15th Residential Course on Clinical Pharmacology of Antiretrovirals
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Two-drug regimens for HIV infection: Pros and Cons from clinical trials

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Disclosures

Diego Ripamonti has received advisory fees, speaker fees, travel and education support from:

- ViiV
- Janssen
- Merck
- Gilead

HAART in history

Anti-HIV therapy = Combination regimens = 3 Drug Regimens (HAART)

Triple regimen does not mean **any triple** combination (2NRTI backbone + 3° drug)

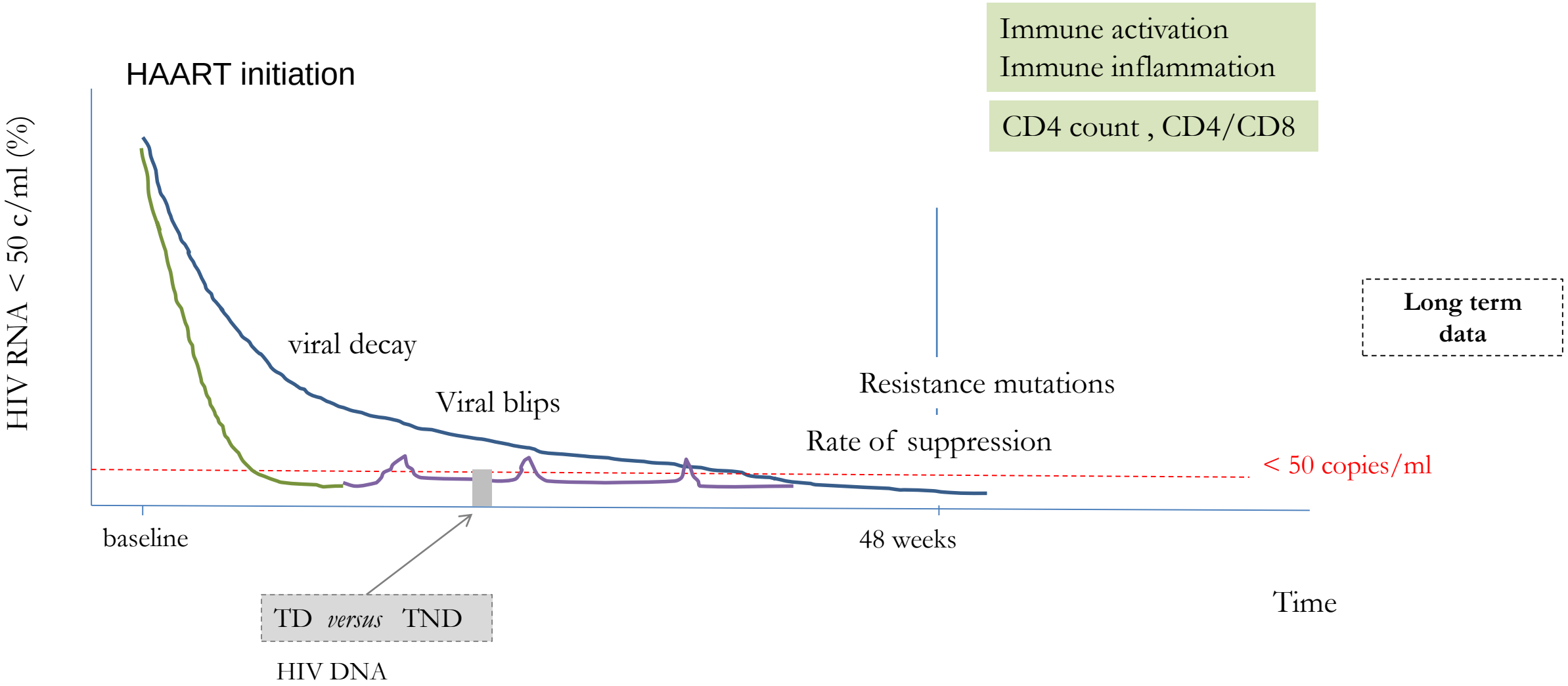
More agents?

Less Drug Regimen (LDR)

LDRs do not mean that **any dual** combinations are effective
LDRs cannot be as simple as “**mono**-therapy”

Treatment response in randomized trials

Proportion of patients with HIV RNA below 50 copies/ml



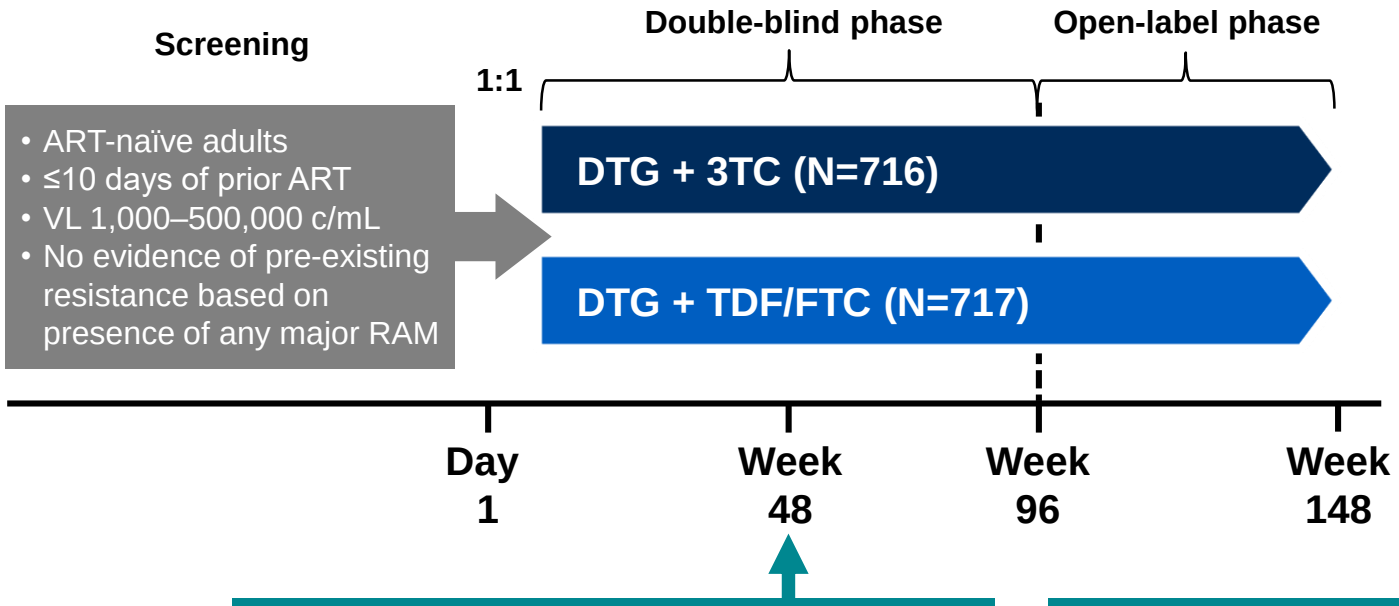
2DR era in HIV therapy

Experimental dual regimen	Study	Design	Baseline regimen	Number of pts	Non-inferiority	F-up weeks	Emergent resistance
LOP/r + 3TC [1]	OLE					48	1
ATV/r + 3TC [2]	SALT	switch	bPI	**1051**	yes	96	1
ATV/r + 3TC [3]	ATLAS-M					96	---
DRV/r + 3TC [4]	DUAL					48	1
DTG + RPV [5]	SWORD 1-2	switch	any	1024	yes	149	6
DTG + 3TC [6]	GEMINI 1-2	NAIVE	-	1433	yes	96	0
DTG + 3TC [7]	TANGO	switch	any	741	yes	48	0
DTG + DRV-r	Dualis	switch				48	0
CAB + RPV LA	ATLAS	switch	any	618	yes	48	3+
	FLAIR	switch	ABC/3TC/DTG	629	yes	48	3+

1. Arribas JR et al. Lancet ID 2015; 2. Perez-Molina JA et al. Lancet ID 2015; 3. Di Giambenedetto S et al. JAC 2017; 4. Pulido F. et al. CID 2017;65:2112-211 ;
5. Llibre JM et al. Lancet 2018;391:839-849; 6. Cahn P et al. IAS 2019; slides WEAB0404LB7. 7. van Wyk et al. IAS 2019; slides WEAB0403LB
7 Overton et al. IAS 2019; Mexico City, Mexico. Poster MOPEB257 8. Spinner CD et al. IAS 2019 Mexico, MOPEB269

GEMINI-1 and -2: Phase III Study Design

Identically designed, randomised, double-blind, parallel-group, multicentre, non-inferiority studies



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

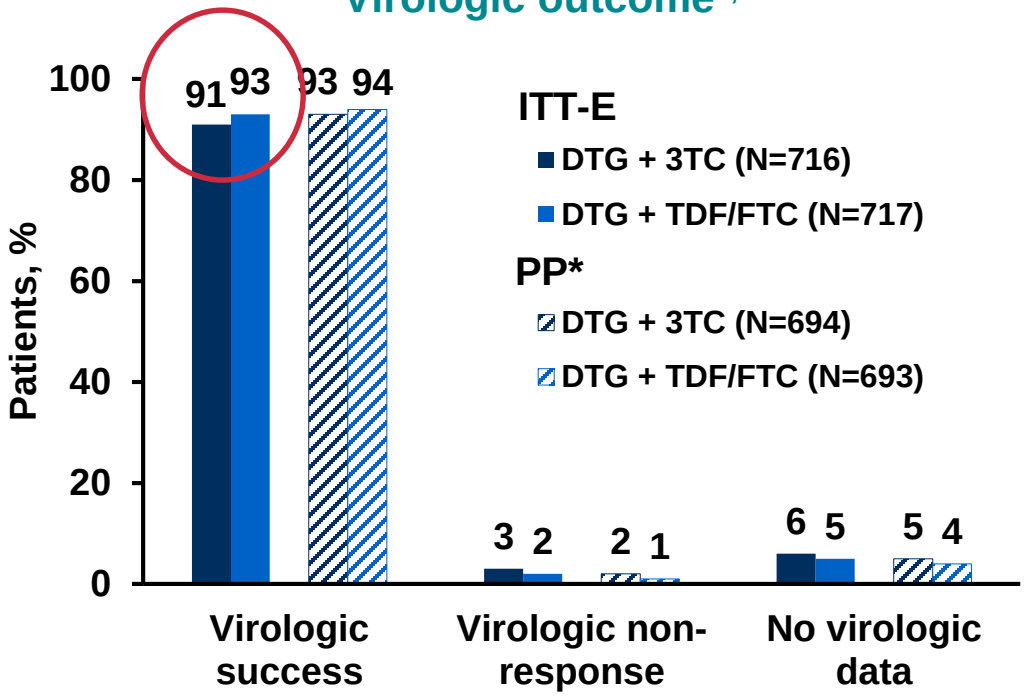
*−10% non-inferiority margin for individual studies
Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3)

Exclusion criteria included severe hepatic impairment or unstable liver disease; evidence of hepatitis B virus infection at screening; anticipated need for hepatitis C virus therapy in the first 48 weeks; creatinine clearance <50 mL/min).

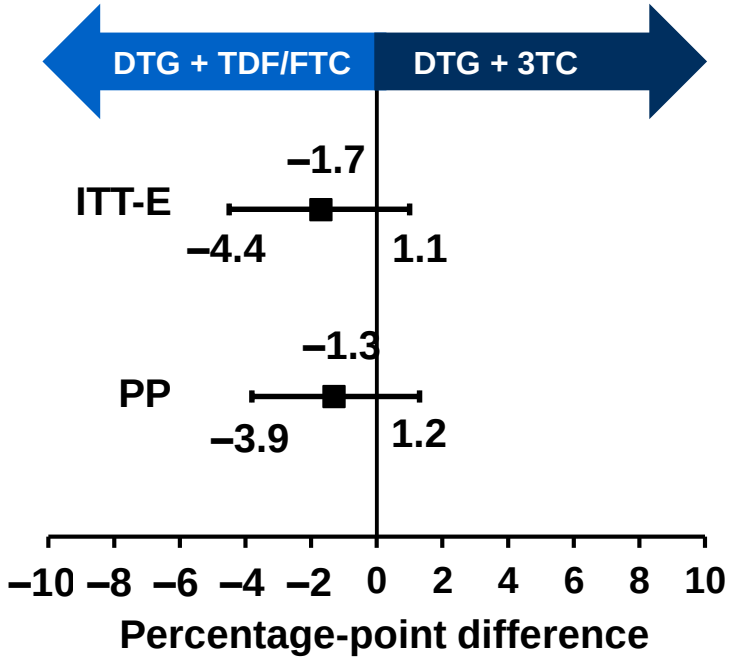
Adapted from: Cahn P, et al. Lancet 2019;393:143–55 plus supplementary appendix

GEMINI-1 and -2: Pooled Snapshot Outcomes at Week 4

Virologic outcome[1,2]



Adjusted treatment difference (95% CI)[1†]

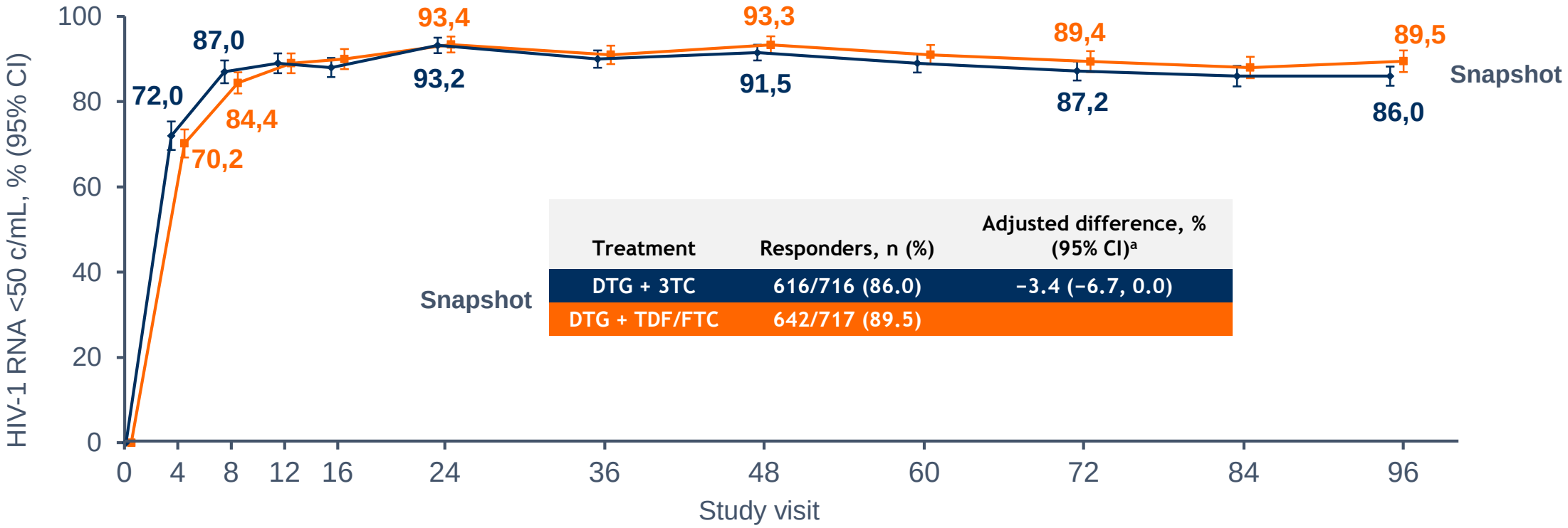


DTG + 3TC was <u>non-inferior</u> to DTG + TDF/FTC in the proportion of patients with <50 c/mL HIV-1 RNA at Week 48 in pooled Snapshot data using either the ITT-E or PP populations[1]

*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/mm^3).[1] PP, per protocol

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

DTG + 3TC is non-inferior to DTG + TDF/FTC in snapshot HIV-1 RNA <50 c/ml at week 96



Non-inferiority criteria were met for GEMINI-1, GEMINI-2 and the pooled analysis[b]

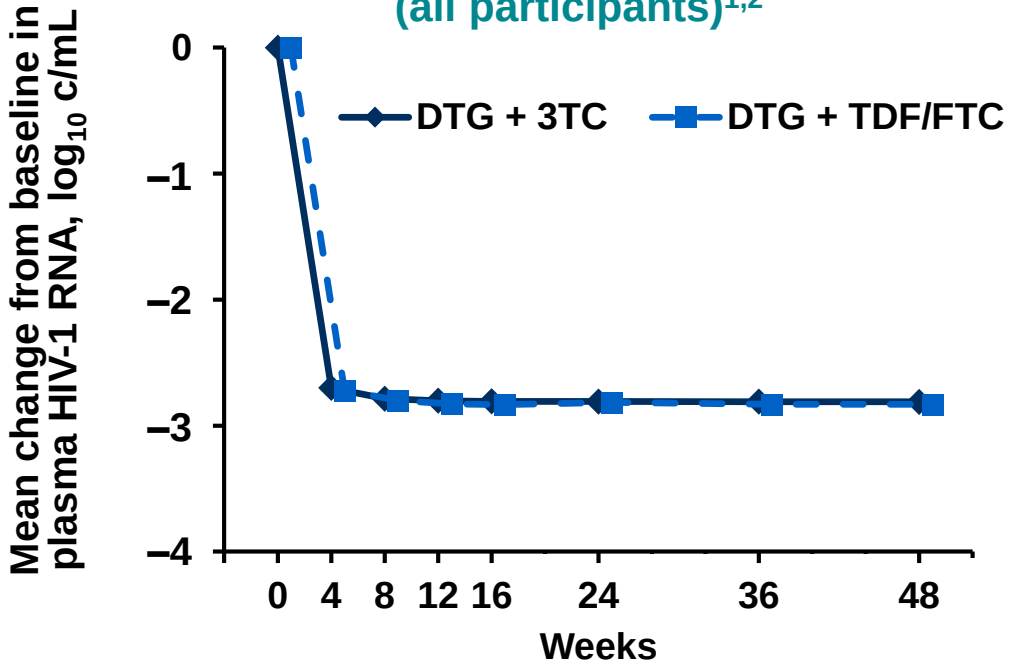
[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), CD4+ cell count (≤200 vs >200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2). The upper limit of the 95% CI for the pooled analysis was 0.0007%.

[b]In GEMINI-1, HIV-1 RNA <50 c/mL (95% CI) was achieved in 300/356 participants (84.3% [80.5-88.1]) in the DTG + 3TC group and 320/358 (89.4% [86.2-92.6]) in the DTG + TDF/FTC group (adjusted treatment difference [95% CI], −4.9% [−9.8, 0.03]). In GEMINI-2, the corresponding values were 316/360 (87.8% [84.4-91.2]) and 322/359 (89.7% [86.5-92.8]), respectively (adjusted treatment difference [95% CI], −1.8% [−6.4, 2.7]).

Adapted from Cahn et al. IAS 2019; Mexico City. Slides WEAB0404LB.

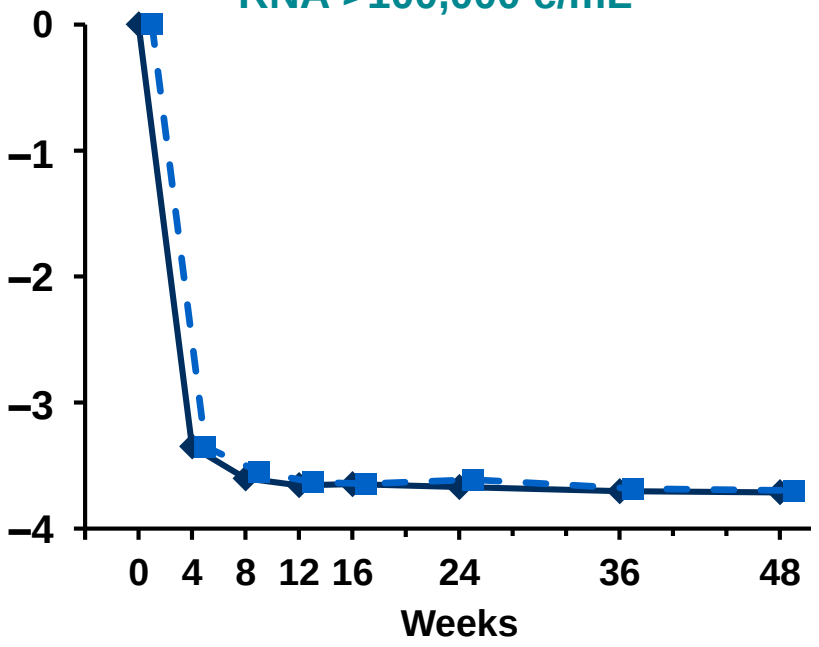
GEMINI-1 and -2: Rapid Viral Load Decline

Overall study population (all participants)[1,2]



DTG + 3TC, n	716	708	704	686	681	688	674	664
DTG + TDF/FTC, n	717	706	699	699	688	688	681	675

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



Magnitude and speed of viral load decline were s arms, irrespective of

	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA, median (range), log_{10} 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)**

Pooled ITT-E population

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

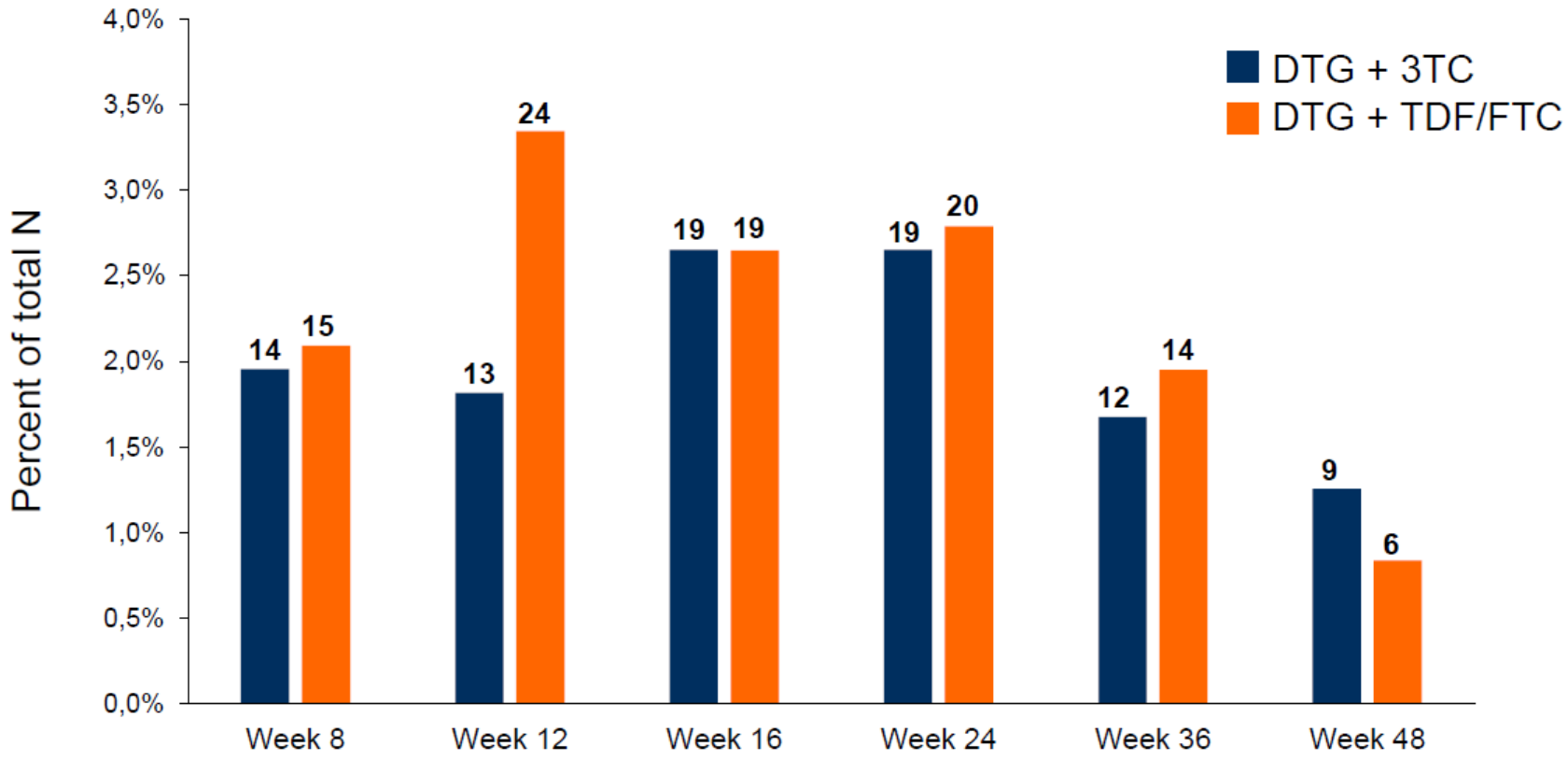
Viral Blips

Target Not Detected

Resistance

Blip Frequencies and Number by Visit

- Similar ‘blip’ frequencies were seen across arms

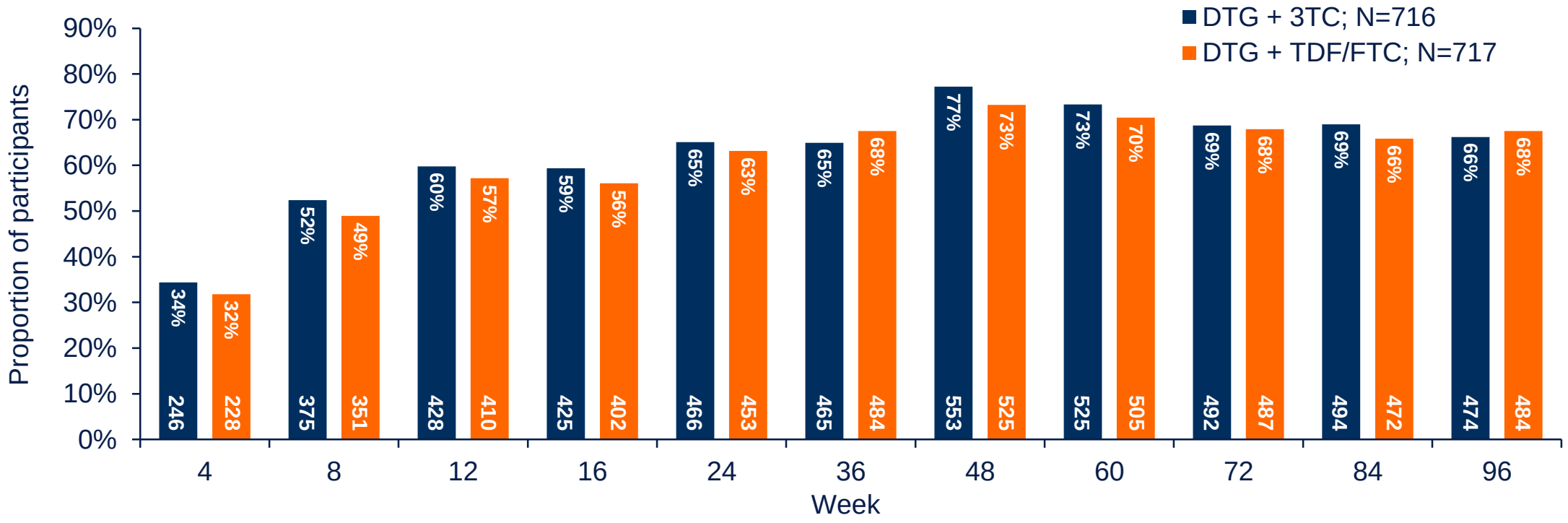


Bold numbers on chart are # of blips at given week visits. Note that individual subjects in Category 1a can have had more than one blip.

Underwood et al. IAS 2019; Mexico City, Mexico. Poster MOPEB231.

Proportions With TND Were Similar Between Groups at All Visits

(Gemini 1,2: week 96)



Proportion of Participants With TND by Visit (Snapshot Analysis, ITT-E Population)

Underwood M et al. EACS 2019; Basel, Switzerland. Slides PS8/2.

No treatment-emergent resistance was observed among participants who met Confirmed Virologic Withdrawal criteria

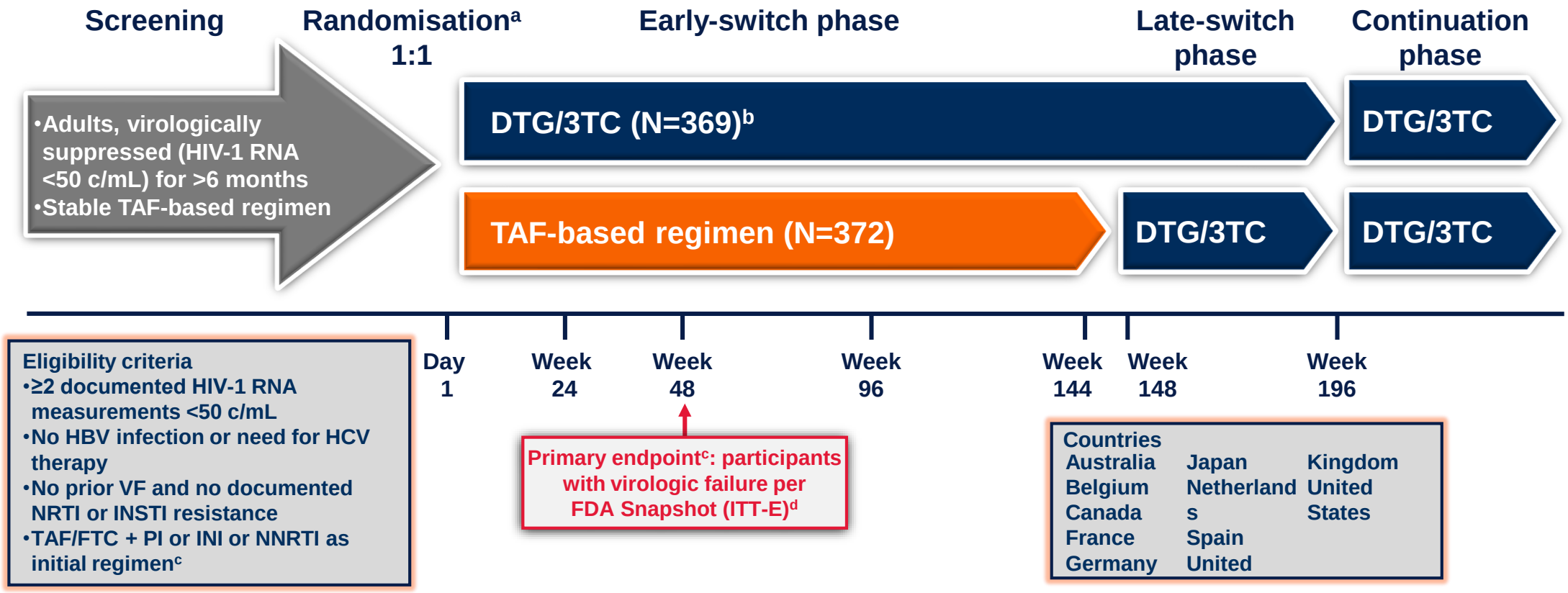
		GEMINI-1		GEMINI-2		Pooled	
	Variable, n (%)	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Week 48	CVW	4 (1.1)	2 (0.6)	2 (0.6)	2 (0.6)	6 (0.8)	4 (0.6)
Week 96	CVW	5 (1.4)	4 (1.1)[a]	6 (1.7)	3 (0.8)	11 (1.5)	7 (1.0)[a]
	Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

[a]One participant met the criteria for CVW at Week 12 but was not reported at the Week 48 analysis because of a laboratory reporting error identified after the Week 48 analysis.

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

TANGO: Phase III Study Design

Randomised, open-label, multicentre, parallel-group, non-inferiority study

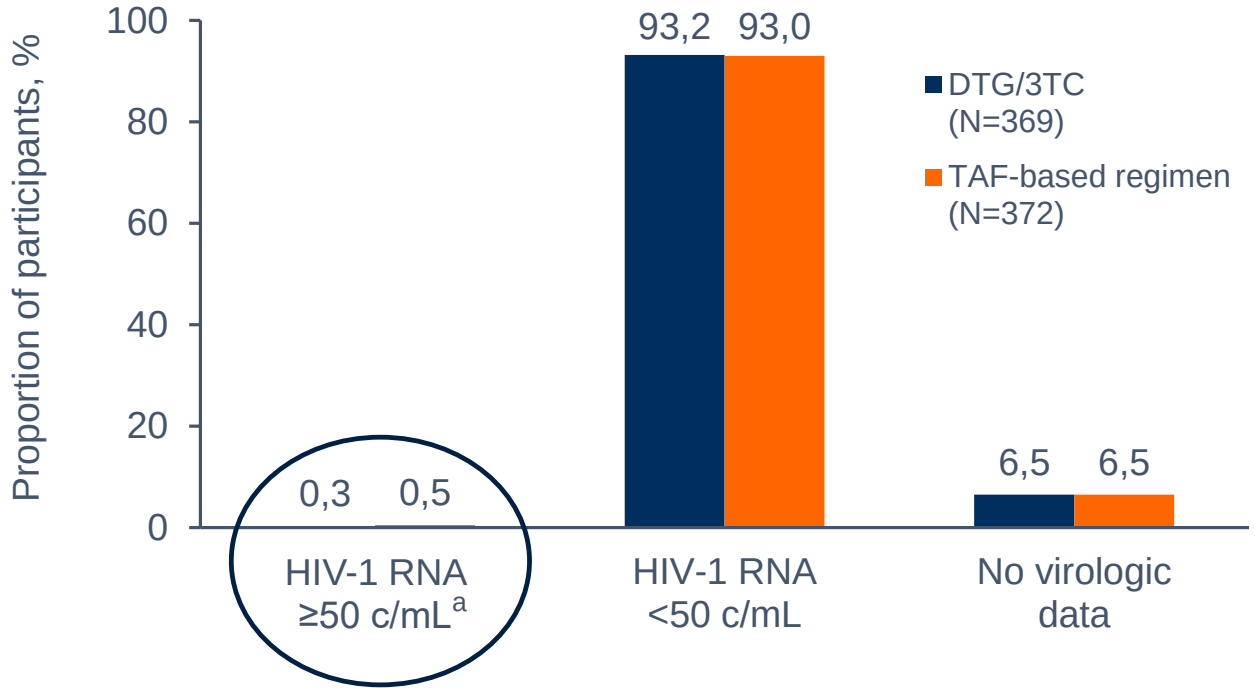


[a]Stratified by baseline third agent class (PI, INI, or NNRTI). [b]Two patients excluded who were randomized but not exposed to study drug. [c]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [d]4% non-inferiority margin. [e]Includes participants who changed a background therapy component or discontinued study treatment for lack of efficacy before Week 48, or who had HIV-1 RNA ≥50 c/mL in the 48-week window.

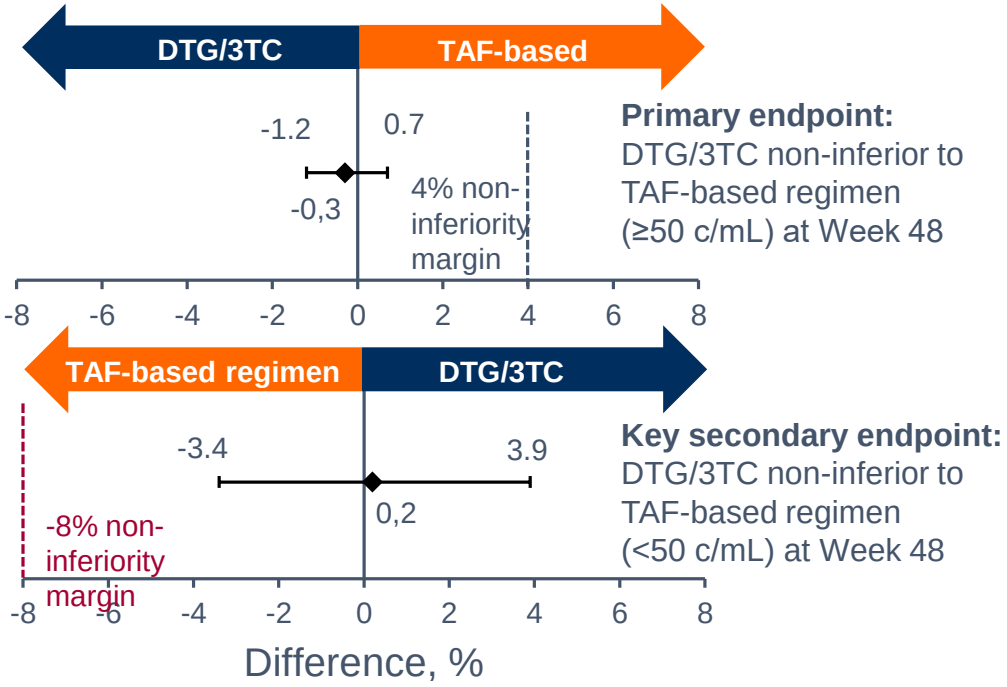
Adapted from van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

DTG/3TC is non-inferior to a TAF-based regimen at 48 weeks in TANGO study

Virologic outcomes



Adjusted treatment difference (95% CI)[b]



Primary endpoint: DTG/3TC non-inferior to TAF-based regimen (≥50 c/mL) at Week 48

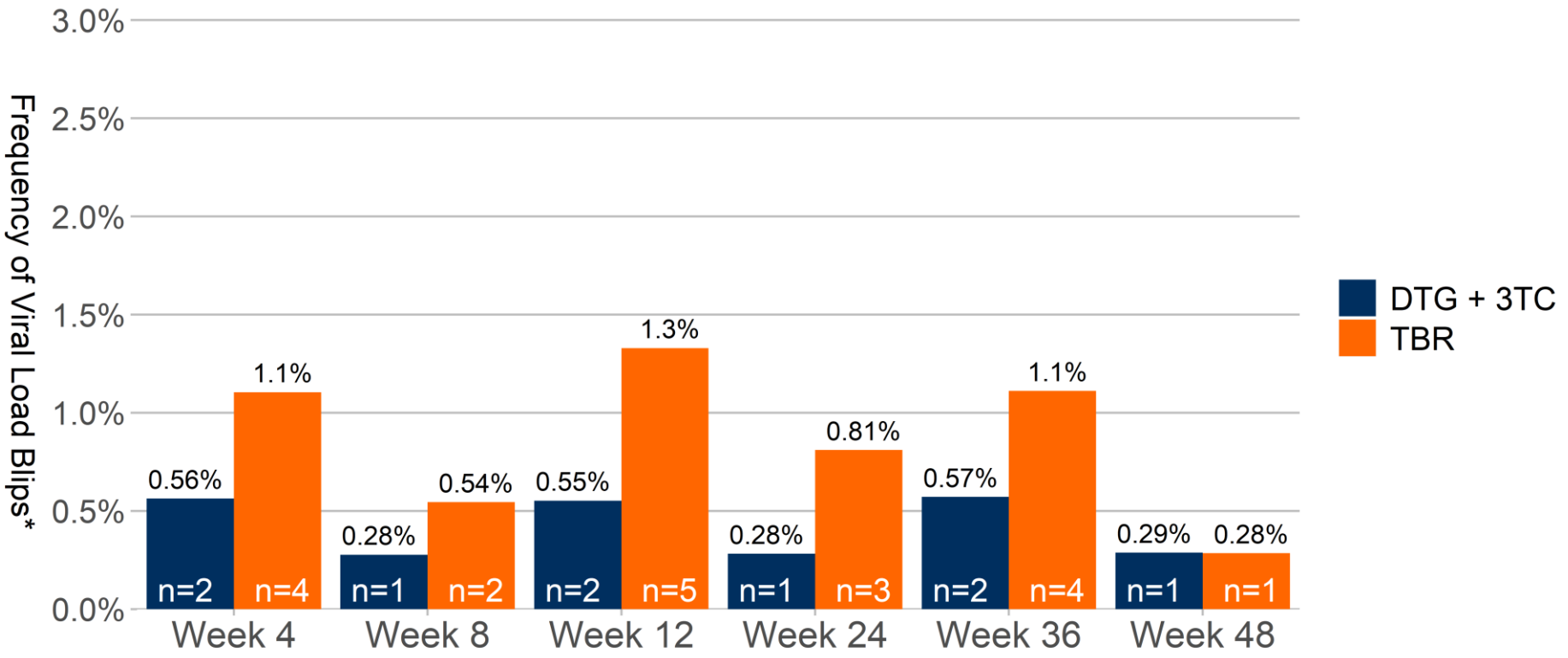
Key secondary endpoint: DTG/3TC non-inferior to TAF-based regimen (<50 c/mL) at Week 48

- In the per-protocol population, 0/352 participants in the DTG/3TC group and 2/358 participants in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.6; 95% CI, −1.3 to 0.2)[b]

[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline third agent class.

Adapted from van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

Frequency of Viral Load Blips in Category 1a Participants by Study Visit Through Week 48



The occurrences of viral blips at each visit by treatment group over 48 weeks were similar

*Percentages were calculated from number of blips in Category 1a participants using post-baseline previously suppressed (<50 c/mL). Participant visit Ns respectively for DTG/3TC and DTG + TDF/FTC at: Wk 4 (N=355) and (N=362); Wk 8 (N=361) and (N=367); Wk 12 (N=362) and (N=376); Wk 24 (N=355) and (N=370); Wk 36 (N=350) and (N=360); Wk 48 (N=348) and (N=351). Numbers on the bottom of each bar represent # of blips at given week visit. Individual participants can have had more than one blip.

Wang et al. EACS 2019; Basel, Switzerland. Poster PE3/15.

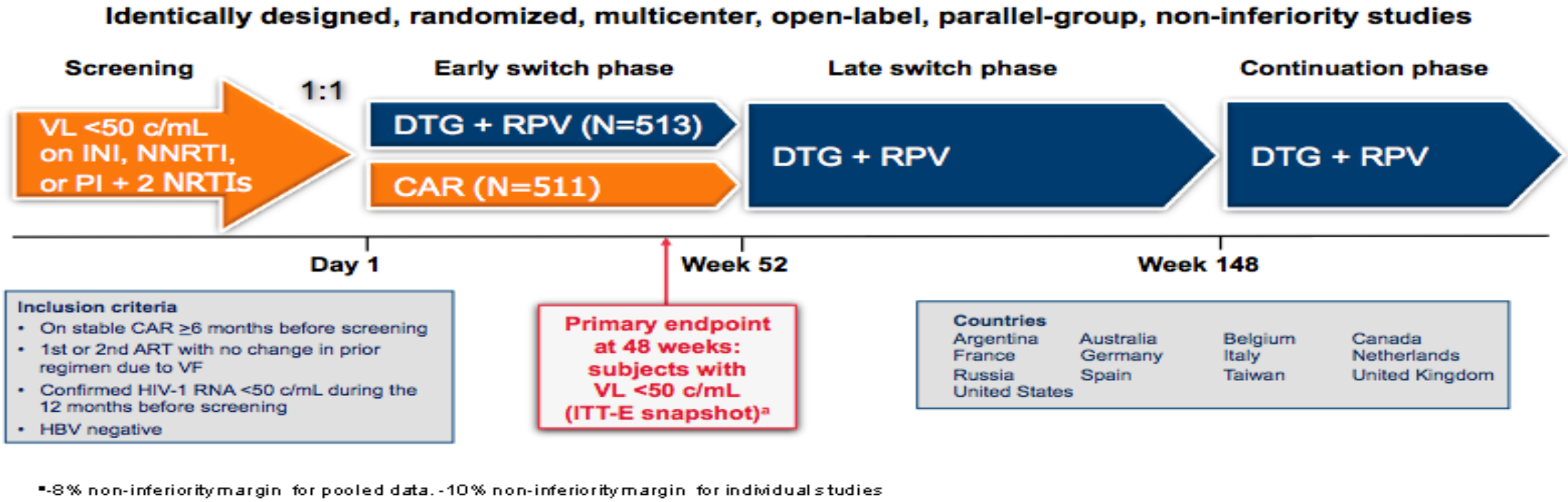
No Confirmed Virologic Withdrawals with DTG/3TC in TANGO through 48 weeks

n (%)	DTG/3TC (N=369)	TAF-based regimen (N=372)
Confirmed virologic withdrawal (CVW)[a]	0	1 (<1)[b]
Observed resistance mutation at failure[c]	0	0

[a]One assessment with HIV-1 RNA ≥200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥50 c/mL.
[b]Treatment interrupted before suspected virologic withdrawal (VL, 38,042 c/mL) and resumed 3 weeks before VL retest (297 c/mL).
[c]Plasma HIV-1 RNA resistance genotype at failure is compared with baseline PBMC pro-viral resistance genotype.

Adapted from van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

SWORD 1, 2 studies



▪-8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies

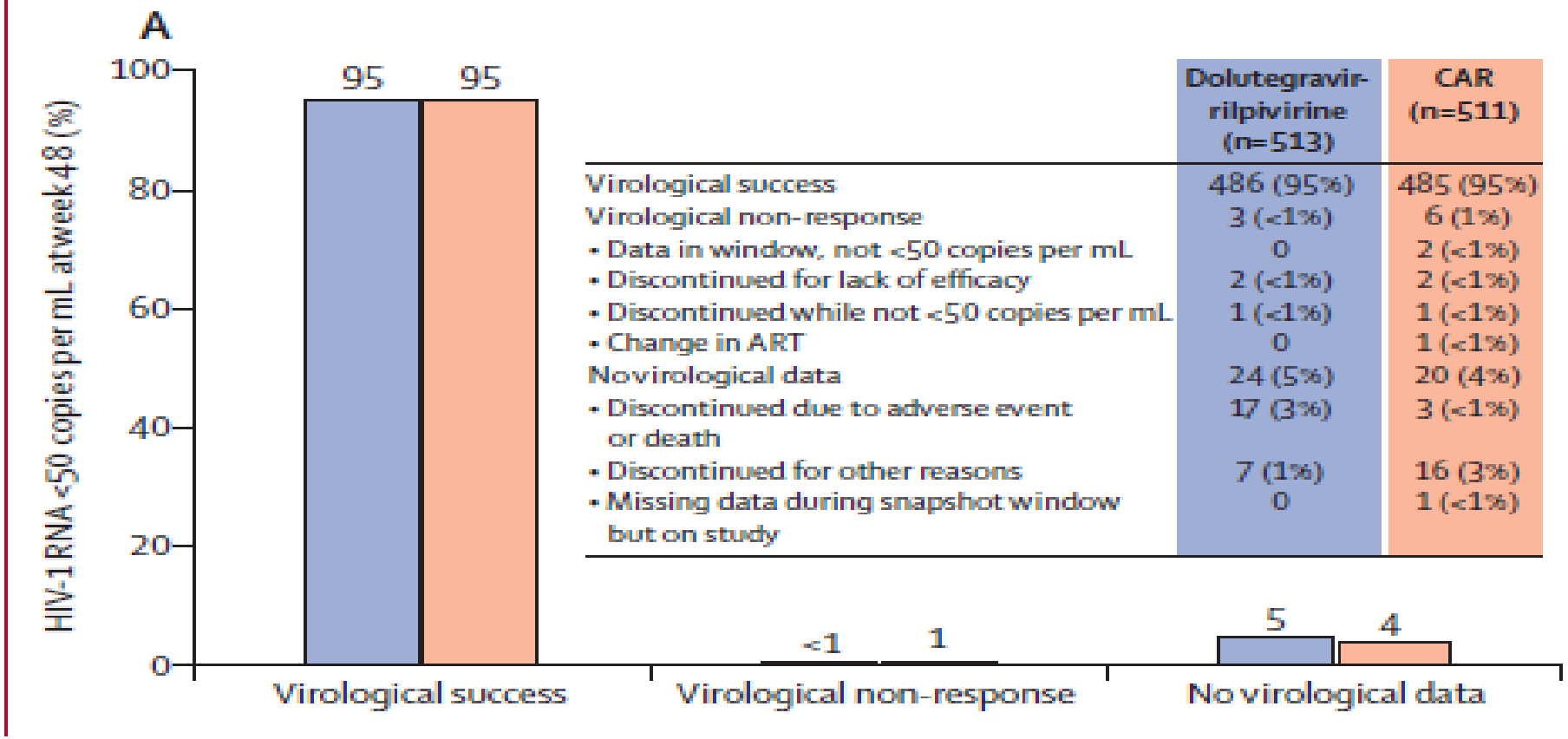
Llibre JM, et al. Lancet. 2018;391:839-849

SWORD 1, 2 studies

HAART at baseline

from PI:	26%
from NNRTI:	54%
from II:	20%

week 48 data



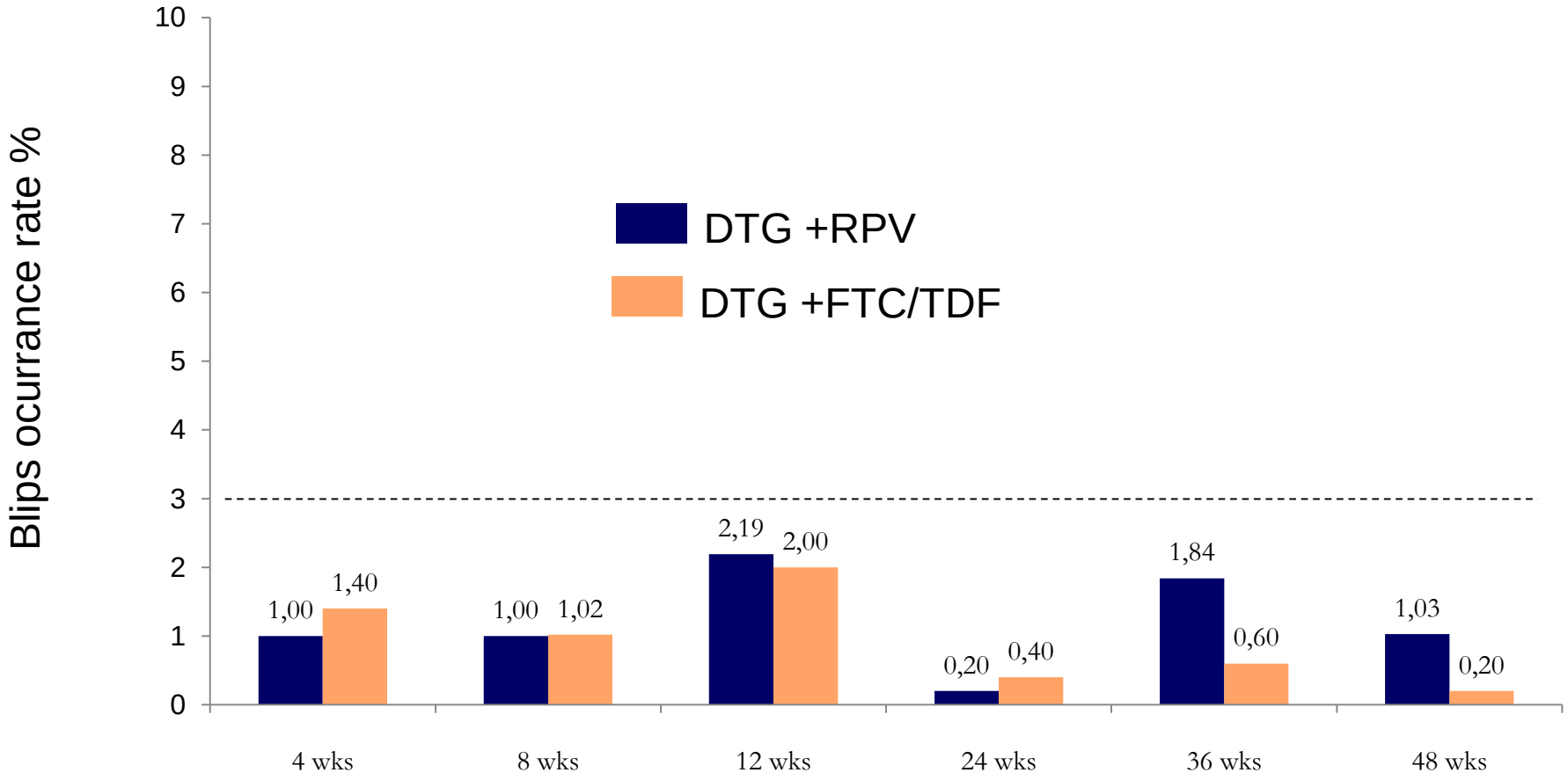
	Dolutegravir-rilpivirine (n=513)	CAR (n=511)
Virological success	486 (95%)	485 (95%)
Virological non-response	3 (<1%)	6 (1%)
• Data in window, not <50 copies per mL	0	2 (<1%)
• Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
• Discontinued while not <50 copies per mL	1 (<1%)	1 (<1%)
• Change in ART	0	1 (<1%)
No virological data	24 (5%)	20 (4%)
• Discontinued due to adverse event or death	17 (3%)	3 (<1%)
• Discontinued for other reasons	7 (1%)	16 (3%)
• Missing data during snapshot window but on study	0	1 (<1%)

10/990 (1%) confirmed virologic withdrawals through week 100 (**NNRTI resistance** in 3/10, all from early switch arm).

Aboud M et al. AIDS 2018. Abs THPEB047. Llibre JM et al. Lancet. 2018;391:839-849.

Viral blips SWORD 1, 2 studies

Rates of blips (HIV RNA >50 c/ml) by through week 48



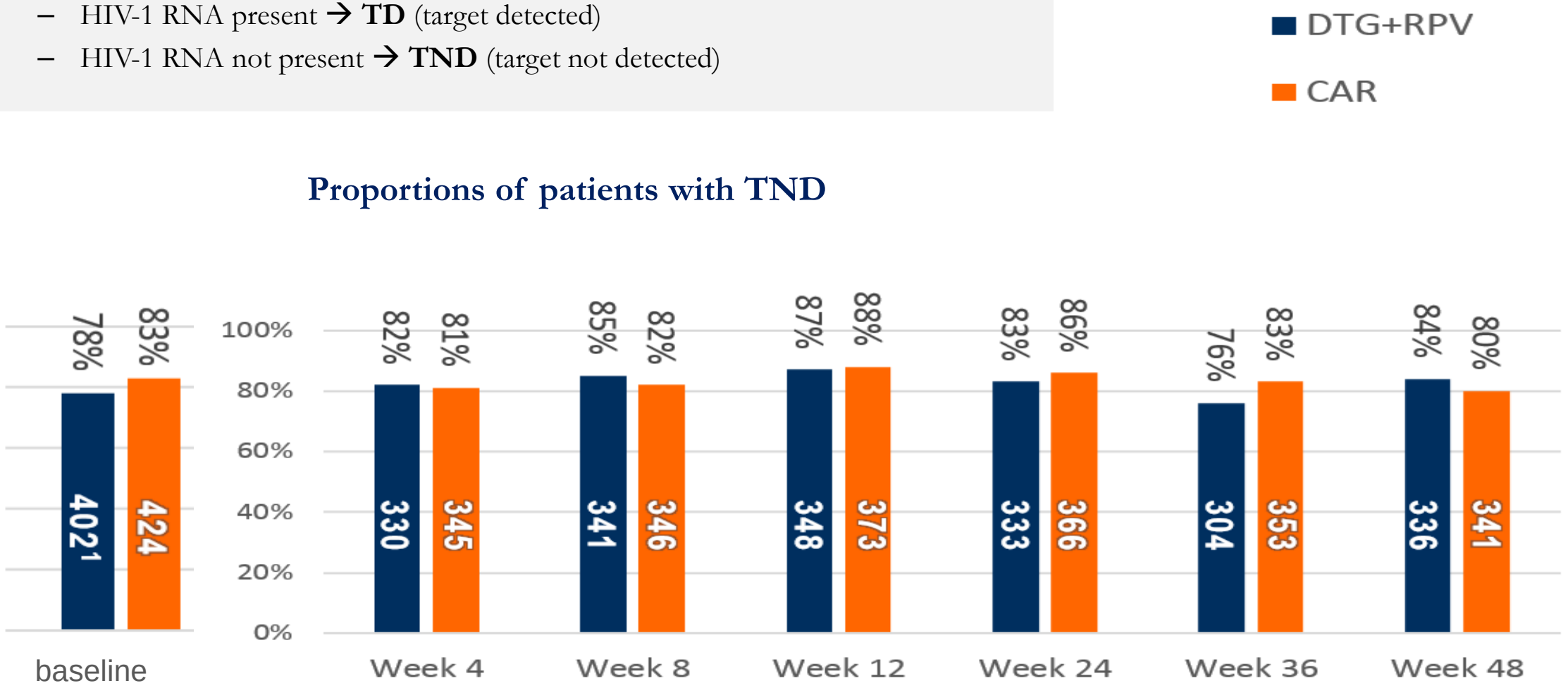
Viral blips were not associated to CVW

Wang R et al. HIV Drug therapy 2018, Glasgow UK; Poster 313.

Target Not Detected (TND) in SWORD 1, 2 studies

Abbott HIV-1 Realtime Assay generates <u>qualitative data</u> for VL <40 c/mL

- HIV-1 RNA present → **TD** (target detected)
- HIV-1 RNA not present → **TND** (target not detected)



Underwood M et al. HIV Drug Therapy 2018, Glasgow UK; Poster 311.

DUALIS Study

Pts on bDRV-r (3DR)
- for >24 weeks
- switch < 50 c/ml
- HBsAg neg

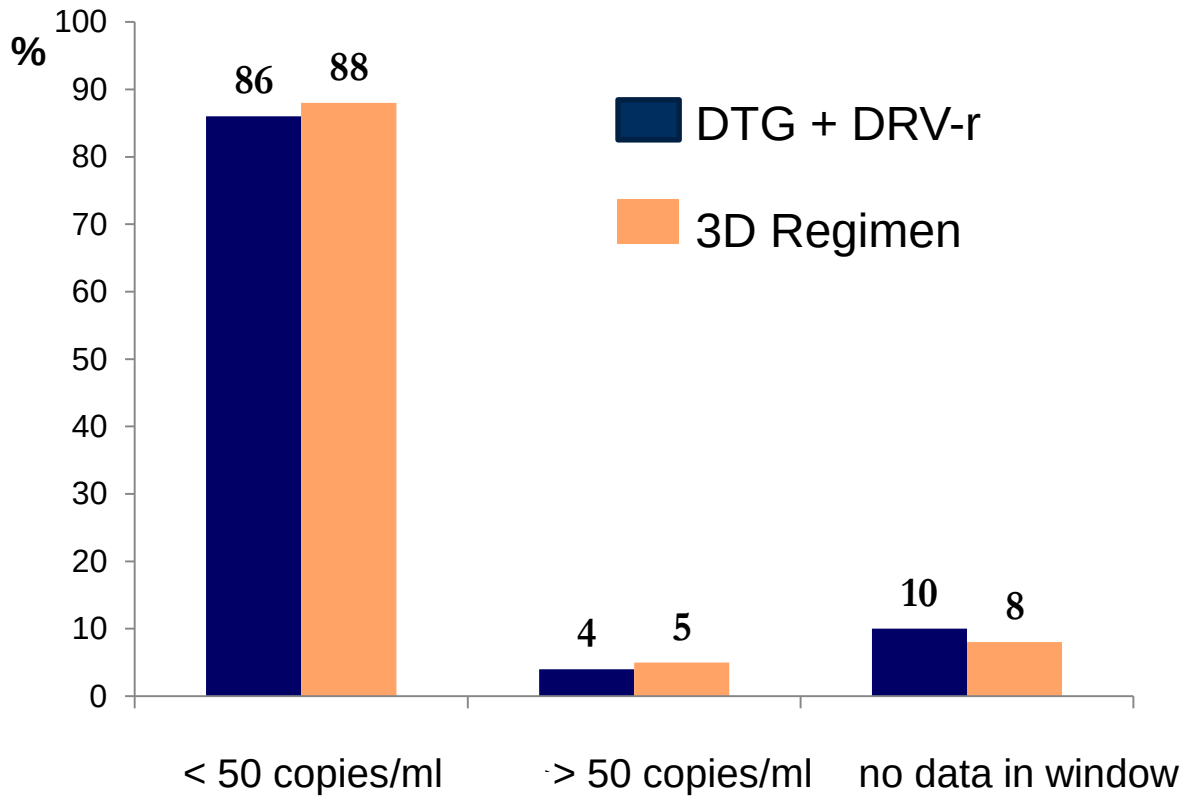
n. 132
DRV-r + 2NRTIs **3DR**

n. 131
DRV-r + DTG **2DR**

mean CD4 count at entry: 598 cells
nadir CD4 count (< 200 cells): 47%

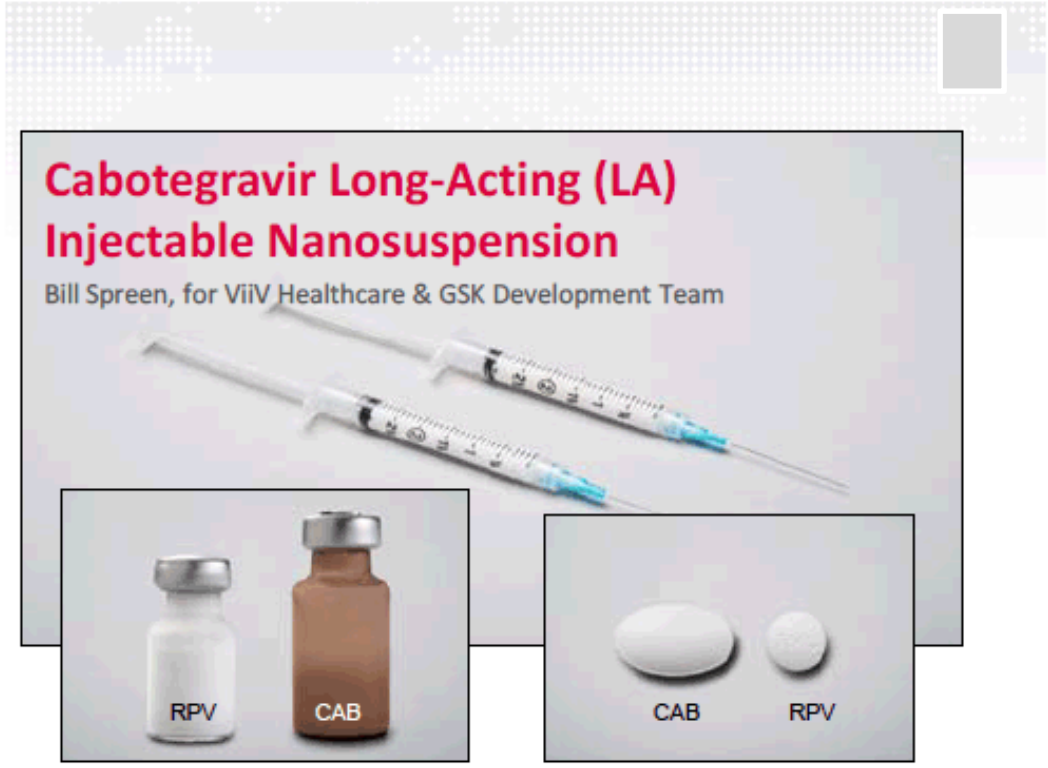
No resistance mutations at failure

HIV RNA < 50 copies/ml, 48 week data



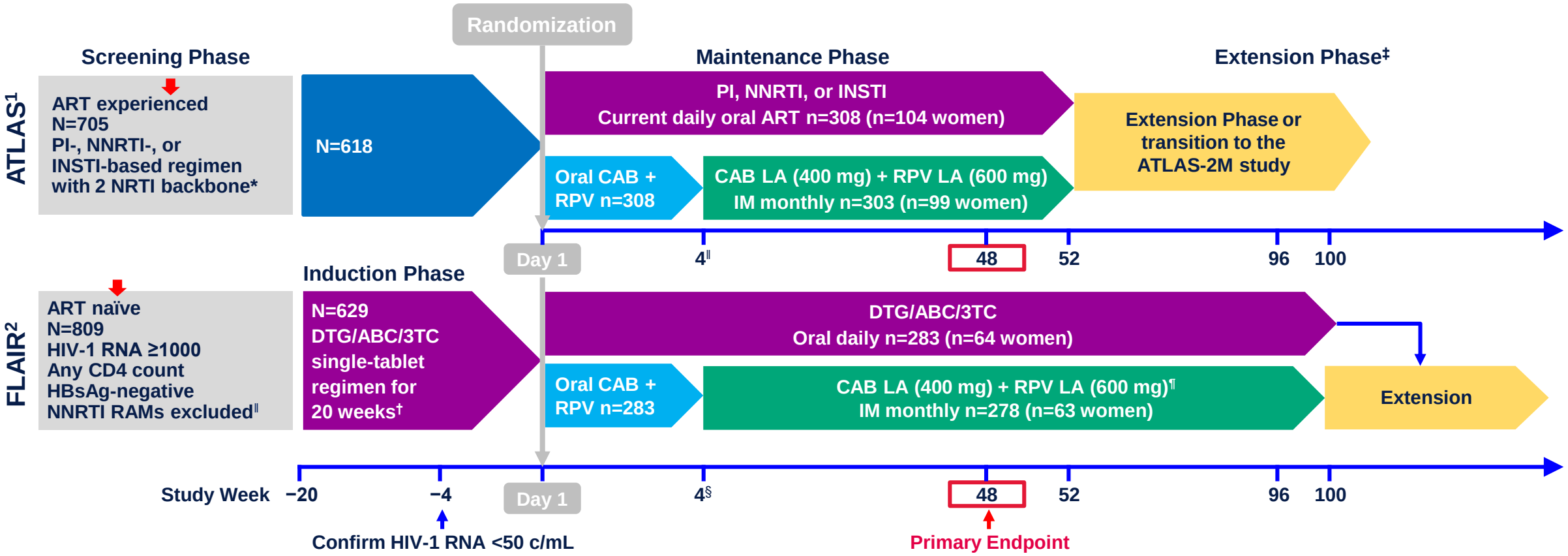
Spinner CD et al. IAS 2019, Mexico, #MOPEB269

Cabotegravir + Rilpivirine Long Acting



CAB + RPV Long acting (ATLAS and FLAIR Study)

Randomized, Multicenter, International, Open-Label, Non-Inferiority Studies



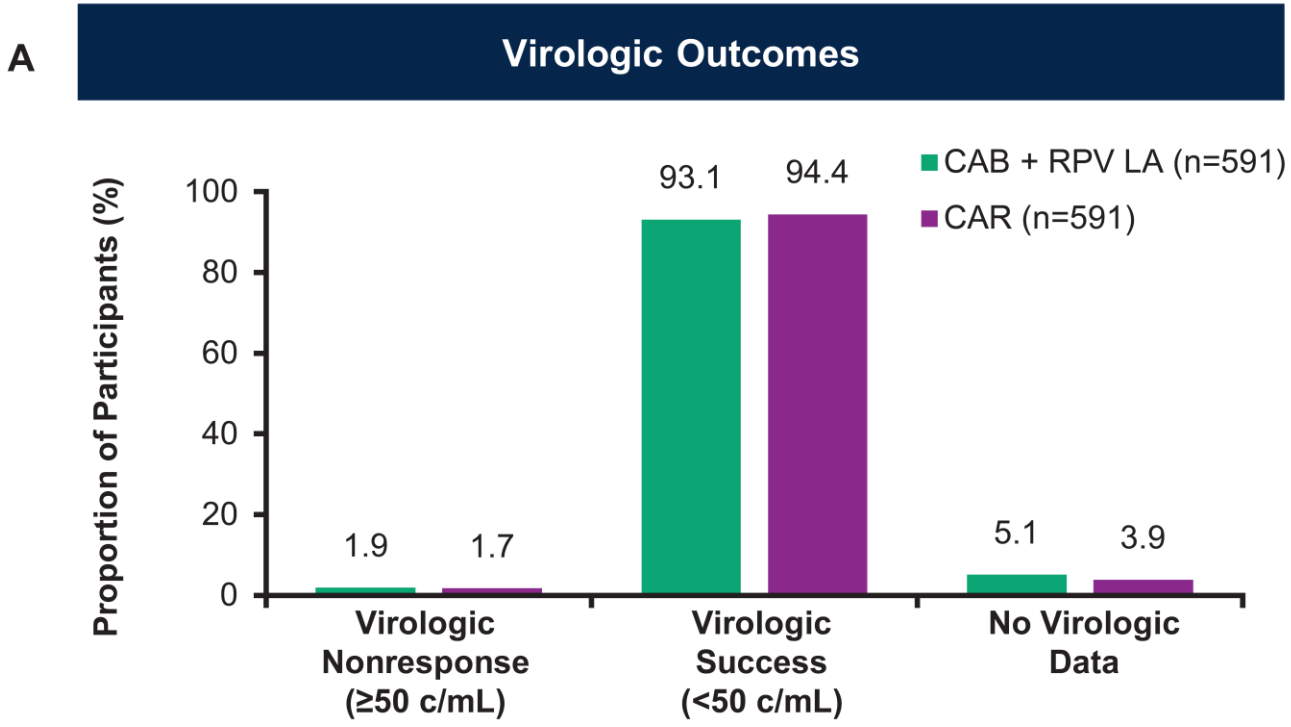
*Uninterrupted ART 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; Triumeq excluded from study. †DTG plus 2 alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive (n=30 as last regimen during induction: n=2 discontinued during induction, n=14 randomized to CAB LA + RPV LA, n=14 randomized to DTG/ABC/3TC arm and continued on DTG plus 2 alternative non-ABC NRTIs in Maintenance Phase). ‡Optional switch to CAB LA + RPV LA at Week 52 for those on CAR. §Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks. ‖NNRTI RAMs but not K103N were exclusionary. ¶Participants who withdraw/complete CAB LA + RPV LA enter 52-week long-term follow-up.

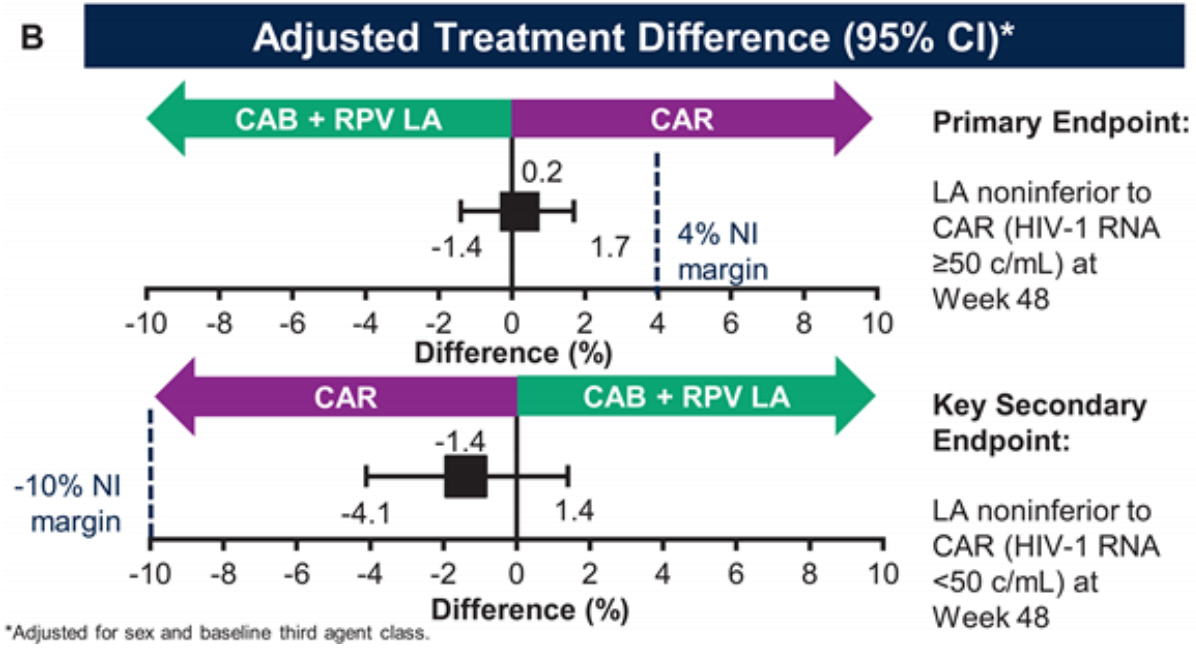
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; DTG, dolutegravir; IM, intramuscular; INSTI, integrase strand transfer inhibitor; HBsAg, hepatitis B surface antigen; HLA, human leukocyte antigen; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; VL, viral load.

1. Swindells S, *et al.* CROI 2019; Seattle, WA. Abstract 139; 2. Orkin C, *et al.* CROI 2019; Seattle, WA. Abstract 140.

CAB + RPV Long Acting

ATLAS and FLAIR Pooled data at week 48





Overton et al. IAS 2019; Mexico City, Mexico. Poster MOPEB257.

ATLAS and FLAIR Confirmed Virologic Failures

Pooled data at week 48

Regimen	ATLAS	FLAIR
3-drug arm (591 patients)	4 virological failures: 1) M184I, 2) M184V+G190S 3) M230M/I 4) no mutations.	3 virological failures: no mutations.
CAB + RPV LA arm § (591 patients)	3 virological failures: All with RPV mutation 1 with CAB mutation*	3 virological failures: 2/3 with RPV mutation 3 with CAB mutation**

§ 5/6 in Russia, all HIV subtype A1

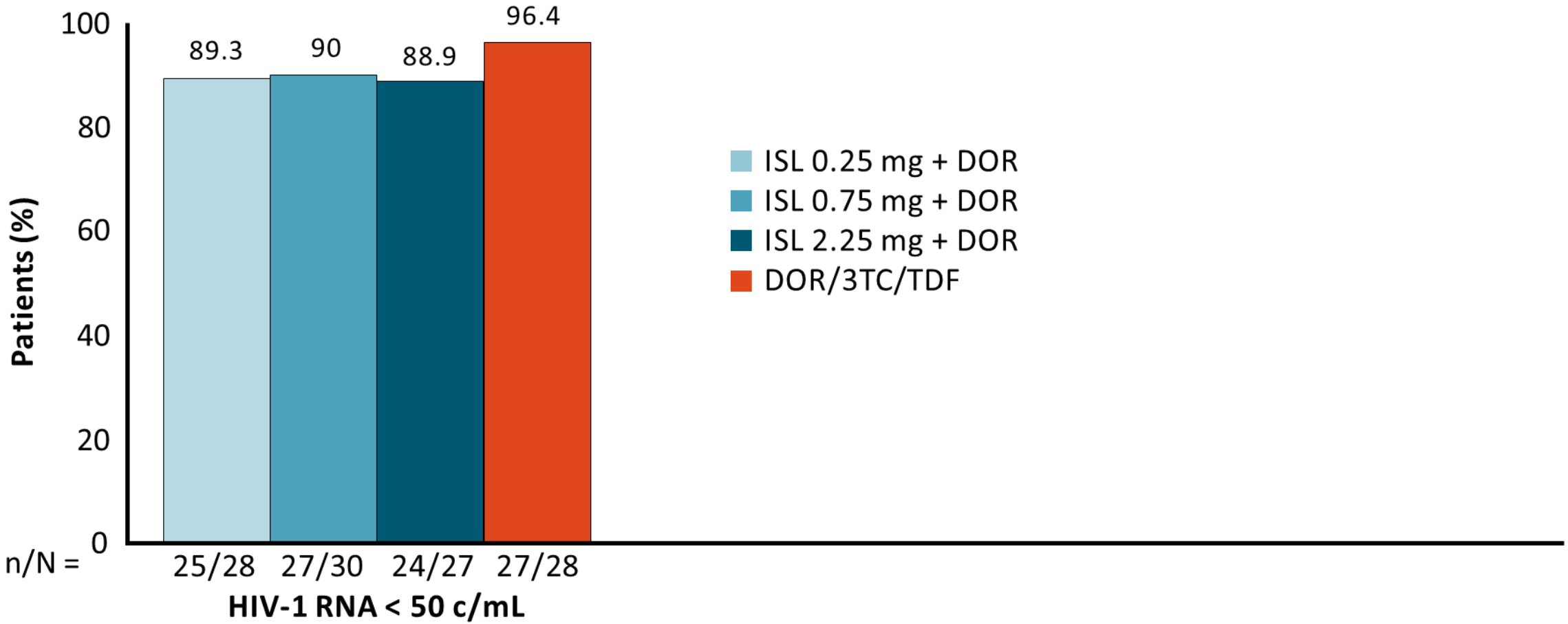
* N155H mutation

** 1 with G140R and 2 with Q148R mutation

Overton et al. IAS 2019; Mexico City, Mexico. Poster MOPEB257.

DRIVE2Simplify Part 2: Virologic Outcomes

24 weeks after entering Part 2 (phase 2 trial)



Molina. IAS 2019. Abstr WEAB0402LB.

When? No HBV coinfection and no resistance to study drugs

	Type of regimen	
	2D Regimen	3D Regimen
Viral decay		
Viral blips		
TD vs TND		
Rate of suppression		
Resistance at failure		

similar

Thanks for the attention