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Co-morbidities: Beyond the heart

Non-inferior efficacy and less weight gain when switching to DTG/3TC than when switching to BIC/FTC/TAF in virologically suppressed people with HIV (PWH): the PASO-DOBLE (GeSIDA 11720) randomized clinical trial.

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Summary

What are your main questions?

Is switching to DTG/3TC non-inferior to switching to BIC/FTC/TAF?

Does switching to BIC/FTC/TAF lead to greater weight gain than switching to DTG/3TC?

What did you find?

At 48 weeks, DTG/3TC was non-inferior to BIC/FTC/TAF [risk difference DTG/3TC (2.2%) minus BIC/FTC/TAF (0.7%) 1.4%, 95%CI -0.5 to 3.4].

Mean adjusted weight increased significantly more with BIC/FTC/TAF (1.81kg, 95%CI 1.28-2.34) than with DTG/3TC (0.89kg, 95%CI 0.37-1.41) [difference 0.92kg, 95%CI 0.17-1.66].

Why is it important?

It provides new evidence on the efficacy and safety of DTG/3TC versus BIC/FTC/TAF as maintenance antiretroviral therapy.

PASO-DOBLE study: Background

As HIV requires life-long therapy, optimising ART in the setting of viral suppression is needed.

DTG/3TC and BIC/FTC/TAF are preferred regimens in major guidelines, but there are no fully powered trials comparing between them.

DTG, BIC, and TAF have been associated with weight gain, but their role remains controversial.

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PASO-DOBLE study: Design

Phase IV, open-label, multicentre, randomised clinical trial[1]

30 sites across Spain

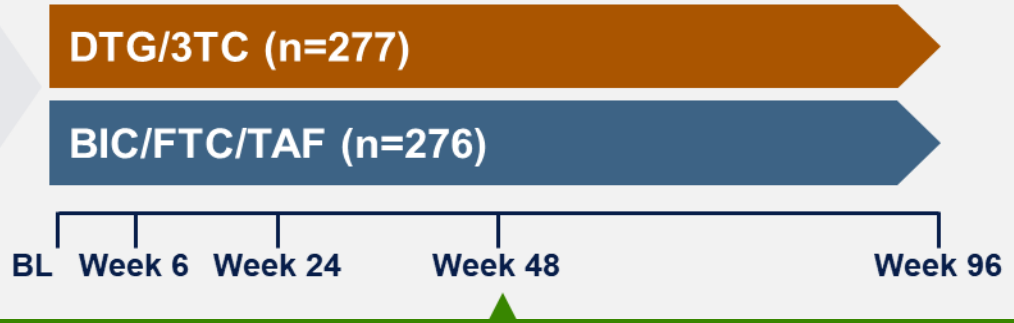
Collaborative study between **Fundación SEIMC-GeSIDA** and ViiV Healthcare

Screening

- HIV-1 RNA <50 c/mL for ≥24 weeks
- Current ART containing >1 pill/day, cobi booster, EFV or TDF
- No prior VF or known/suspected resistance
- No prior DTG or BIC
- No chronic hepatitis B

Randomised 1:1

Stratified by BL TAF use and sex at birth



Primary endpoint: Participants with plasma HIV-1 RNA ≥50 c/mL (FDA Snapshot; non-inferiority margin 4%)
Key secondary endpoint: Weight change (study was powered to assess differences)

Other secondary endpoints include efficacy, safety, tolerability, immune recovery, metabolic parameters, kidney function, blood pressure, body composition and bone mineral density, PROs, and genotypic resistance analysis in case of virological failure

Four sub-studies: Omics | Senescence | Fat biopsies | Liver steatosis

1. PASO DOBLE. Available at: https://clinicaltrials.gov/ct2/show/NCT04884139.

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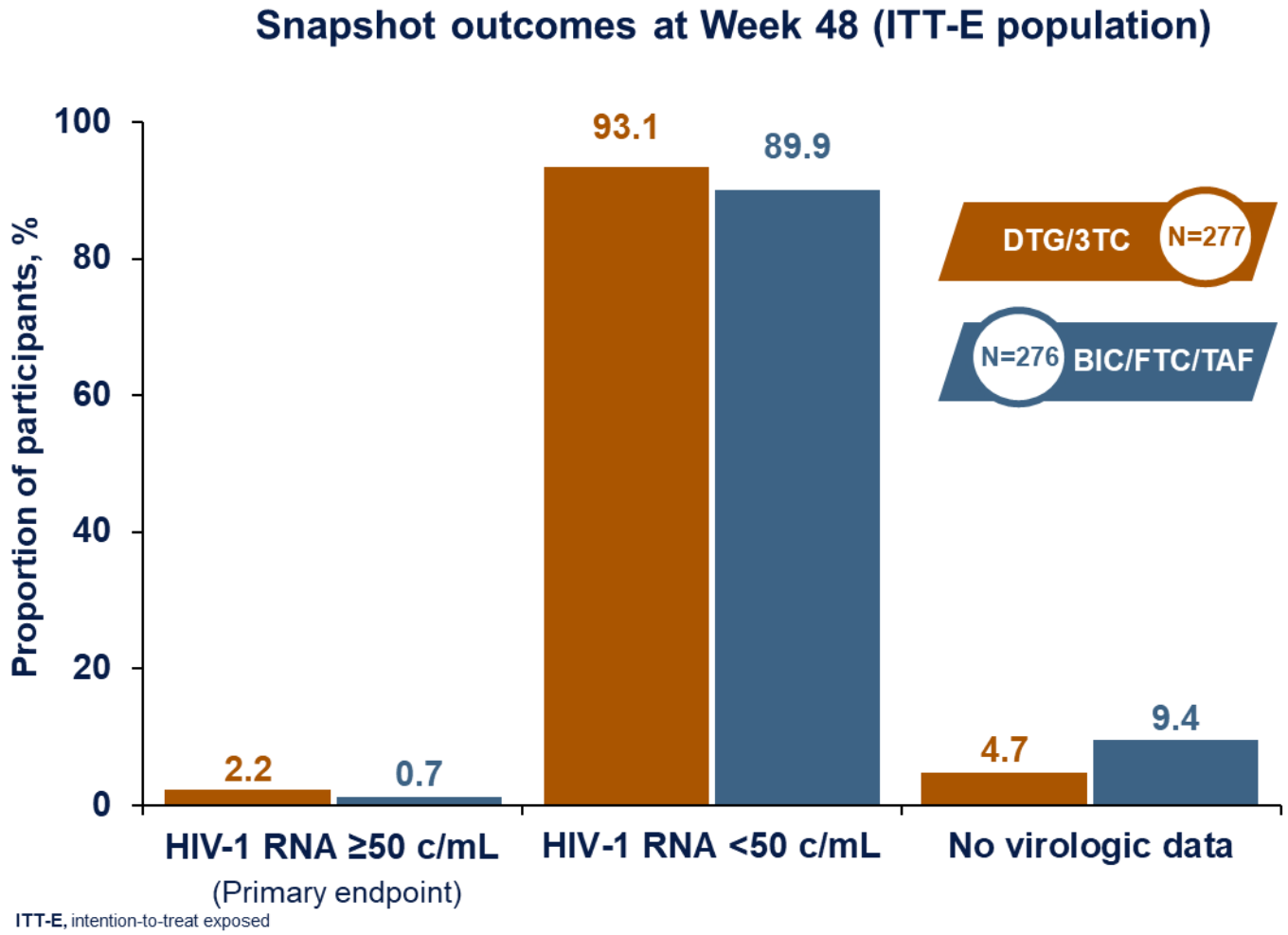
PASO-DOBLE study: Baseline characteristics

	DTG/3TC (n=277)	BIC/FTC/TAF (n=276)
Age, years	50 (41-57)	51 (39-58)
Female sex at birth	74 (26.7%)	73 (26.4%)
Ethnicity		
Caucasian	201 (72.6%)	201 (72.8%)
Latinx	66 (23.8%)	67 (24.3%)
Black	4 (1.4%)	5 (1.8%)
Other/unknown	6 (2.2%)	3 (1.1%)
Total time on ART, years	11.7 (7.2-19.3)	11.1 (7.0-19.2)
Time with HIV RNA <50 cp/mL, months	103.4 (43.0-170.2)	97.7 (41.5-163.3)
Duration of prior ART regimen, months	66.2 (43.5-97.0)	62.8 (41.1-88.7)
CD4 cells/mm^3	712 (516-918)	684 (473-859)
CD4 <350 cells/mm^3	26 (9.4%)	24 (8.7%)
CD4 nadir cells/mm^3	293 (144-472)	302 (159-476)
BMI, kg/m^2	25.1 (22.3-28.49)	24.8 (22.2-28.2)
Overweight/obese (BMI >25 kg/m^2)	143 (51.8%)	134 (48.6%)

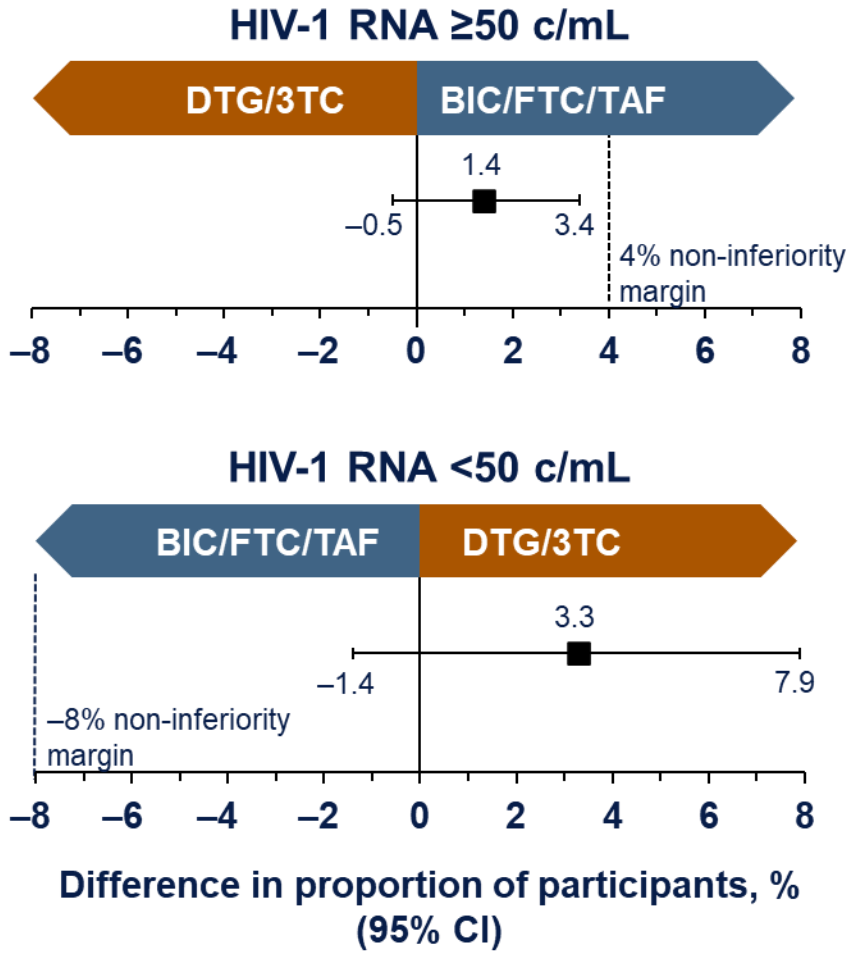
PASO-DOBLE study: Pre-switch ART

	DTG/3TC (n=277)	BIC/FTC/TAF (n=276)
NRTI 1 in previous ART regimen		
TAF	77 (27.8%)	78 (28.3%)
ABC	59 (21.3%)	52 (18.8%)
TDF	92 (33.2%)	103 (37.3%)
No NRTI 1	49 (17.7%)	43 (15.6%)
NRTI 2 in previous ART regimen		
3TC	70 (25.3%)	64 (23.2%)
FTC	182 (65.7%)	190 (68.8%)
No NRTI 2	25 (9.0%)	22 (8.0%)
Core drug in previous ART regimen		
NNRTI only	138 (49.8%)	141 (51.1%)
INSTI only	44 (15.9%)	49 (17.8%)
PI only	93 (33.6%)	82 (29.7%)
>1 core drugs	2 (0.7%)	4 (1.4%)

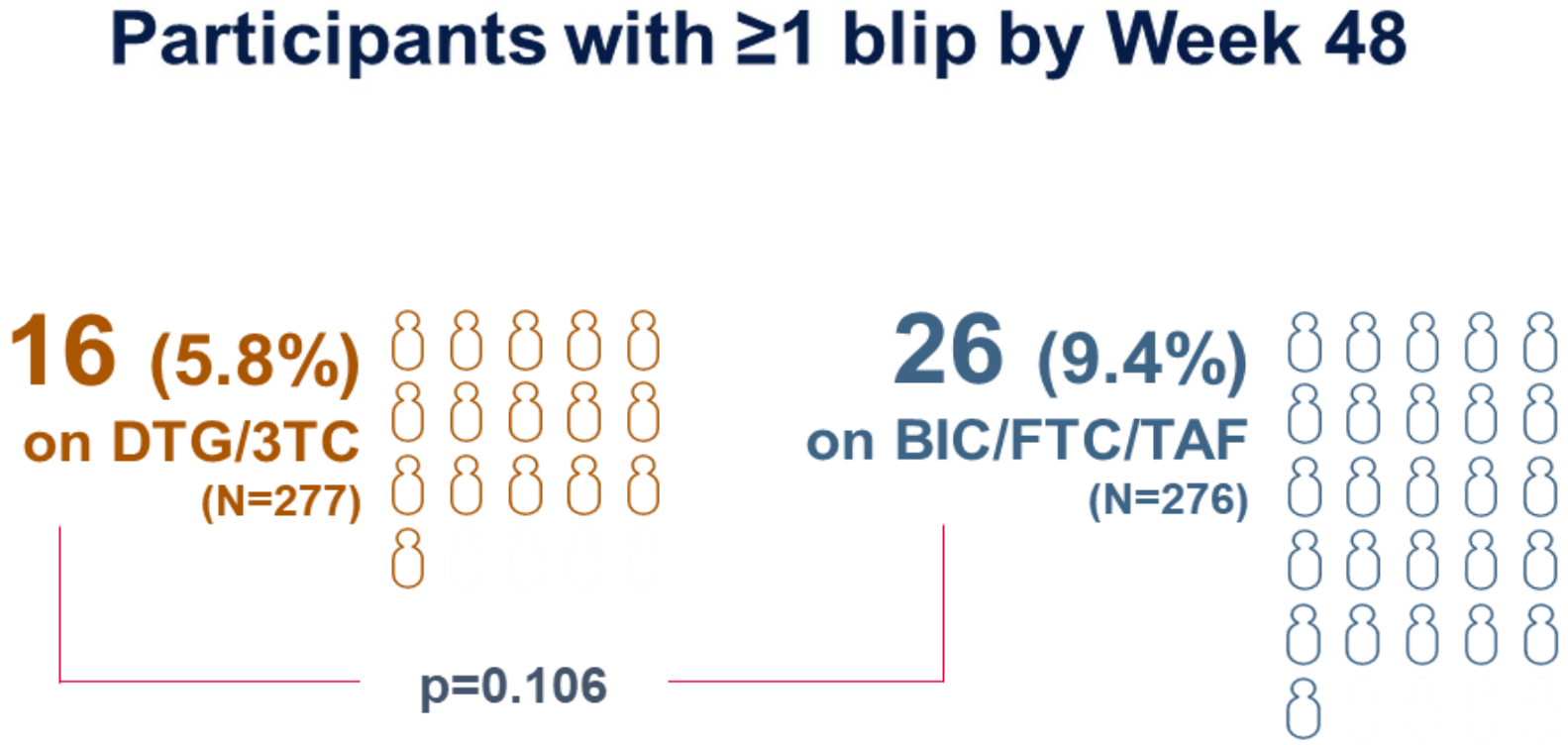
PASO-DOBLE study: Virologic efficacy



ITT-E, intention-to-treat exposed



PASO-DOBLE study: Blips



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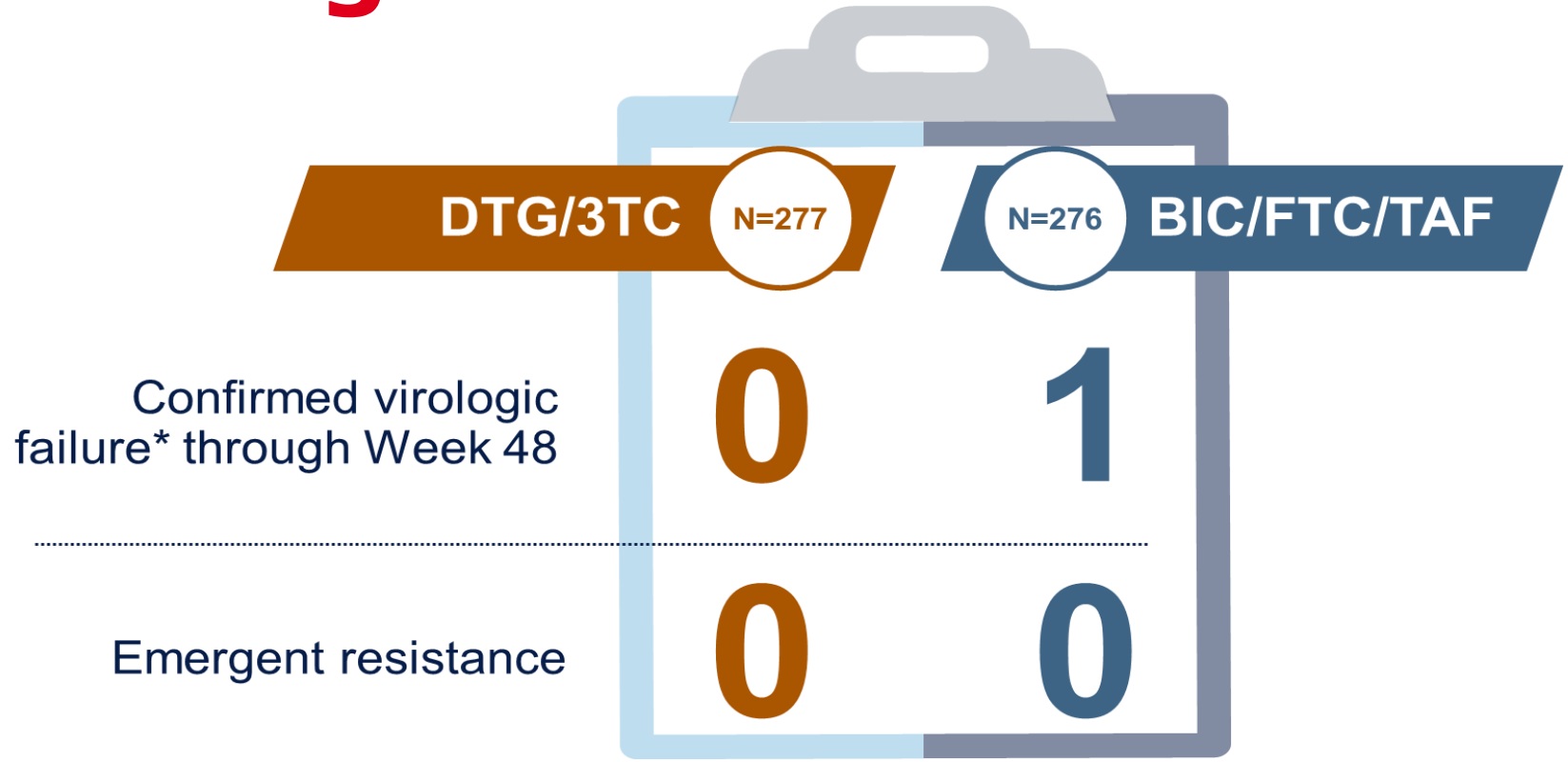
PASO-DOBLE study: Virological failure and emergent resistance



*Confirmed virologic failure was defined as HIV-1 RNA ≥50 cp/mL followed by a second consecutive HIV-1 RNA assessment ≥200 cp/mL

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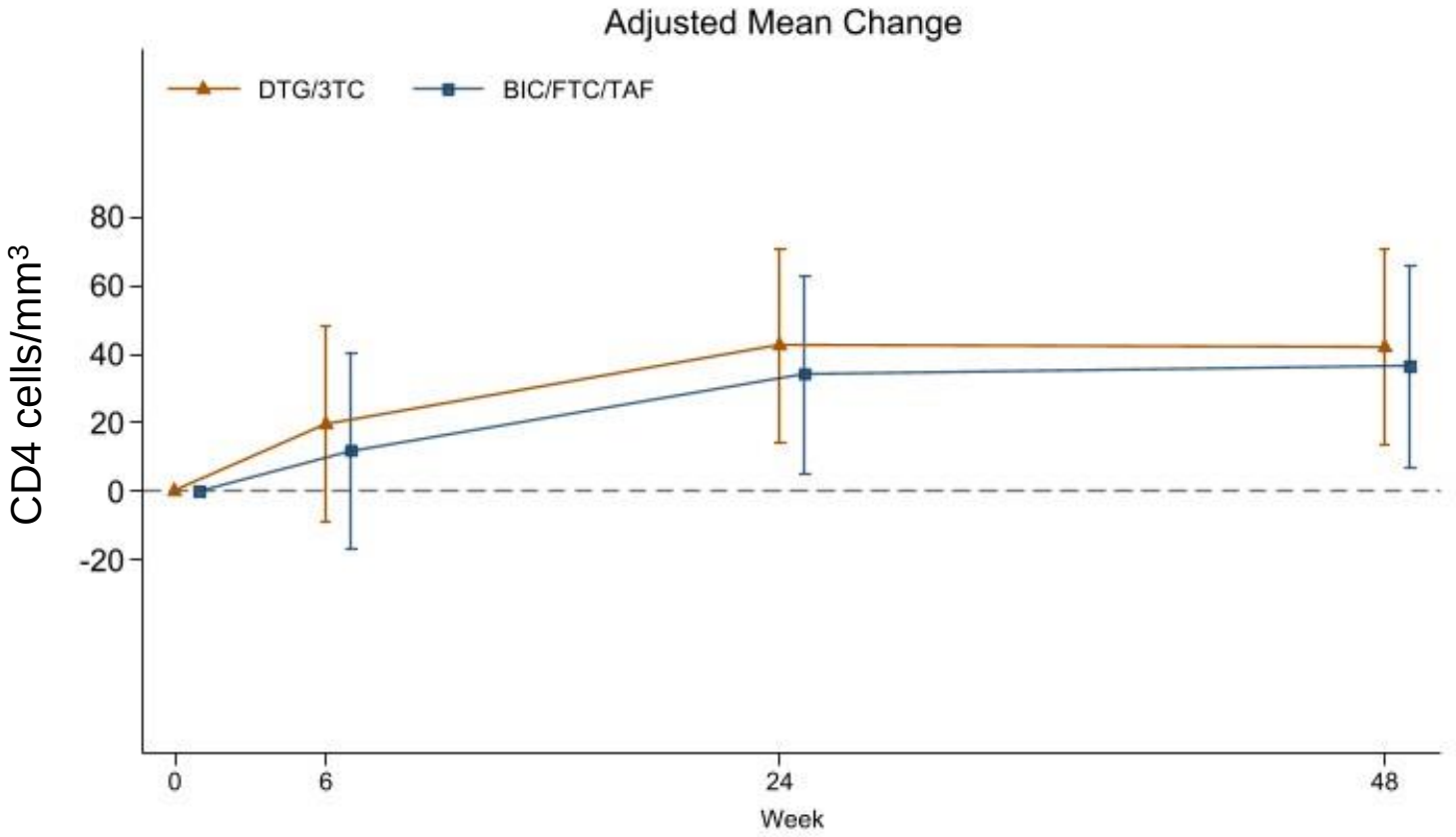
PASO-DOBLE study: CD4 cell/mm³ changes



Adjusted by baseline value, sex, presence of TAF in previous ART, age and ethnicity

PASO-DOBLE study: Adverse events

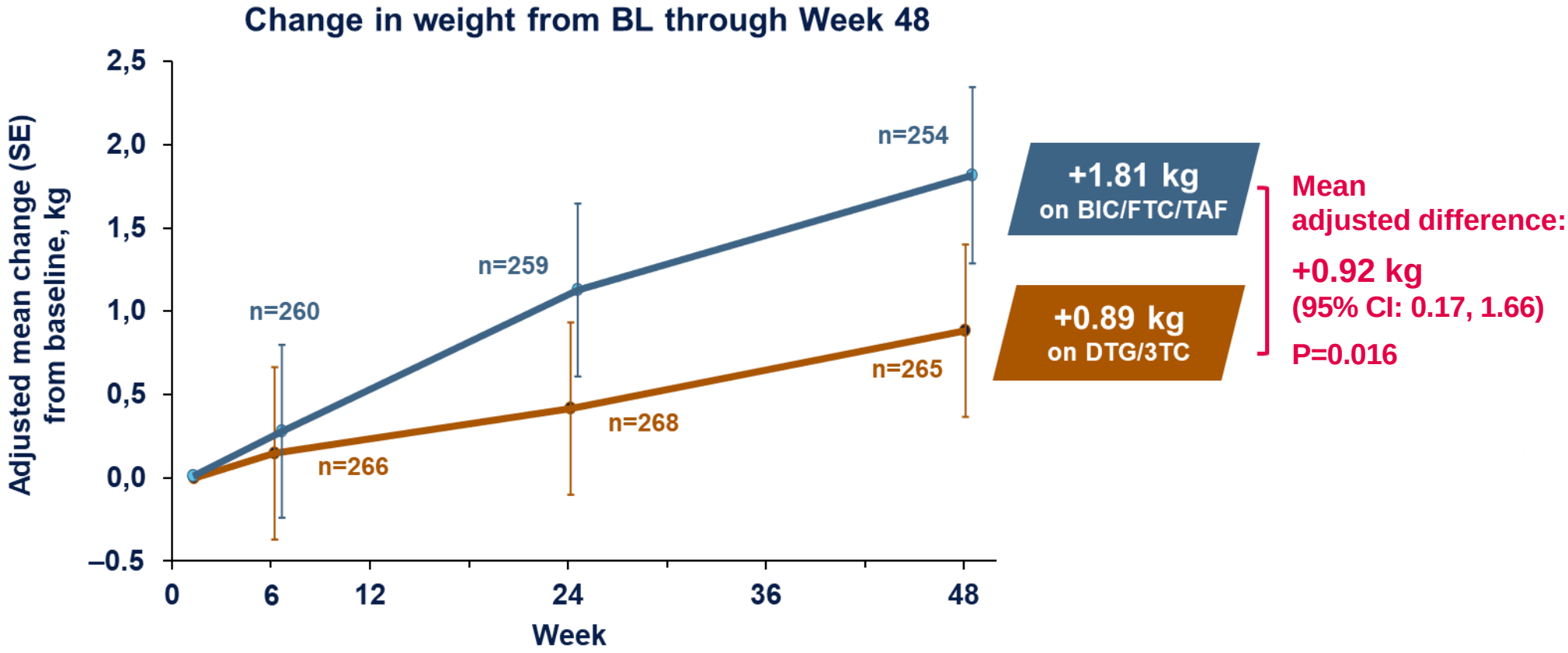
Participants with AEs, n (%)	DTG/3TC n=277	BIC/FTC/TAF n=276	p-value
Any AE *	207 (74.7)	216 (78.3)	0.327
Grade 3–4 AEs	3 (1.1)	10 (3.6)	0.049
Serious AE	12 (4.3)	13 (4.7)	0.831
Drug-related AEs	19 (6.9)	27 (9.8)	0.213
AEs leading to withdrawal #	1 (0.4)	2 (0.7)	0.561

DTG/3TC: General discomfort and arthromyalgia (n=1)
BIC/FTC/TAF: Insomnia (n=1), sleep disturbances (n=1)

* Most common AEs (>10% in either arm) per system organ class for DTG/3TC and BIC/FTC/TAF arms were:

- infections (36.8% and 45.3%)
- musculoskeletal (19.5% and 18.5%)
- gastrointestinal (17.3% an 10.5%),
- metabolism (13.7% and 9.4%), and
- psychiatric (9.7% and 13.4%)

PASO-DOBLE study: Weight change



Adjusted by baseline value, sex, presence of TAF in previous ART, age and ethnicity.
The only association that was statistically significant in the model was treatment group

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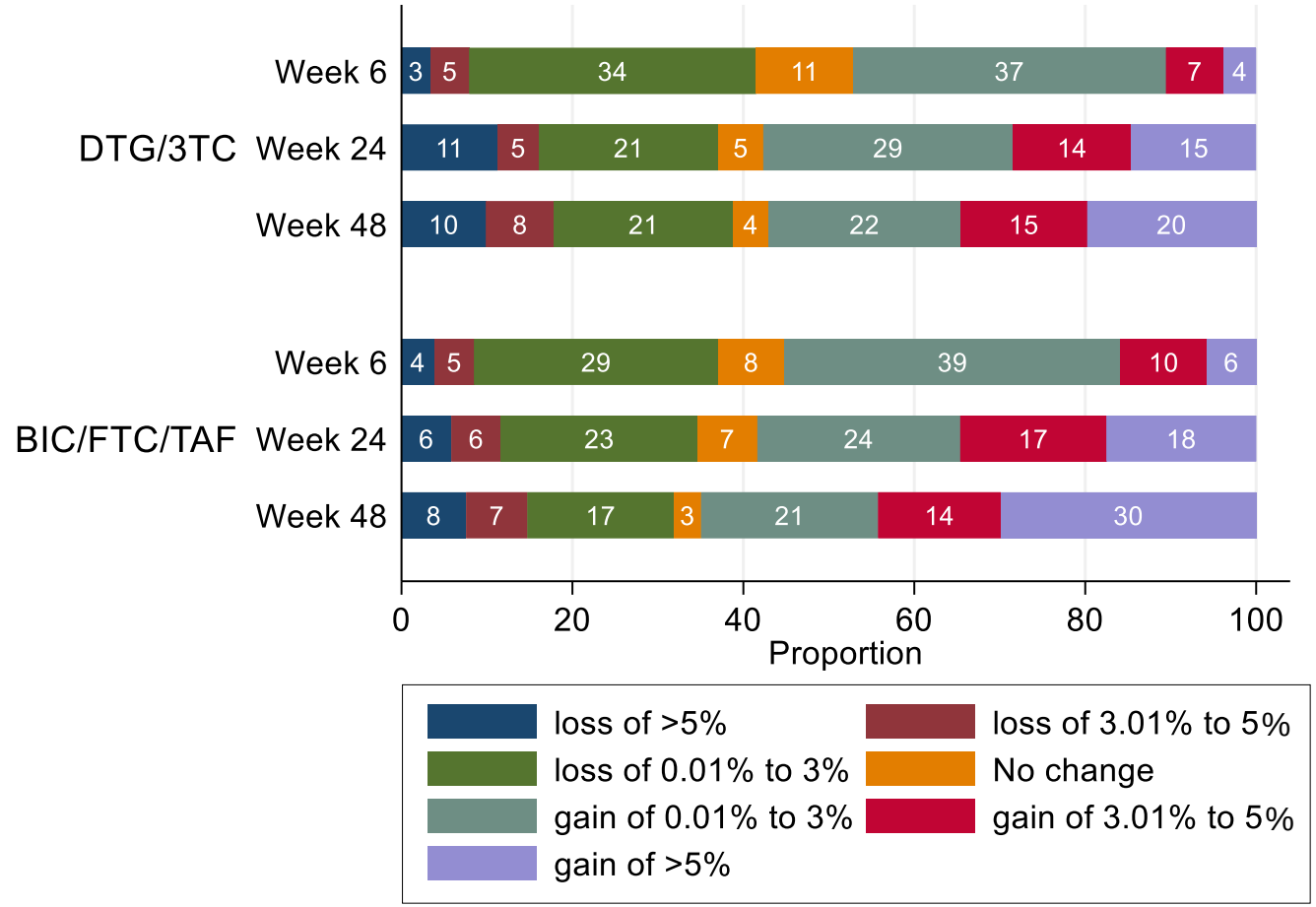
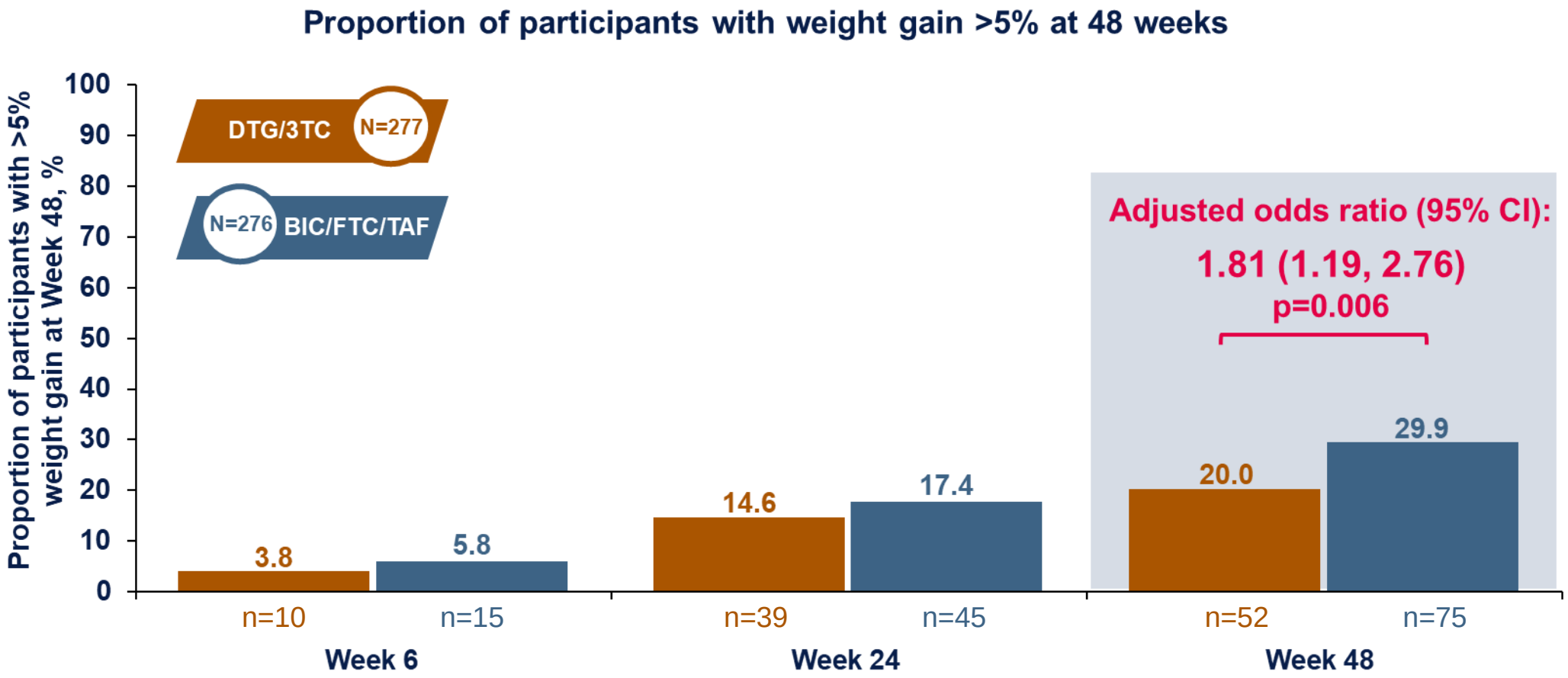
PASO-DOBLE study: % weight change strata

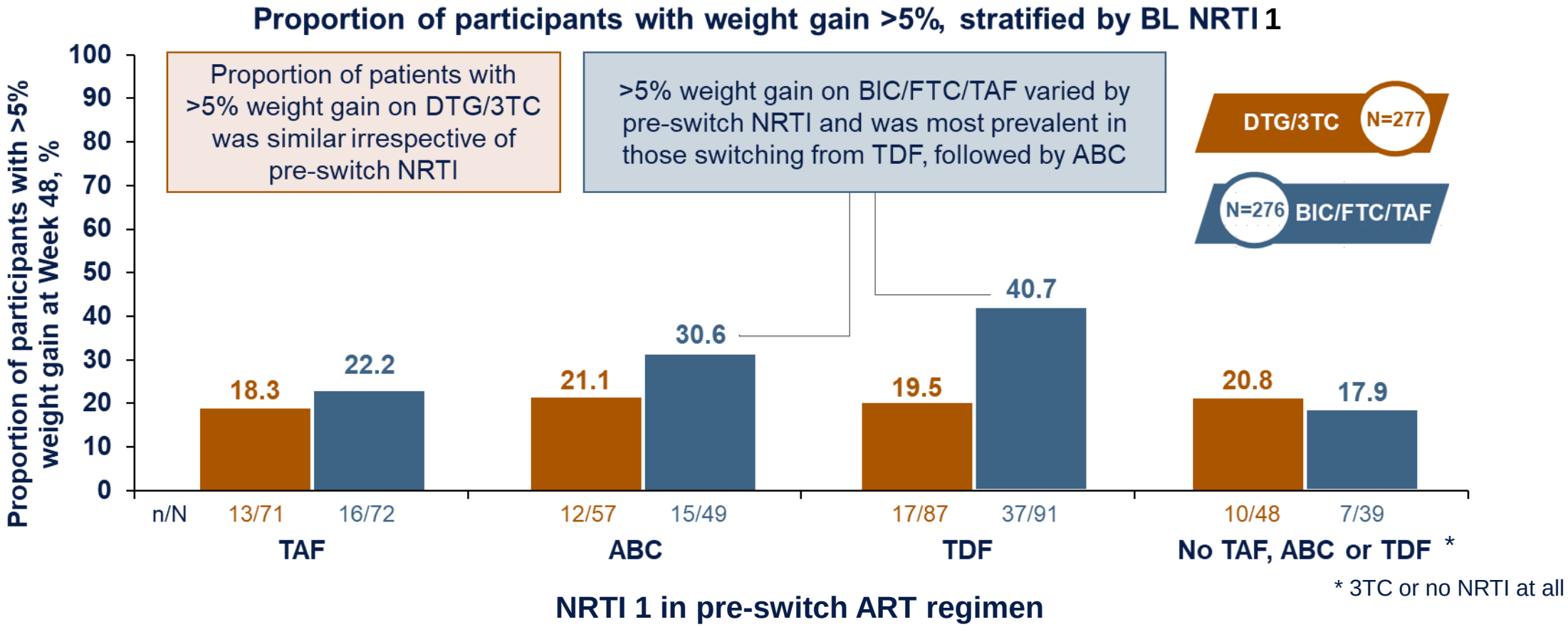


PASO-DOBLE study: Weight gain >5%



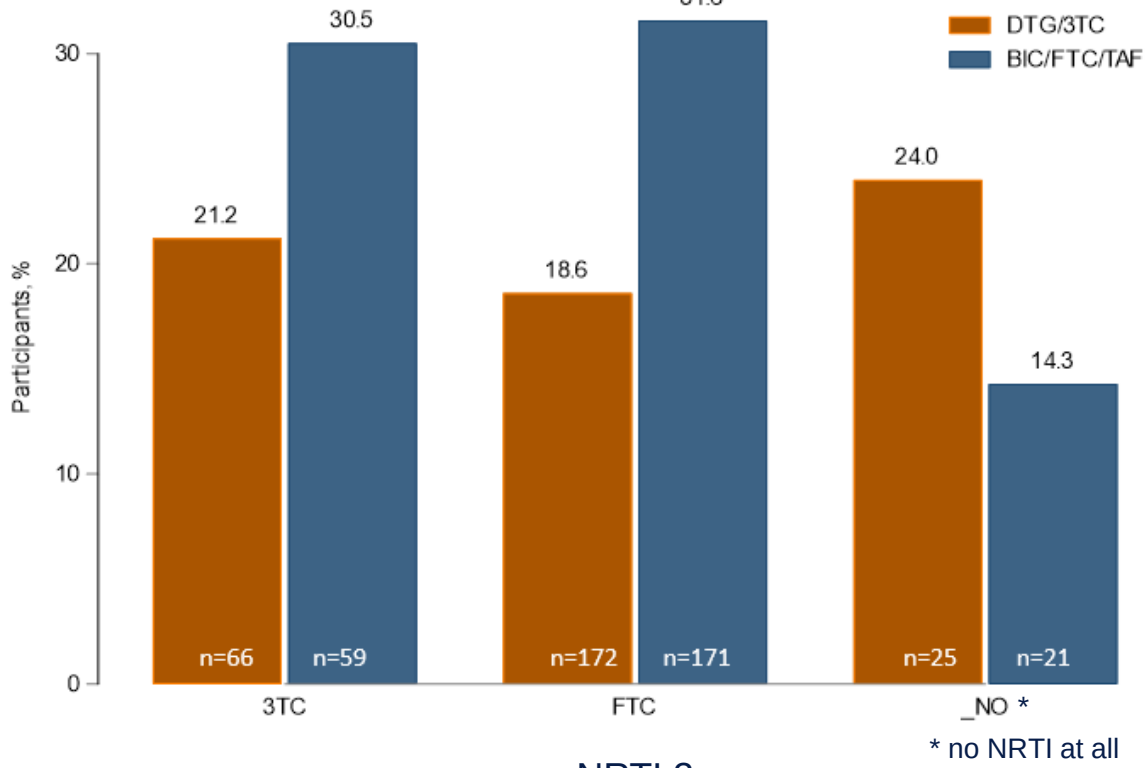
Adjusted by baseline value, sex, presence of TAF in previous ART, age and ethnicity

PASO-DOBLE study: Weight gain >5% by pre-switch NRTI 1



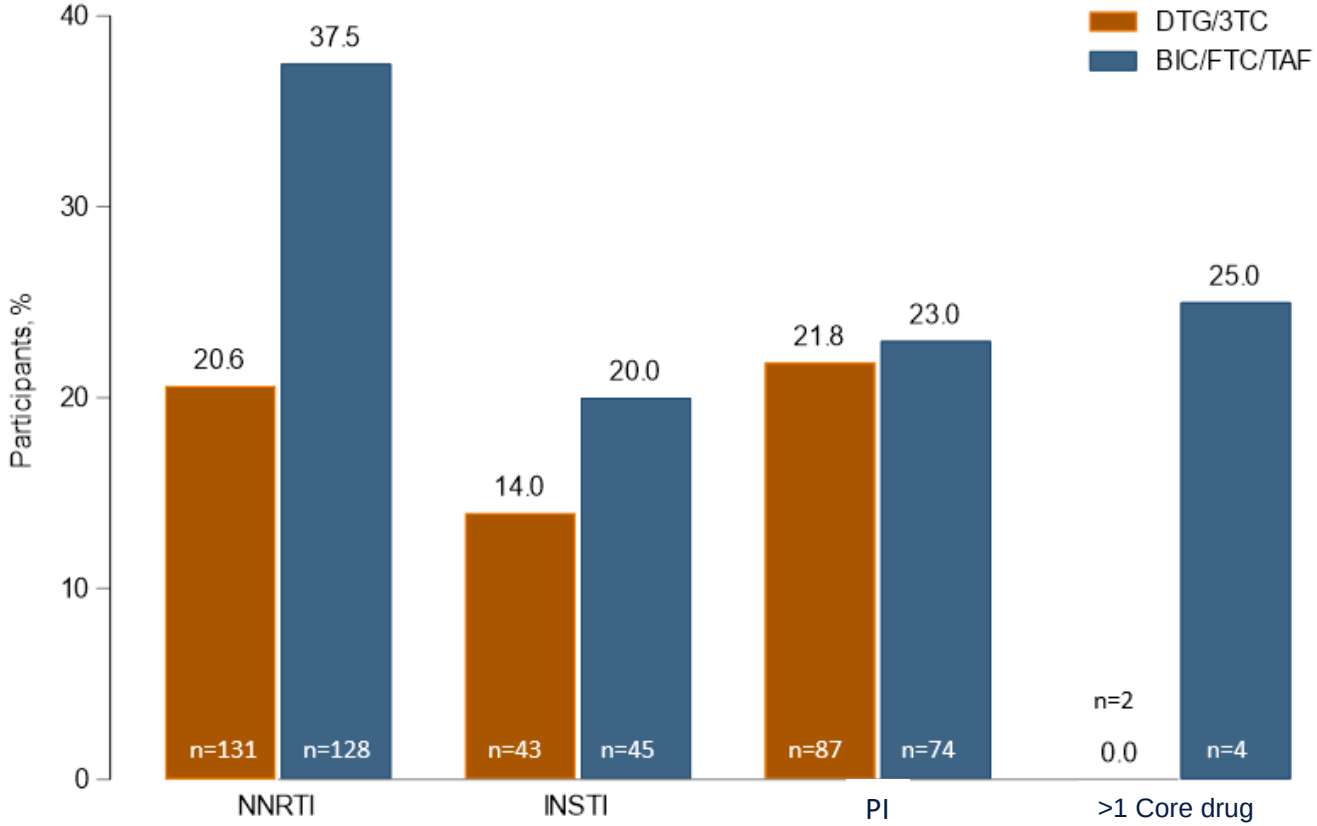
* 3TC or no NRTI at all

PASO-DOBLE study: Weight gain >5% by pre-switch NRTI 2 & core drug



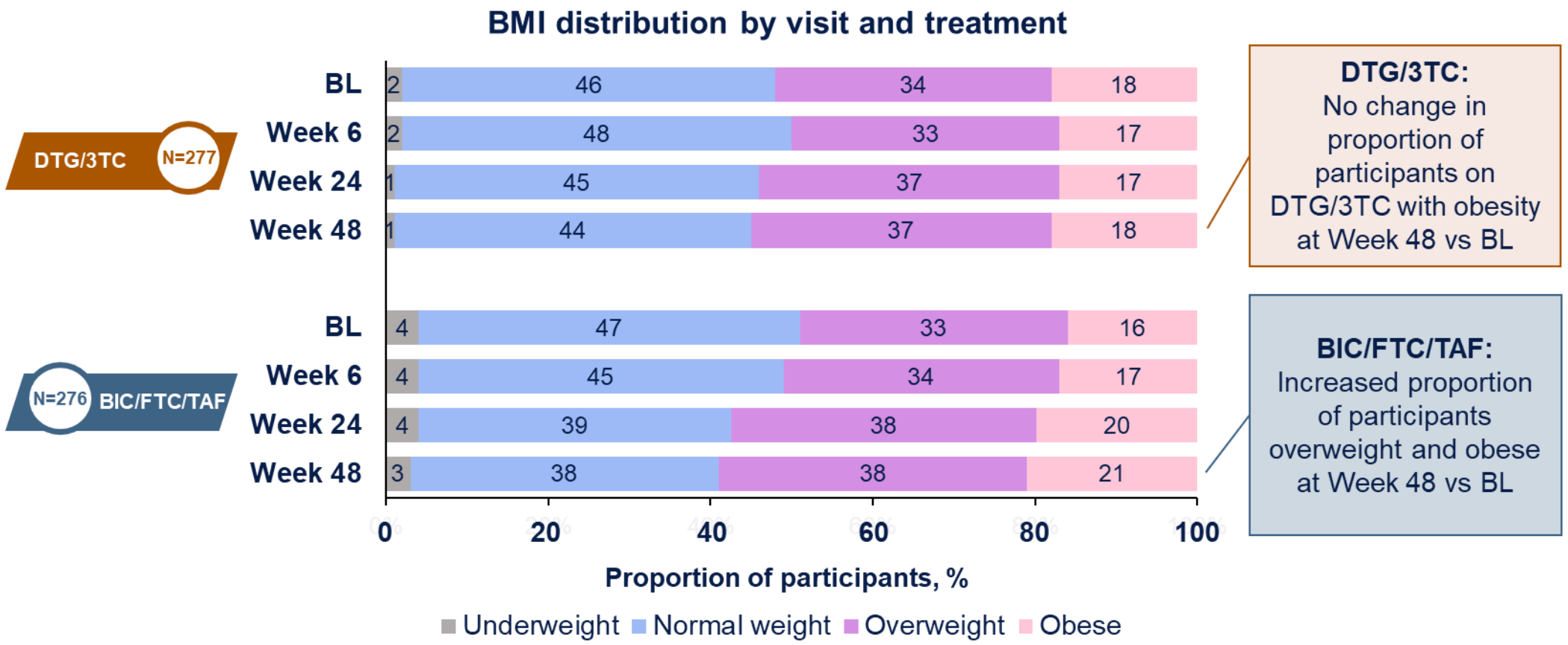
* no NRTI at all

NRTI 2



Core drugs

PASO-DOBLE study: BMI distribution by visit



Conclusions

In virologically suppressed people with HIV receiving ART regimens who are eligible and may benefit,

1. Switching to DTG/3TC demonstrated non-inferior efficacy than switching to BIC/FTC/TAF at 48 weeks.
2. DTG/3TC and BIC/FTC/TAF showed similarly high barrier to resistance.
3. DTG/3TC and BIC/FTC/TAF were both well tolerated, with exceptional discontinuations due to adverse effects.
4. Switching to BIC/FTC/TAF led to more weight gain than switching to DTG/3TC at 48 weeks.
5. Weight gain with BIC/FTC/TAF, but not with DTG/3TC, depended on the NRTI 1 in the ART regimen discontinued.

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PASO DOBLE study

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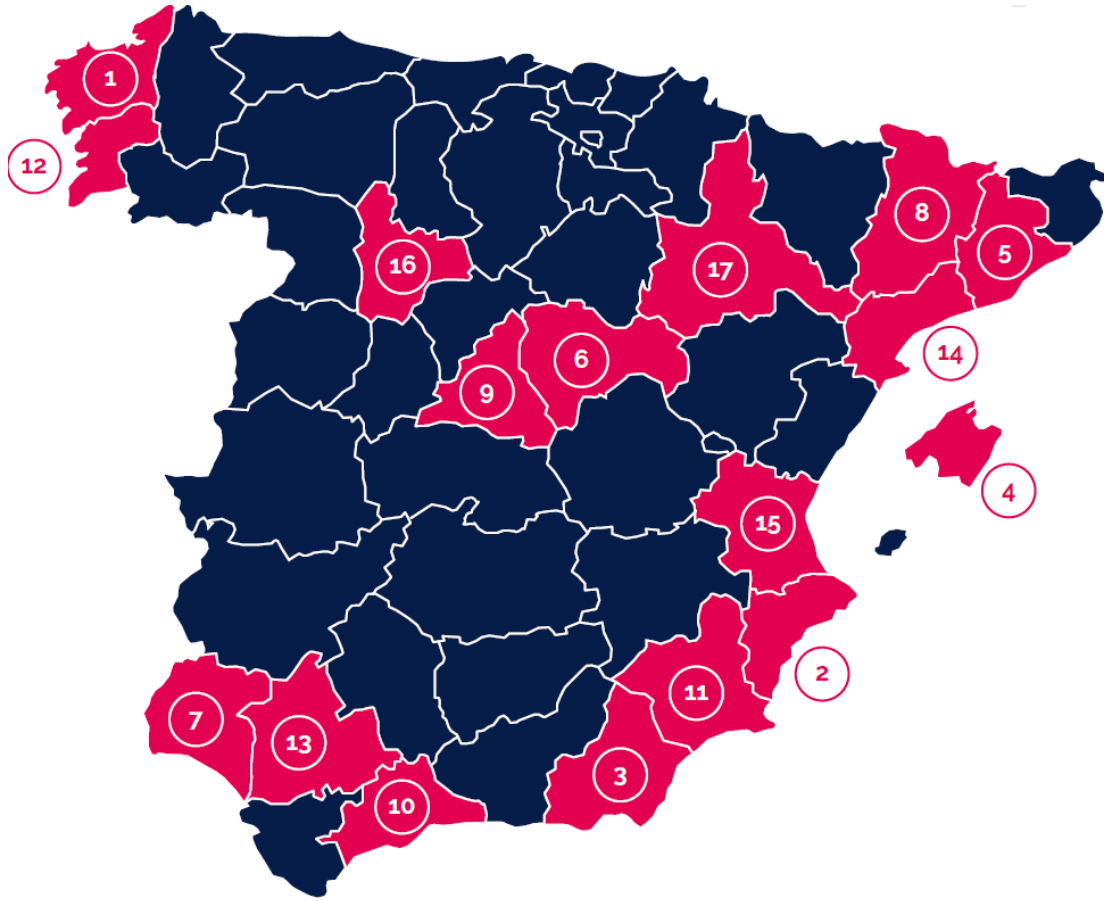

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