SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 25

TIME TO WEBINAR IN INFECTIOUS DISEASES

PROGETTO DI FORMAZIONE

Anno Accademico 24/25

LATE PRESENTER (LP) E INR: DUE FACCE DELLA STESSA MEDAGLIA?

Milano, 8 Settembre 2025

ASST Santi Paolo e Carlo – Aula Fleming

Terapia antiretrovirale

La terapia antiretrovirale oggi nei LP

- **Quale spazio per la terapia a 3 farmaci**
  Stefano Rusconi (Legnano-Milano)
- **Quale spazio per la terapia a 2 farmaci**
  Diego Ripamonti (Bergamo)

Disclosures

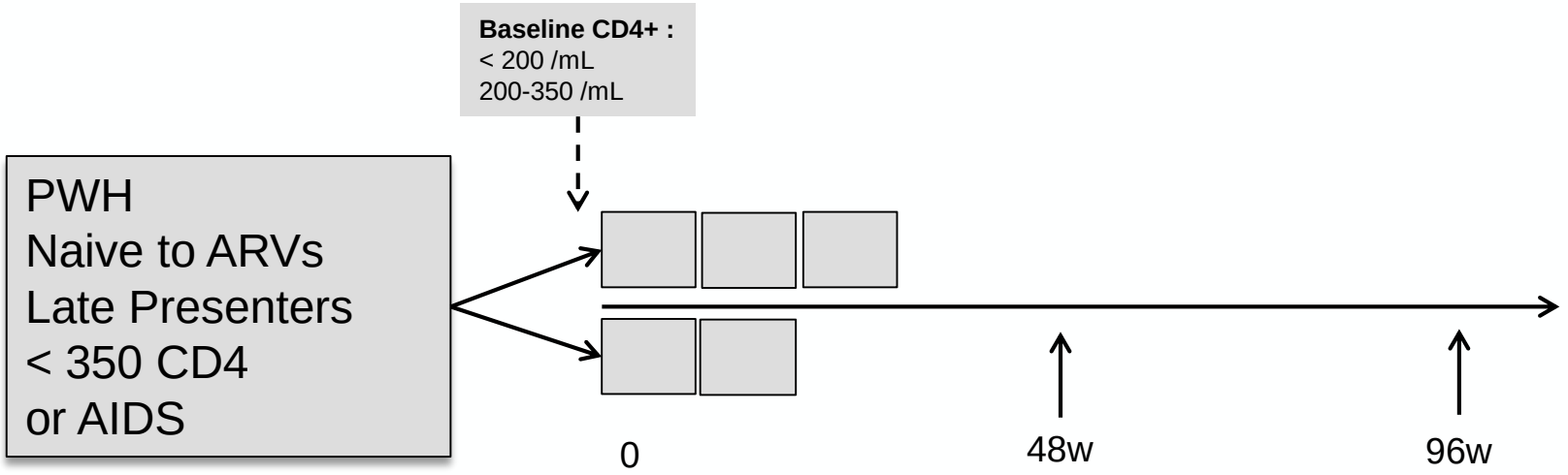
Il sottoscritto RIPAMONTI DIEGO
in qualità di relatore

ai sensi dell’art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Janssen, Merck, Gilead, ViiV Healthcare

HIV therapy in late presenters: study design for 2vs 3DR

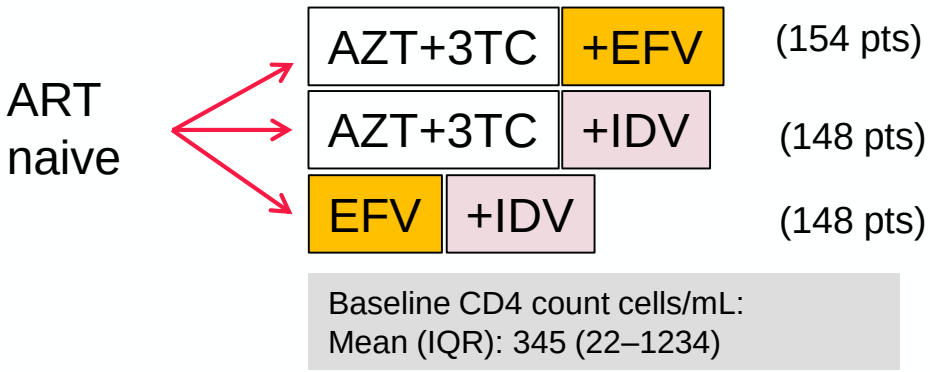


Primary end point:
< 50 copies/ml, ITT analysis

Secondary end points:
CD4+ count increase
.....

HIV therapy in late presenters: study design for 2vs 3DR

Study ACTG 006 (year:1999)



Stazewski S. et al. N Engl J Med 1999;341:1865-73.

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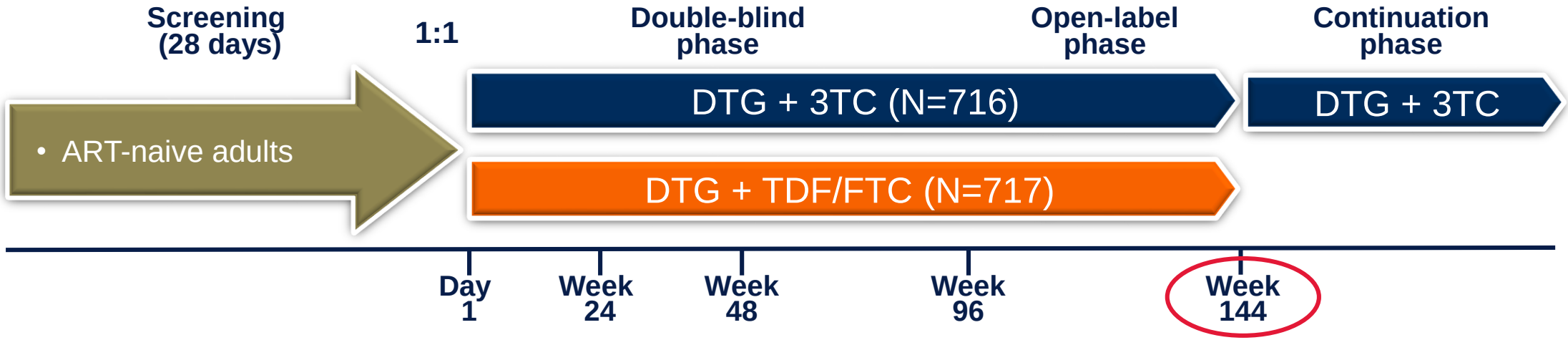
GEMINI 1&2 trials

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



Eligibility criteria
- VL 1000-500,000 c/mL at screening
- ≤10 days of prior ART
- No major RT or PI resistance mutation
- 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

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).

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

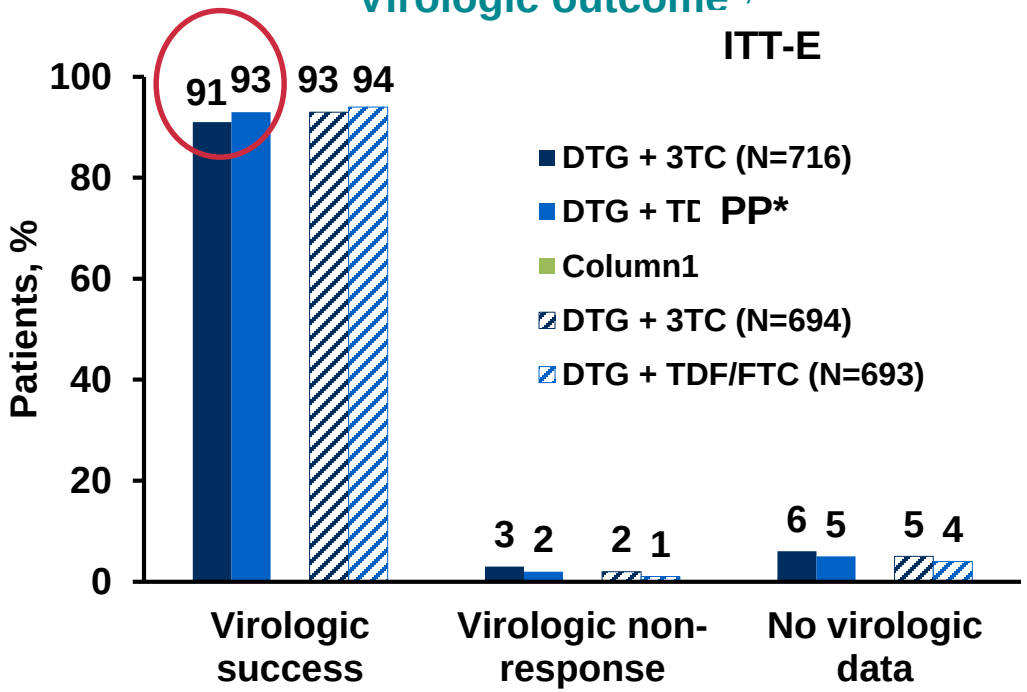
Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

GEMINI 1&2 trials

Baseline CD4 count
mean (SD): 462 (219)
< 200 c/mL: 9%

week 48

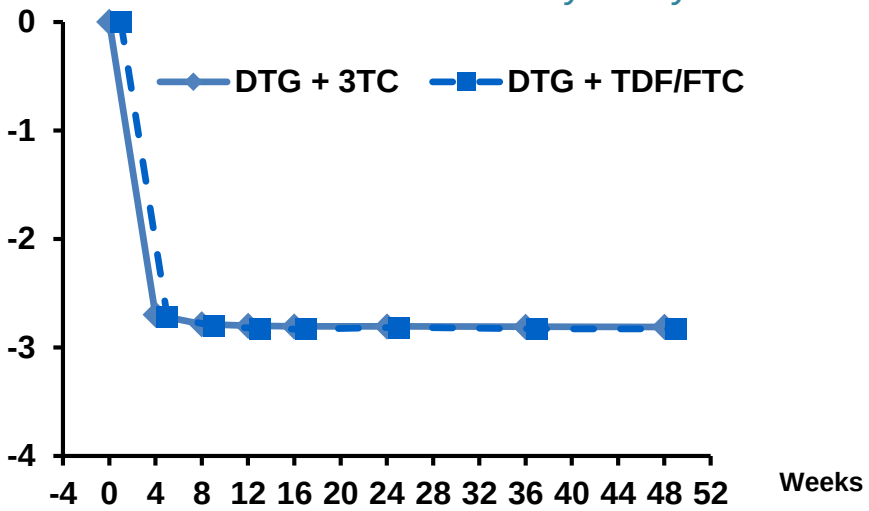
Virologic outcome[1,2]



- Data pooled from both GEMINI-1 and -2 studies
*PP population consisted of subjects in the ITT-E population except those with protocol violations that could affect assessment of antiviral activity; †Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm³).[1] PP, per protocol

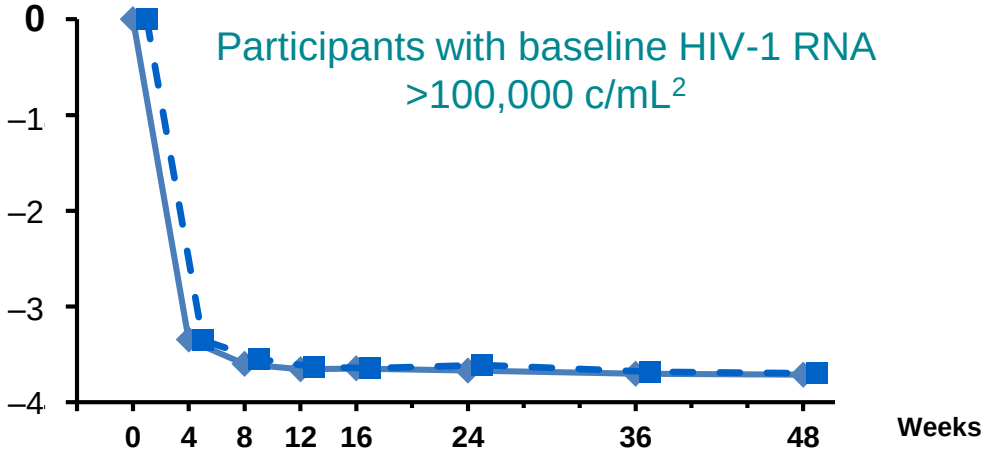
Adapted from: 1. Cahn P, et al. Lancet 2019;393:143–55
2. Cahn P, et al. IAS 2018. TUAB0106LB

Viral Load Decline by study arm



DTG + 3TC, n	716	704	681	688	674	664
DTG + TDF/FTC, n	717	699	688	688	681	675

Participants with baseline HIV-1 RNA >100,000 c/mL[2]

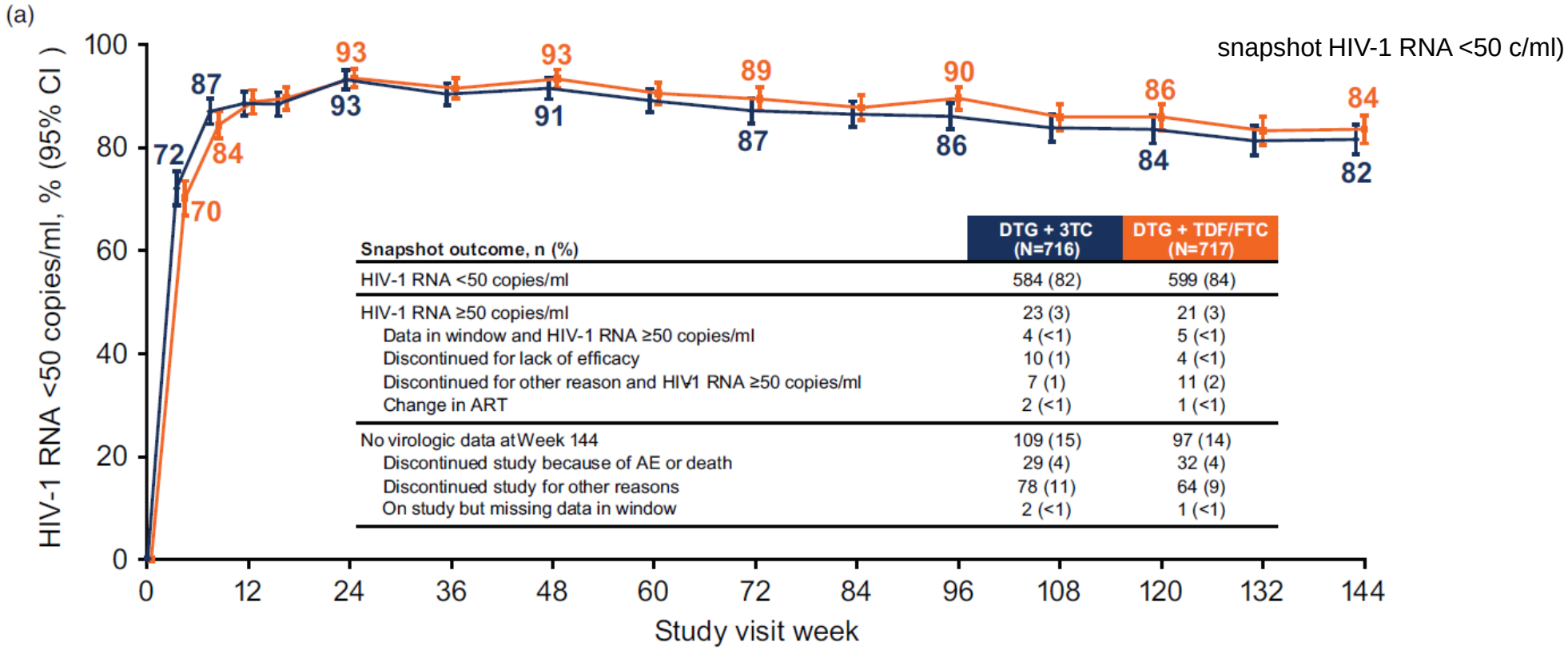


	140	138	139	135	135	138	132	132
	153	152	153	151	149	145	141	139

Adapted from: 1. Cahn P, et al. Lancet 2019;393:143–55 plus supplementary appendix
2. Eron J, et al. HIV DART and Emerging Viruses 2018. Oral Presentation 7

GEMINI 1&2 trials

No emergence of resistance



Snapshot outcome, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA <50 copies/ml	584 (82)	599 (84)
HIV-1 RNA ≥50 copies/ml	23 (3)	21 (3)
Data in window and HIV-1 RNA ≥50 copies/ml	4 (<1)	5 (<1)
Discontinued for lack of efficacy	10 (1)	4 (<1)
Discontinued for other reason and HIV1 RNA ≥50 copies/ml	7 (1)	11 (2)
Change in ART	2 (<1)	1 (<1)
No virologic data at Week 144	109 (15)	97 (14)
Discontinued study because of AE or death	29 (4)	32 (4)
Discontinued study for other reasons	78 (11)	64 (9)
On study but missing data in window	2 (<1)	1 (<1)

One DTG + 3TC participant (with no adherence), not meeting CVW criteria, developed M184V (week 132) and R263R/K (week 144) conferring a 1.8-fold change in susceptibility to DTG.

Cahn P et al. AIDS. 2022;36:39-48.

DTG+3TC in ART-naive: guidelines

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].

1. Gandhi RT, Landovitz RJ, Sax PE, et al. Antiretroviral drugs for treatment and prevention of HIV in adults: 2024 recommendations of the International Antiviral Society—USA panel. JAMA 2025; 333:609–28.
2. Clinical Info HIV.gov. What's new: adult and adolescent ARV HIV clinical guidelines. NIH. 2024. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv- clinical-guidelines-adult-and-adolescent-arv/whats-new. Accessed 5 May 2025.
3. EACS guidelines, versión 12.0. October 2023. 2024. Available at: https://www. eacsociety.org/media/guidelines-12.0.pdf. Accessed 5 May 2025.

Observational cohort: DTG+3TC in naive with high viremia

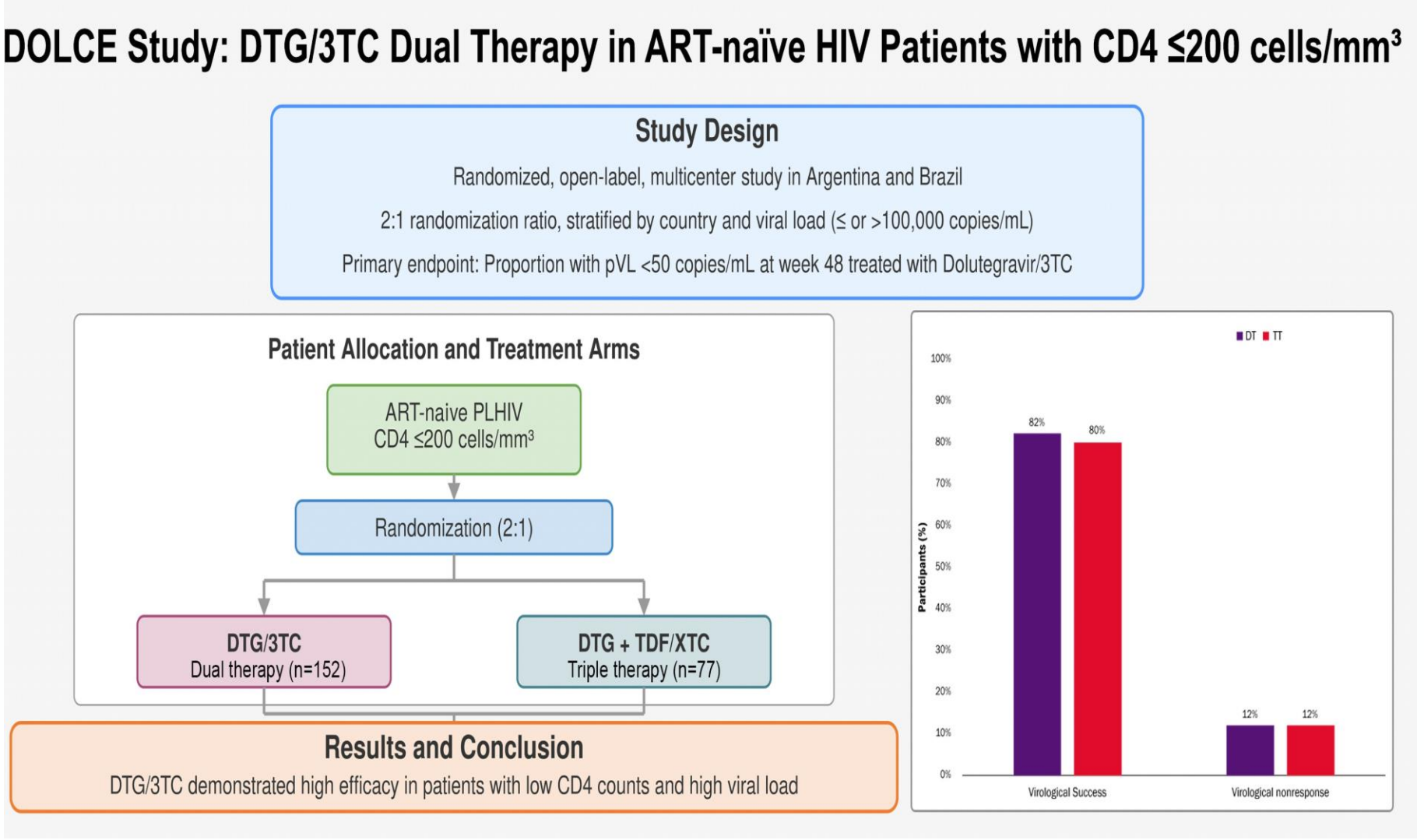
Calza L, Colangeli V, Giglia M, et al. Efficacy and safety of dolutegravir/lamivudine in antiretroviral therapy-naive people living with HIV-1 and with high-level viremia. JAIDS 2025; 99:93–7.
Number of PWH: **58 pts**, HIV-1 RNA (from 100,000 to 500,000), mean CD4+: **488** cells/mm 3, at month 12: HIV RNA <50 copies/mL (91%).

Dou Y, Liao G, Lu R, et al. DTG + 3TC DT for the treatment naïve patients with viral load exceeding 500,000 copies/mL: a retrospective study. BMC Infect Dis 2024; 24:720.
Number of PWH: **30 pts,** median HIV RNA: 1,080,720 (649,624 - 2,261,758) c/mL, median CD4: **55** (25 -198) cells/mm 3, at month 12: HIV RNA <50 copies/mL (78%).

Zhao F, Rao M, Chen W, et al. Dolutegravir plus lamivudine dual-drug regimen in treatment-naive HIV-1 infected patients with high-level viral load: preliminary data from the real world. JAIDS. 2022; 91(S1):S16–9.
Number of PWH: **22 pts**, median Log HIV RNA: 6.12 (5.91–6.39) c/mL, median CD4: **36** (30–98) cells/mm 3, at month 12: HIV RNA <50 copies/mL (90%). *NB: 2DR used for drug interaction, renal impairment, age, and other related comorbidities.*

2DR vs 3DR in ART-naive with CD4 < 200 c/mL?

DOLCE study: 2DR vs 3DR in ART-naive with CD4 < 200 c/mL



Figueroa MI et al. Clin Infect Dis, 2025

DOLCE study: DTG+3TC in naive with CD4 < 200 c/mL

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/mm3
- ✓ and be able to consent to participation.

Key exclusion criteria:

- ✓ included a positive hepatitis B coinfection
- ✓ Pre-existing major viral resistance mutations to DTG, 3TC, or TDF/TAF
- ✓ active opportunistic infections
- ✓ and liver or kidney disease.

Figueroa MI et al. Clin Infect Dis, 2025

DOLCE study: DTG+3TC in naive with CD4 < 200 c/mL

Table 1. Participant Demographics and Baseline Characteristics

DTG plus TDF/XTC | DTG/3TC

	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%)
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)

Figueroa MI et al. Clin Infect Dis, 2025

DOLCE study: DTG+3TC in naive with CD4 < 200 c/mL

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

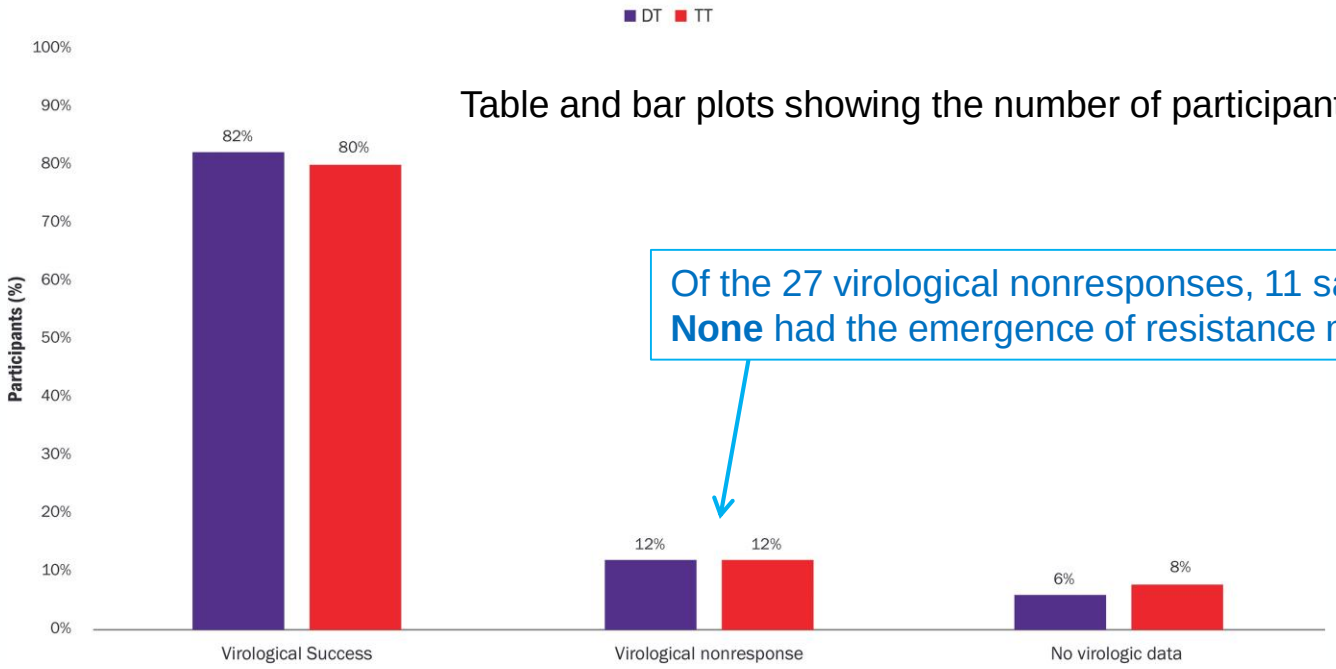


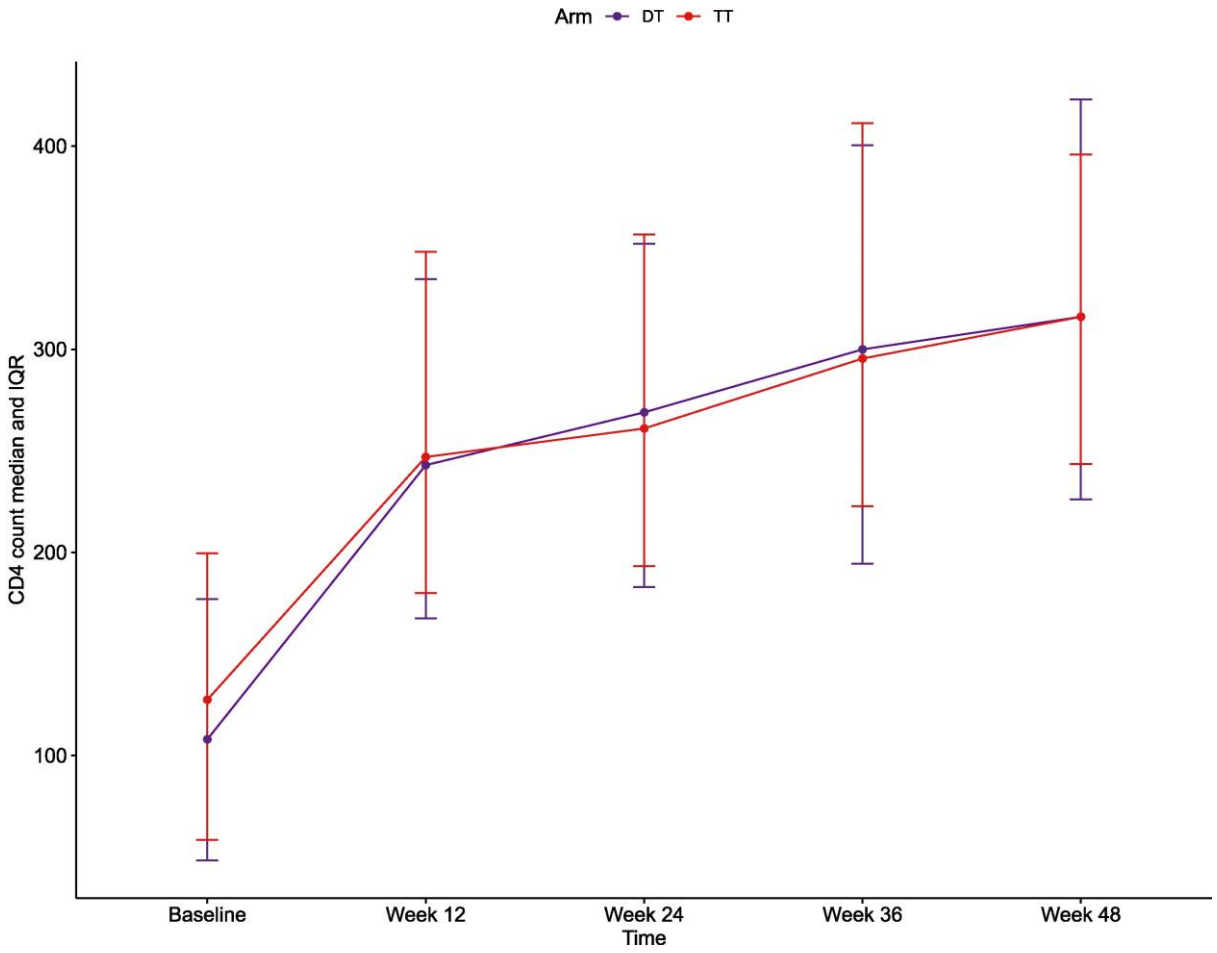
Table and bar plots showing the number of participants who achieved virological suppressions

Of the 27 virological nonresponses, 11 samples were successfully amplified.
None had the emergence of resistance mutations to INSTIs or NRTIs.

Figueroa MI et al. Clin Infect Dis, 2025

DOLCE study: DTG+3TC in naive with CD4 < 200 c/mL

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



Figueroa MI et al. Clin Infect Dis, 2025

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%)
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%)

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.

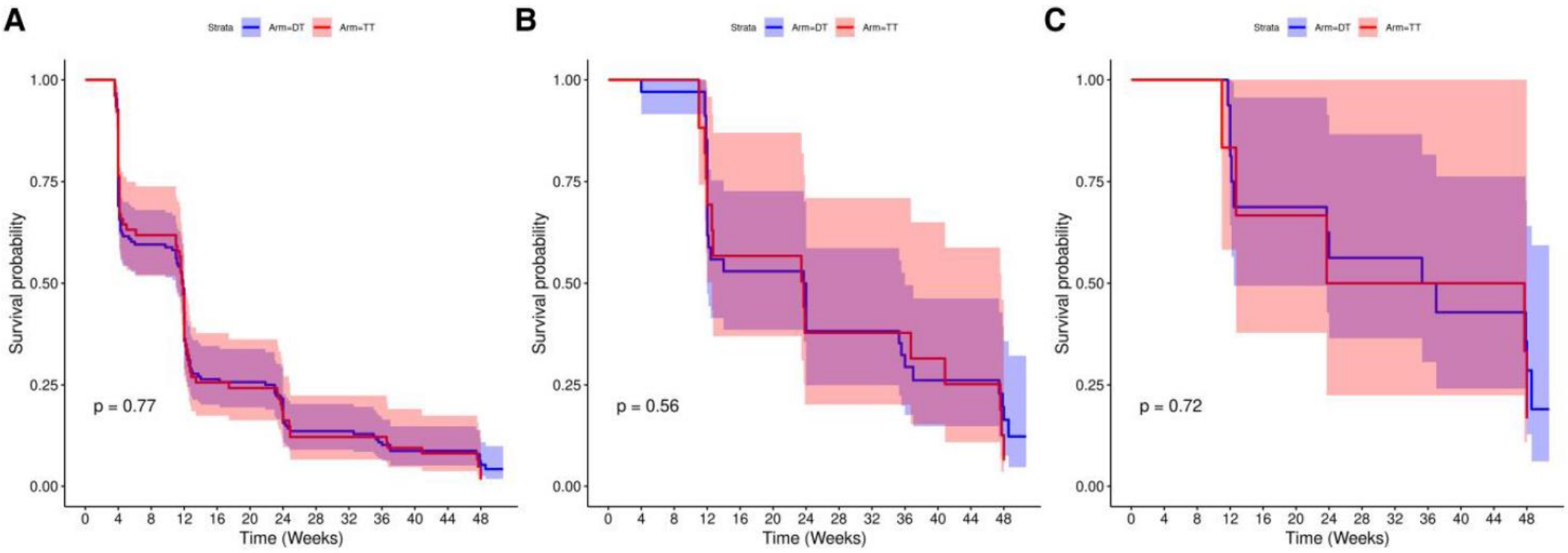
Figueroa MI et al. Clin Infect Dis, 2025

DOLCE study: DTG+3TC in naive with CD4 < 200 c/mL

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).

HIV RNA > 10^5 copies/mL

HIV RNA > 10^6 copies/mL



Of the 27 virological nonresponses, 11 samples were successfully amplified.
None had the emergence of mutations conferring resistance to INSTIs or NRTIs.

Figueroa MI et al. Clin Infect Dis, 2025

DOLCE study: DTG+3TC in naive with CD4 < 200 c/mL

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.

Figueroa MI et al. Clin Infect Dis, 2025

Clinical Infectious Diseases

EDITORIAL COMMENTARY

DOLCE: Sweet Success for Dolutegravir/Lamivudine?

Laura J. Waters[1,2]

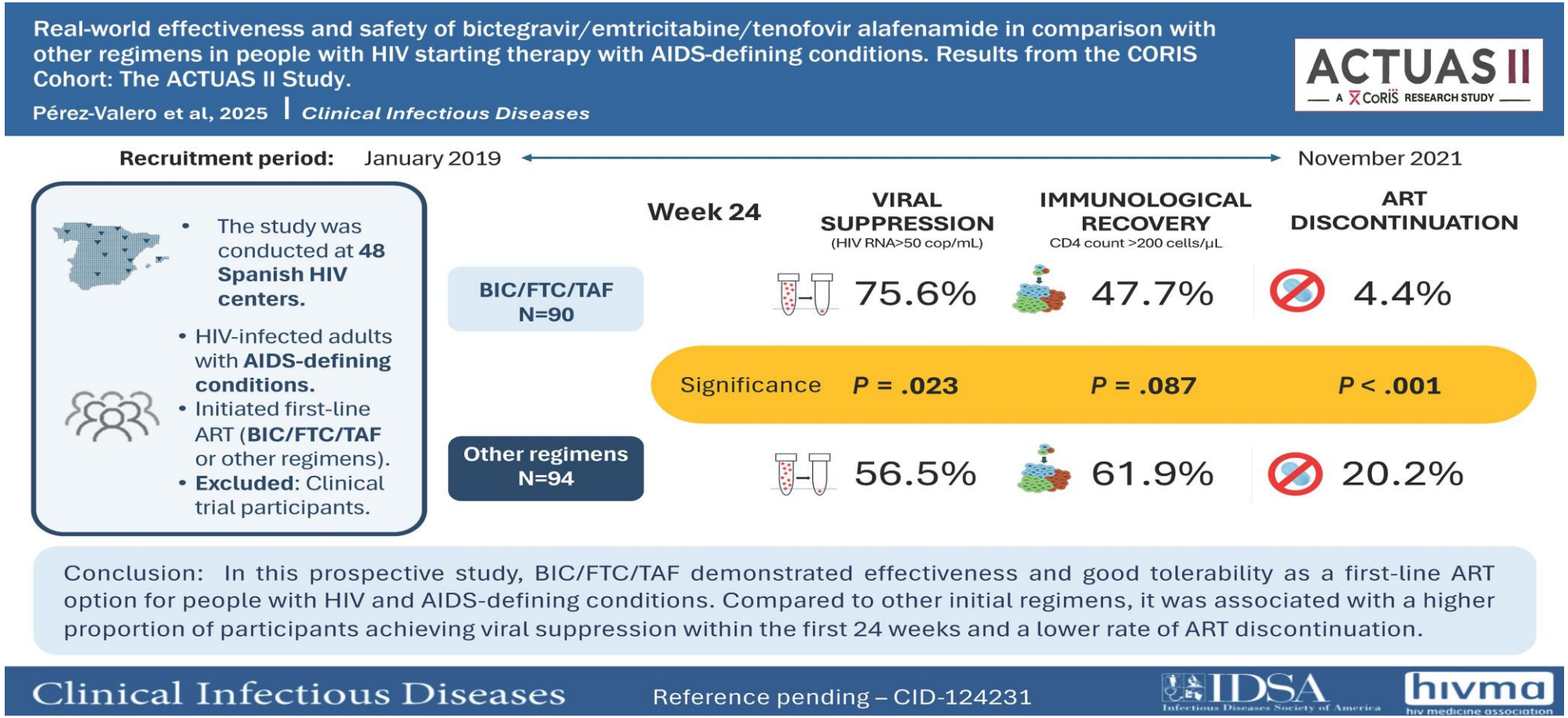
[1]Department of HIV Medicine and Sexual Health, Central and North West London NHS Trust, London, United Kingdom; and [2]Institute of Global Health, University College London, London, United Kingdom

DOLCE study has some limitations:

- a relatively small sample size
- it's open label
- pill burden was higher for people on 3 drugs
- 2 people randomized to 3 drugs received the 2-drug regimen "by mistake"

- high proportion of participants with very high viral loads (23% and 10% had viral loads exceeding 500,000 and 1,000 000 copies/mL, respectively)

The ACTUAS II Study: ART Regimens in AIDS



Clin Infect Dis, ciaf162, https://doi.org/10.1093/cid/ciaf162

Cohorte de la Red Española de Investigación en SIDA (CoRIS) Cohort

The ACTUAS II Study: ART Regimens in AIDS

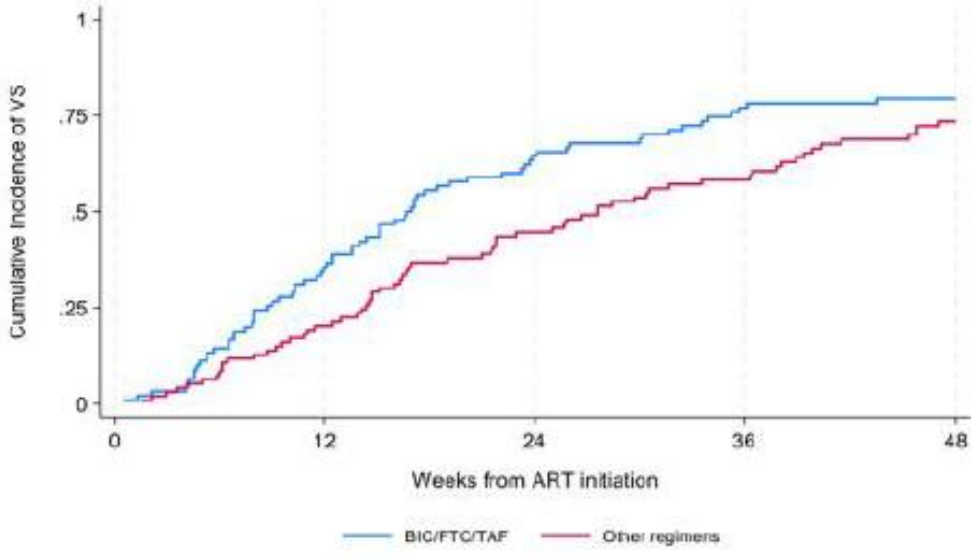
Characteristic	BIC/FTC/TAF (n = 90)	Other Regimens (n = 94)	*P* Value
Sex			.931
Male	77 (85.6)	80 (85.1)	
Female	13 (14.4)	14 (14.9)	
CD4 count, cells/μL			
Median (IQR)	58 (26–153)	78 (29–207)	.230
<50	33 (36.7)	28 (29.8)	.553
≥50	41 (45.6)	45 (47.9)	
Unknown	16 (17.8)	21 (22.3)	

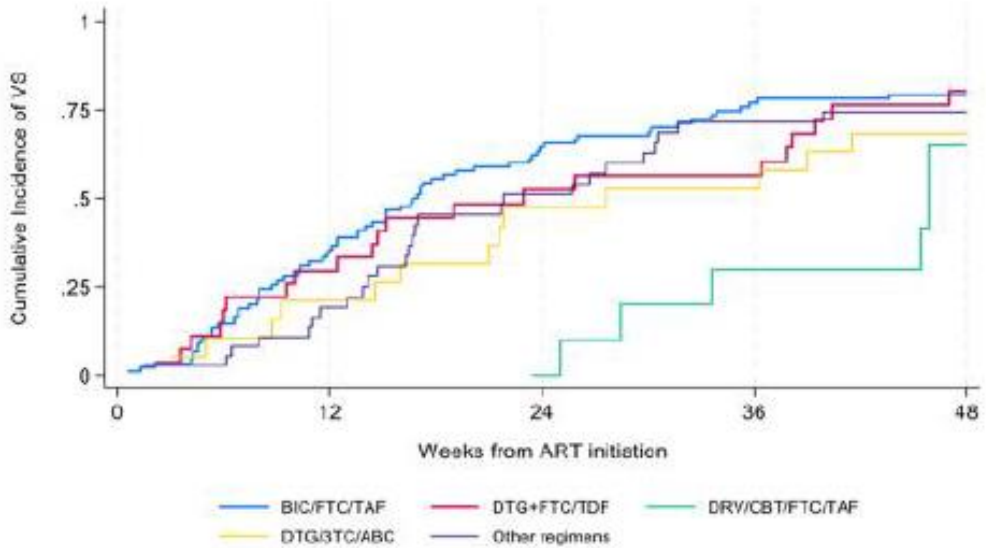
Viral suppression						
BIC/FTC/TAF	65/86 (75.6)	1.00	1.00	68/78 (87.2)	1.00	1.00
DTG + FTC/TDF	14/26 (53.8)	0.38 (.11–1.34)	0.29 (.08–1.02)	20/24 (83.3)	0.74 (.32–1.68)	0.77 (.29–2.03)
DRV/COBI/FTC/TAF	3/11 (27.3)	0.12 (.04–.41)	0.16 (.04–.63)	8/10 (80.0)	0.59 (.13–2.57)	0.48 (.09–2.51)
DTG/3TC/ABC	9/17 (52.9)	0.36 (.12–1.11)	0.29 (.10–.83)	10/17 (58.8)	0.21 (.07–.65)	0.23 (.05–.99)
Other regimens	22/31 (71.0)	0.79 (.35–1.79)	0.75 (.25–2.24)	24/25 (96.0)	3.53 (.54–22.96)	4.34 (.60–31.26)
P value		.004	.008		.011	.049

Pérez-Valero et al. CID 2025

Cohorte de la Red Española de Investigación en SIDA (CoRIS) Cohort

Time to viral suppression during the first 48 weeks after ART initiation according to initial regimen.





	BIC/FTC/TAF vs other ART regimens (pooled)		
	Time to VS Median (IQR)	Crude sHR (95% CI)	Adjusted sHR (95% CI)
BIC/FTC/TAF	17 (9 – 35)	1.00	1.00
Other regimens	28 (14 – 48+)	0.70 (.50 – .98)	0.76 (.52 – 1.10)
P value		.040	.151

	BIC/FTC/TAF vs other AR regimens (individual regimens)		
	Time to VS Median (IQR)	Crude sHR (95% CI)	Adjusted sHR (95% CI)
BIC/FTC/TAF	17 (9 – 35)	1.00	1.00
DTG+FTC/TDF	23 (10 – 40)	0.87 (.53 – 1.42)	1.09 (.64 – 1.86)
DRV/COBI/FTC/TAF	46 (34 – 48+)	0.38 (.20 – .70)	0.38 (.20 – .73)
DTG/3TC/ABC	28 (15 – 48+)	0.64 (.36 – 1.16)	0.61 (.32 – 1.17)
Other regimens	22 (14 – 48+)	0.77 (.49 – 1.20)	0.89 (.54 – 1.44)
P value		.031	.025

Pérez-Valero et al. CID 2025

HIV regimens in advanced and ART naive patients

— The ACTUAS II Study

The rate of VS in participants enrolled in the GS-US-380-1489/1490 clinical trials with advanced HIV disease was **99%**, slightly higher than the 87.2% observed in our study .
This difference may be due to the exclusion of candidates with AIDS in these 2 trials and the controlled follow-up within a clinical trial setting.

Under real-life conditions, the performance of BIC/FTC/TAF in advanced HIV disease has been evaluated in 3 cohort studies:
- CoRIS
- OPERA (Observational Pharmaco-Epidemiology Research and Analysis)
- Taiwanese cohort

All of these studies reported a low rate of ART discontinuations with BIC/FTC/TAF compared to other ART regimens

LAPTOP trial (CROI 2025) B/F/TAF better than DRVc-based in ART naive with advanced disease (median CD4 count: 41 (17-79)

Corona D, et al. Int J Antimicrob Agents 2024; 63:107016.
Mounzer K, et al. Open Forum Infect Dis 2022; 9:ofac018.
Mounzer K, et al. HIV Med 2023; 24:716–26.
Chun-Yuan L, et al. Infect Dis Ther 2023; 12:843–61.
Behrens et al. CROI 2025. Abstr 658

2DRs in HIV advanced disease

More studies are needed, but available data sugget that DTG/3TC dual therapy may be an option in LPs and in PWH with baseline CD4+ count ≤ 200 cells/mL.

B/F/T is the best comparator in this setting