the lab procedures for the study in Argentina. P. C., C. B., and M. I. F. contributed to the interpretation of the results. M. I. F., D. C., and G. M. prepared the final report. E. S., M. I. F., and P. C. wrote the original draft, and all authors reviewed and approved the final version of the paper. All authors had full access to all the data in the study, and M. I. F. had final responsibility for the decision to submit for publication.

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Potential conflict of interest. M. I. F. served as an investigator for GlaxoSmithKline, ViiV Healthcare, and Merck; C. B. has participated on advisory boards and served as speaker for Gilead, GSK, and Merck and served as an investigator for GSK and Merck. P. C. has participated at advisory boards for Gilead, ViiV, and Merck and DSMB for Moderna. A. R. served as an investigator for GlaxoSmithKline, ViiV Healthcare, Gilead, and Johnson; A. R. has participated on advisory boards for Johnson and as a speaker for Johnson, AbbVie, and Novartis. D. C. served as an Advisory Board and speaker for GSK and also as a speaker for Gilead/Gador and MSD. M. J. R. has participated in advisory boards for ViiV Healthcare. P. P. has no conflict of interest in this study.

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