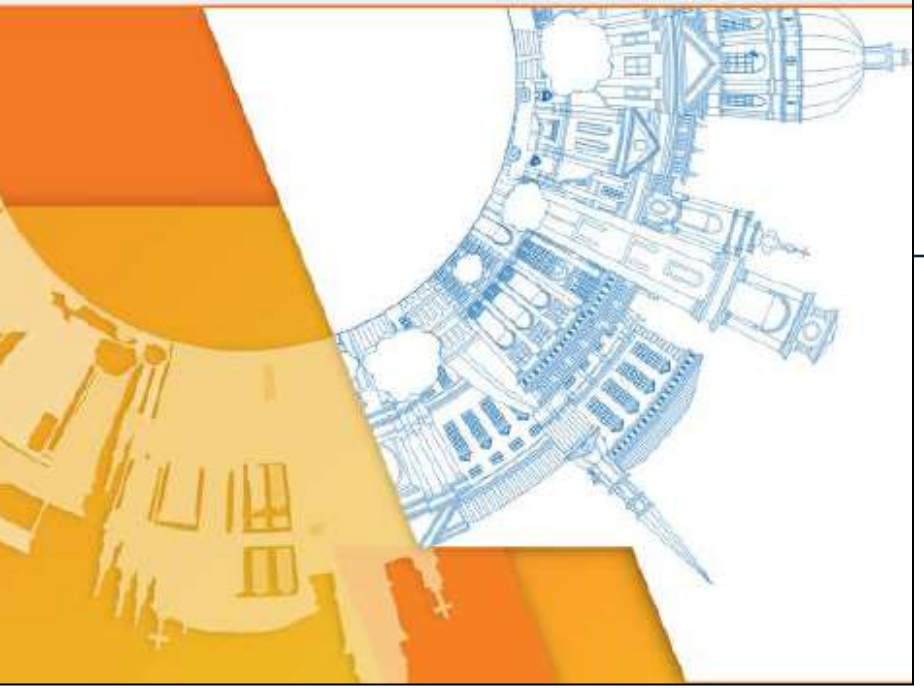

16° Residential Course on Clinical Pharmaology and Antiretrovirals

January 13-15, 2021

TWO-DRUG REGIMENS FOR HIV INFECTION:
Pros and Cons from clinical trials

Diego Ripamonti
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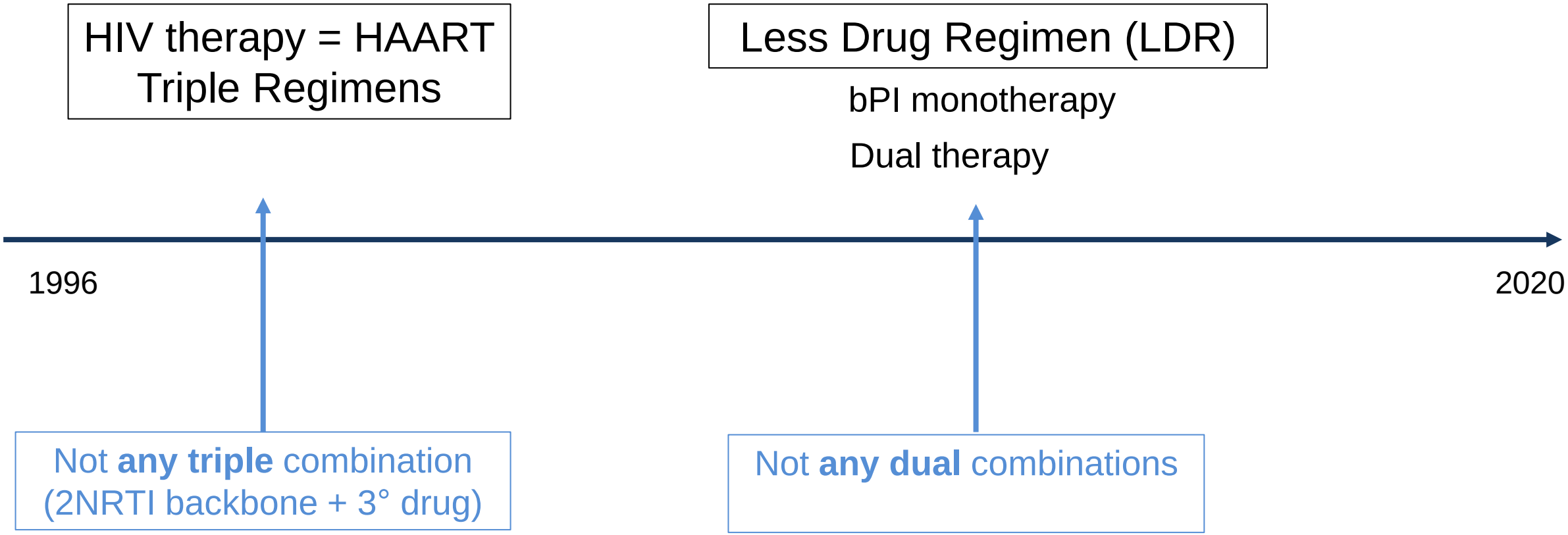
Disclosures

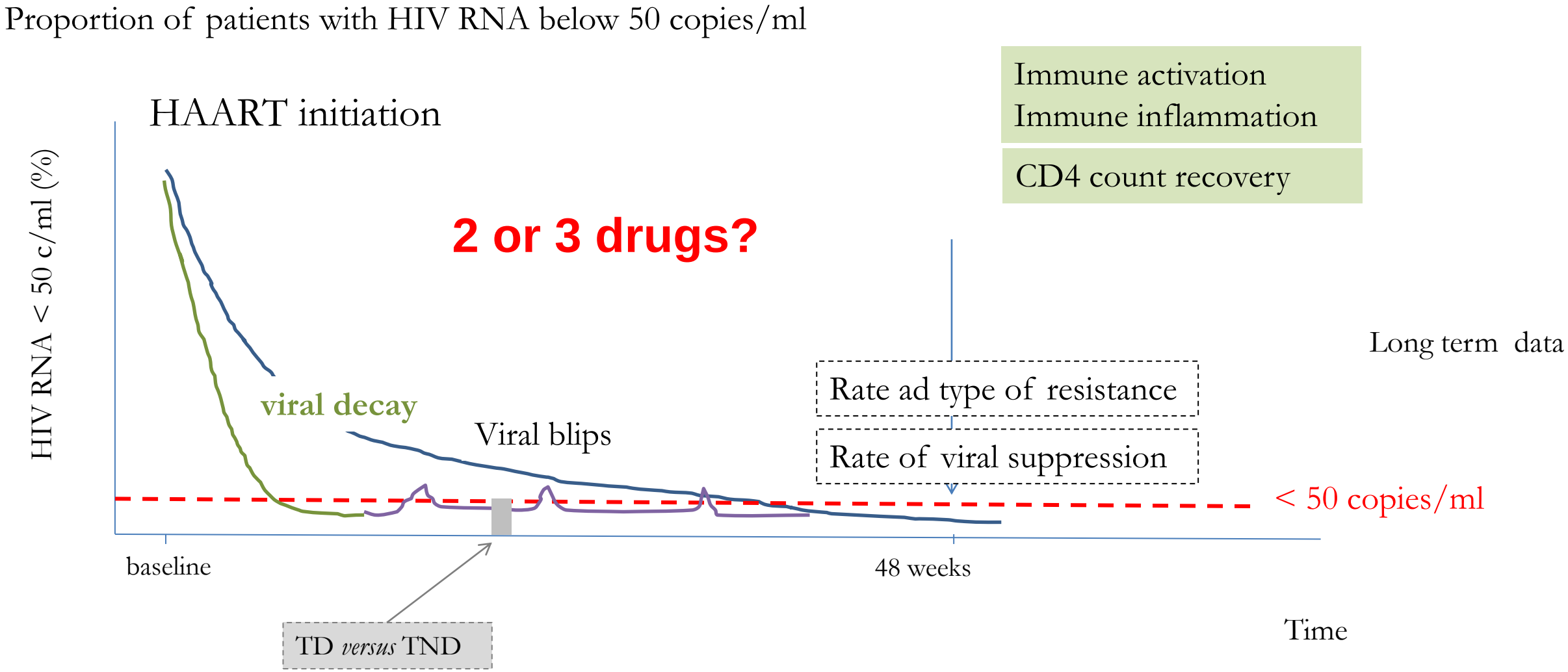
Diego Ripamonti has received advisory fees, speaker fees, travel and education support from:

- ViiV
- Janssen
- Merck
- Gilead

HAART in history



Treatment response in randomized trials



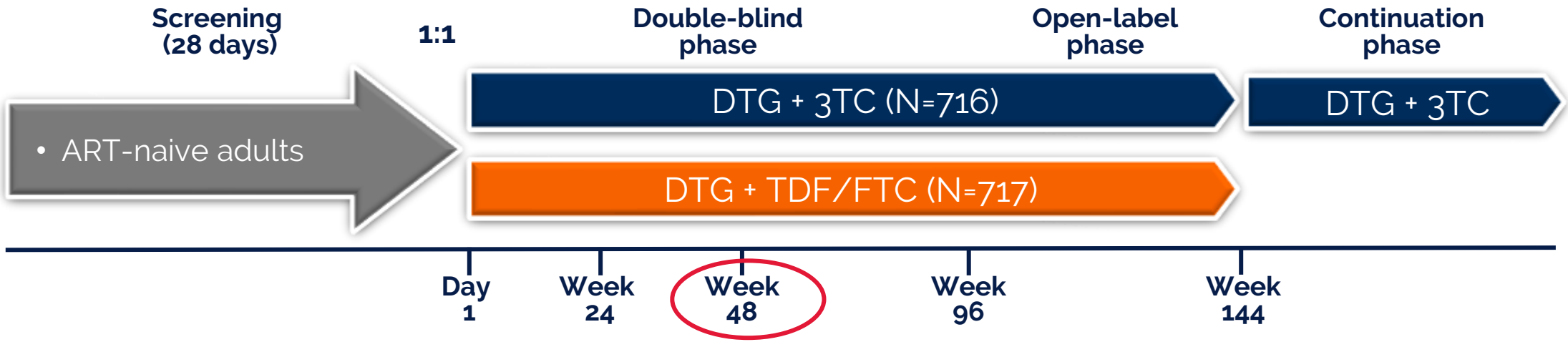
2DR era in HIV therapy

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	144	0
DTG + 3TC [7]	TANGO	switch	any	741	yes	48	0
DTG + DRV-r [8]	Dualis	switch	DRV/r	263	yes	48	0
CAB + RPV LA [9]	ATLAS	switch	any	618	yes	48	3+
	FLAIR	switch	ABC/3TC/DTG	629	yes	48 - 124	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
8. Spinner CD et al. Open Forum Infect Dis 2020 9. IAS Conference, Mexico, 2019

GEMINI-1 AND GEMINI-2 PHASE III STUDY DESIGN

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

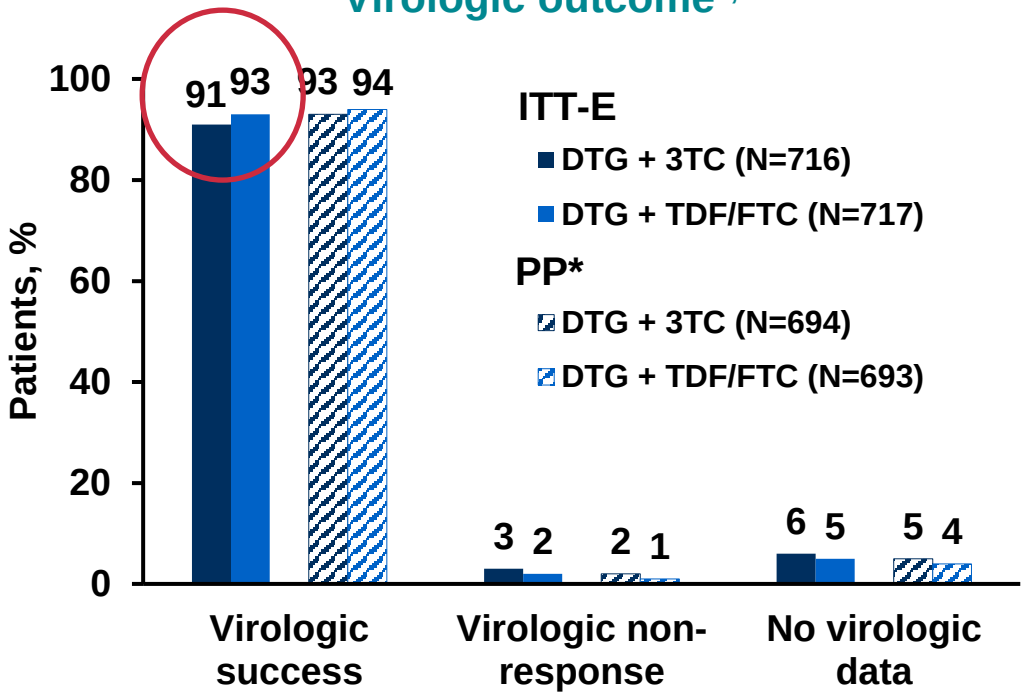
Baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).

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

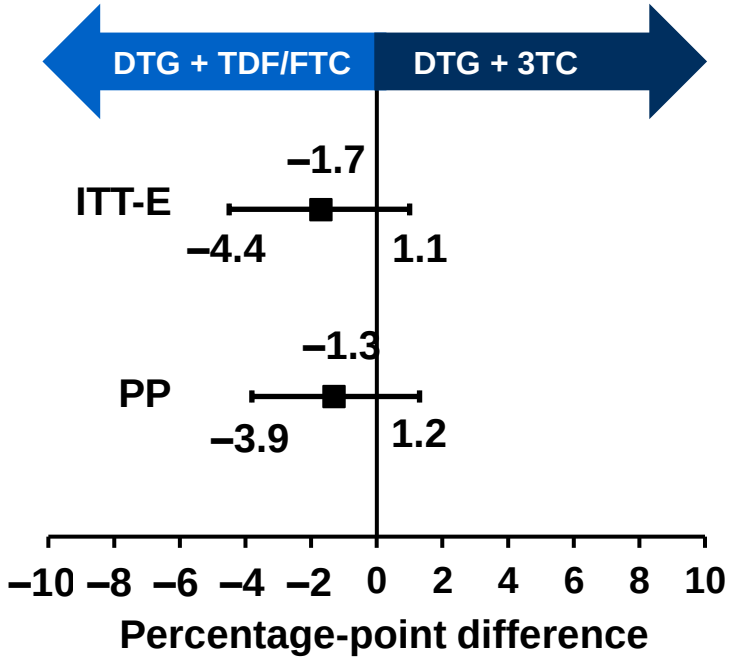
Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

GEMINI-1 and -2: Pooled Snapshot Outcomes at Week 48

Virologic outcome[1,2]



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



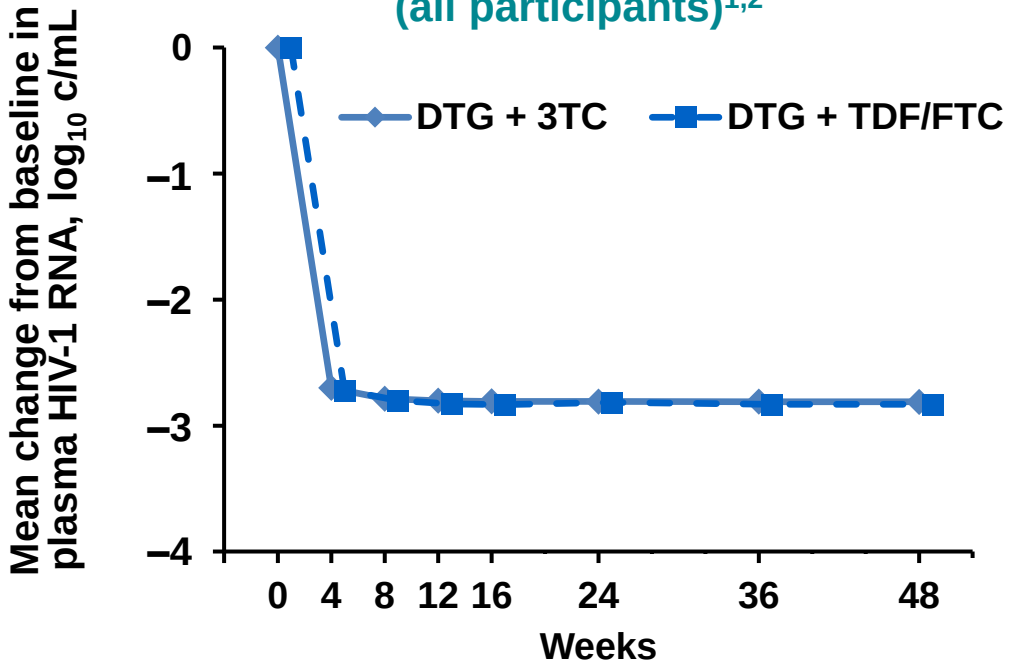
DTG + 3TC was <u>non-inferior</u> to DTG + TDF/FTC in the proportion of patients with <50 c/mL HIV-1 RNA at Week 48 in pooled Snapshot data using either the ITT-E or PP populations[1]

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). ‡PP, per protocol

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

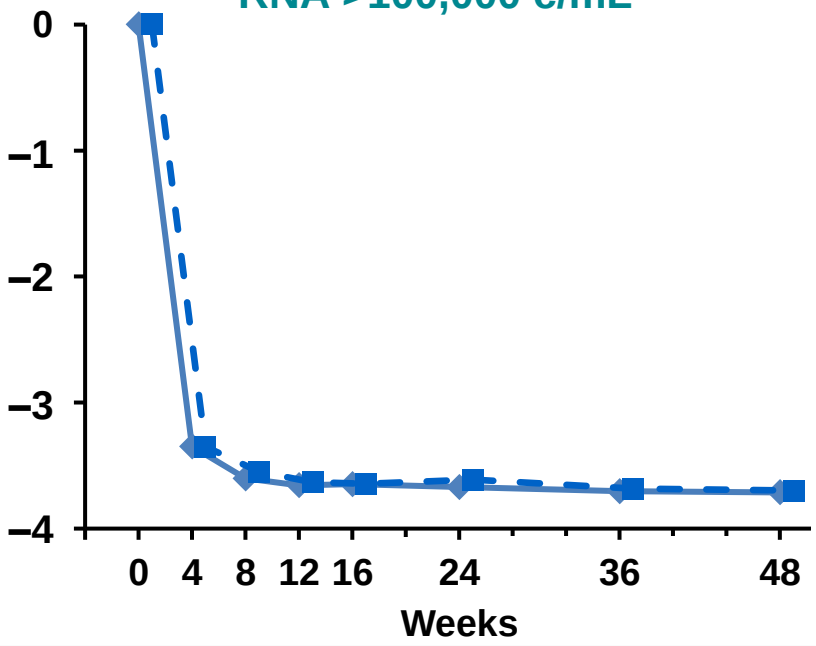
GEMINI-1 and -2: Rapid Viral Load Decline

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 wer rms, irrespective

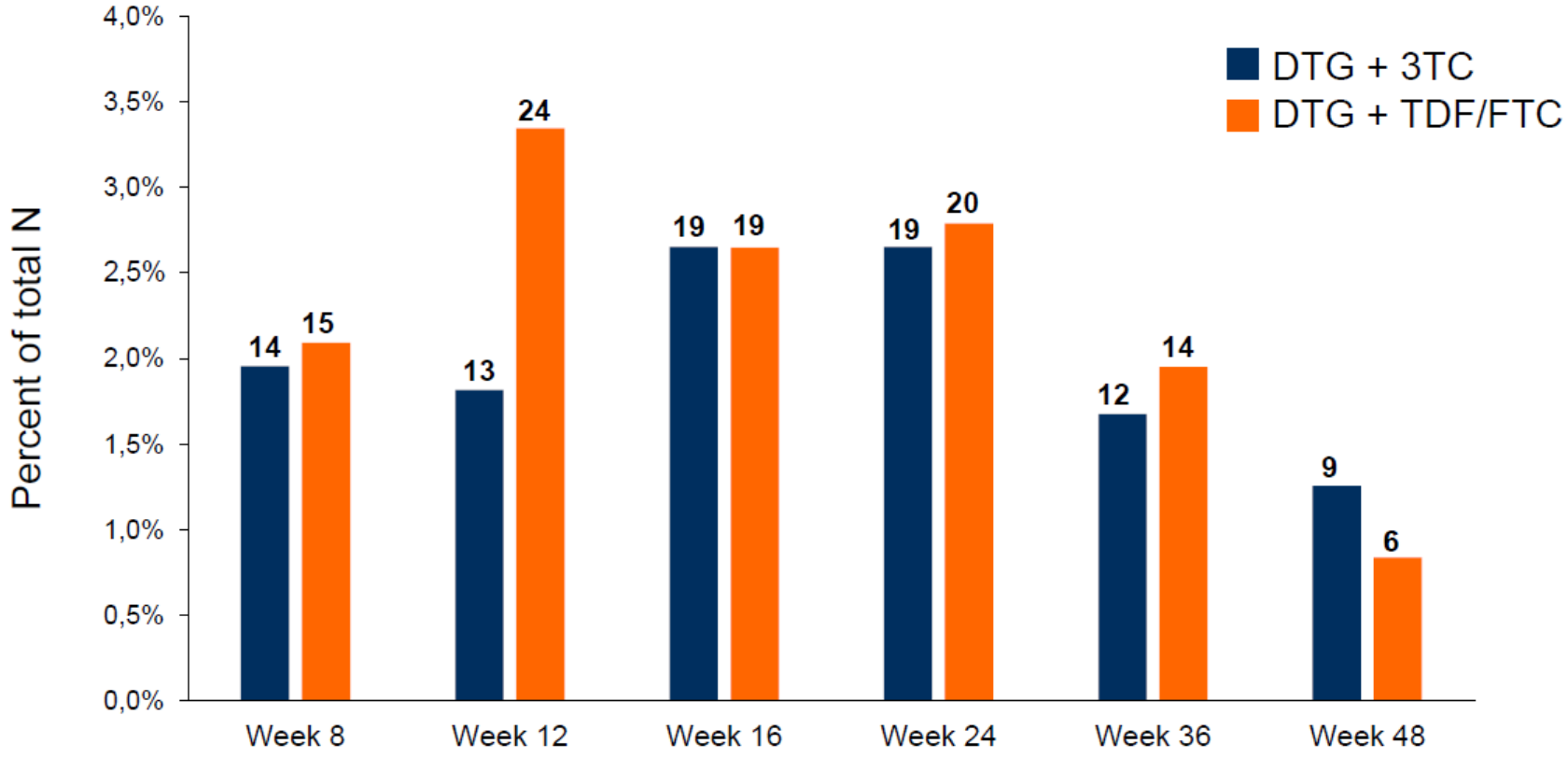
	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59–6.27)	4.46 (2.11–6.37)
≤100,000	576 (80)	564 (79)
>100,000*	**140 (20)**	**153 (21)**

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

Blip Frequencies and Number by Visit

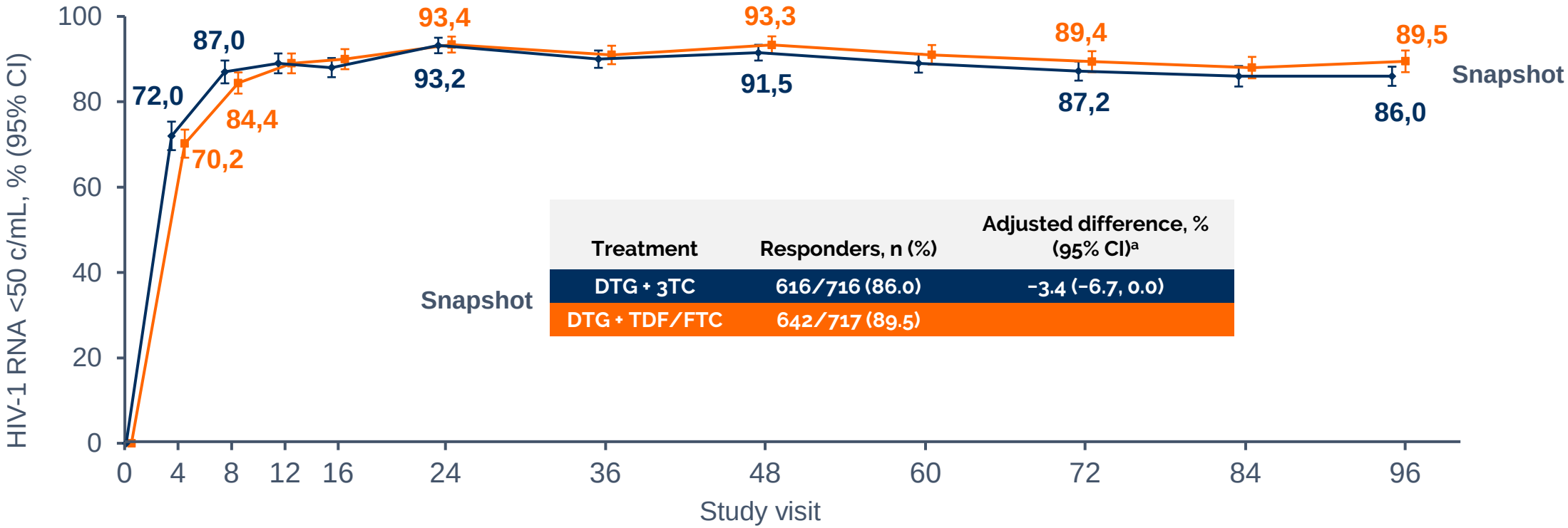
- Similar ‘blip’ frequencies were seen across arms



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.

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



	Treatment	Responders, n (%)	Adjusted difference, % (95% CI)[a]
Snapshot	DTG + 3TC	616/716 (86.0)	−3.4 (−6.7, 0.0)
	DTG + TDF/FTC	642/717 (89.5)	

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.

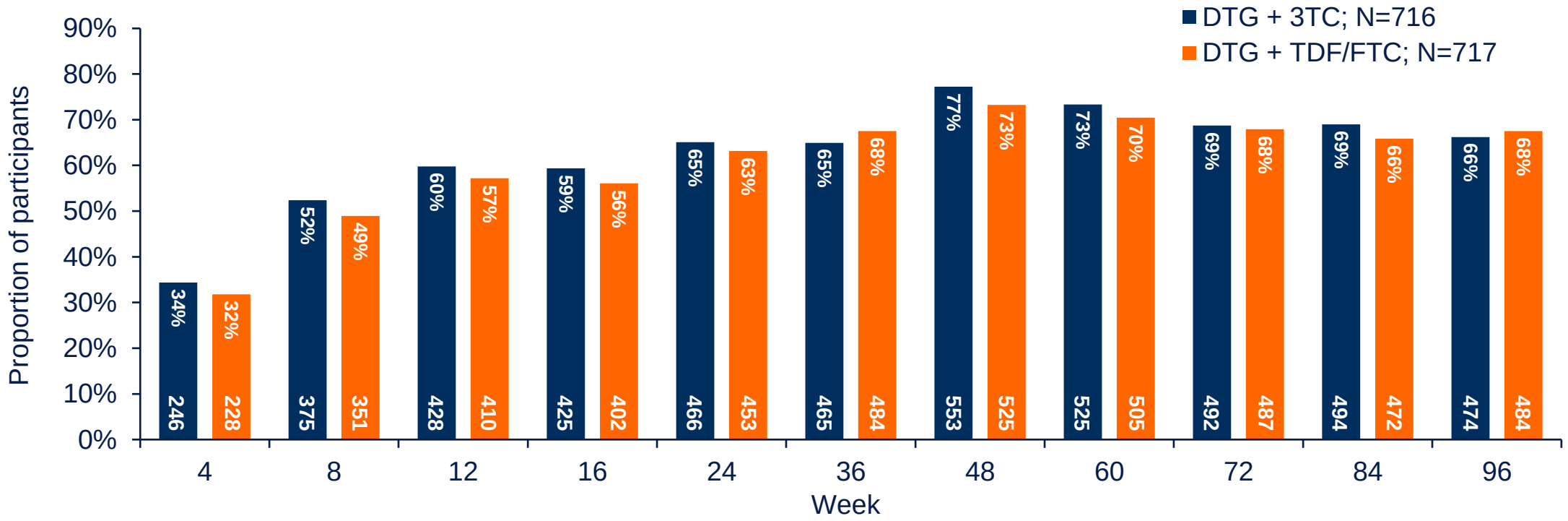
No treatment-emergent resistance was observed among participants with confirmed virologic withdrawal criteria

		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.

Proportions with TND were similar between groups at all visits *(Gemini 1,2: week 96)*

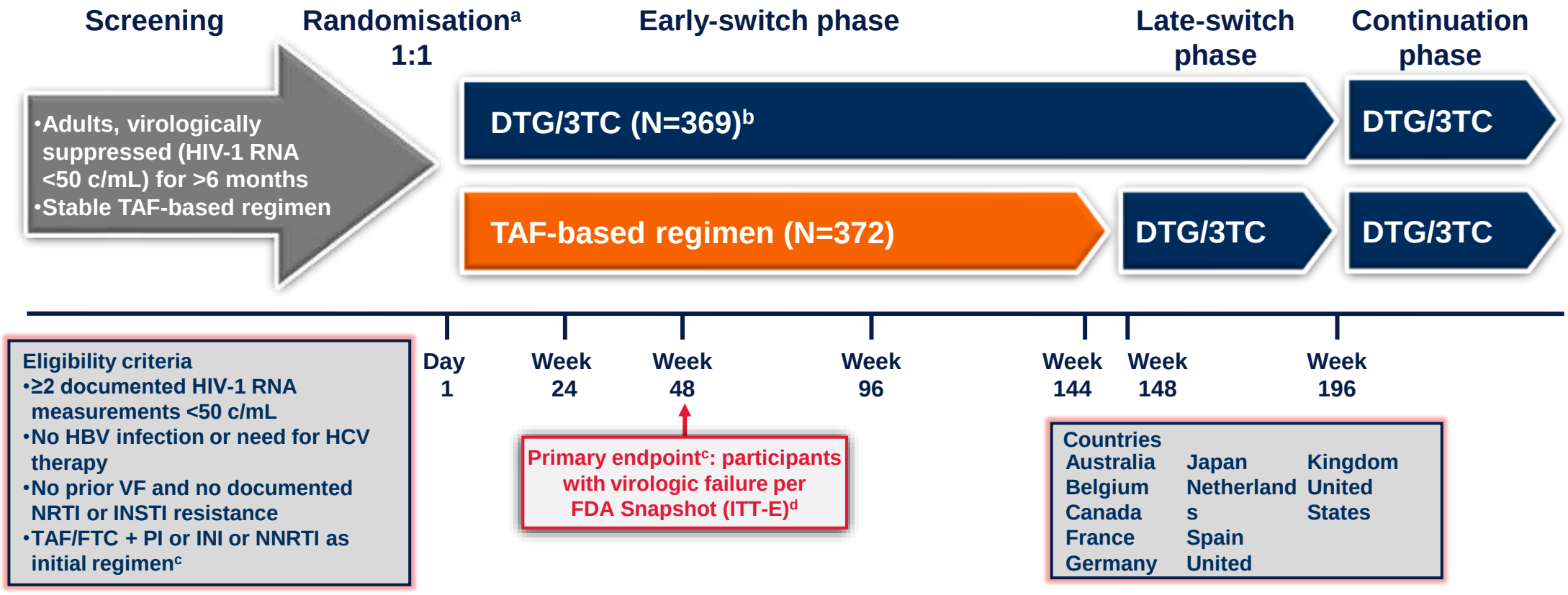


Proportion of Participants With TND by Visit (Snapshot Analysis, ITT-E Population)

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

TANGO: Phase III Study Design

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

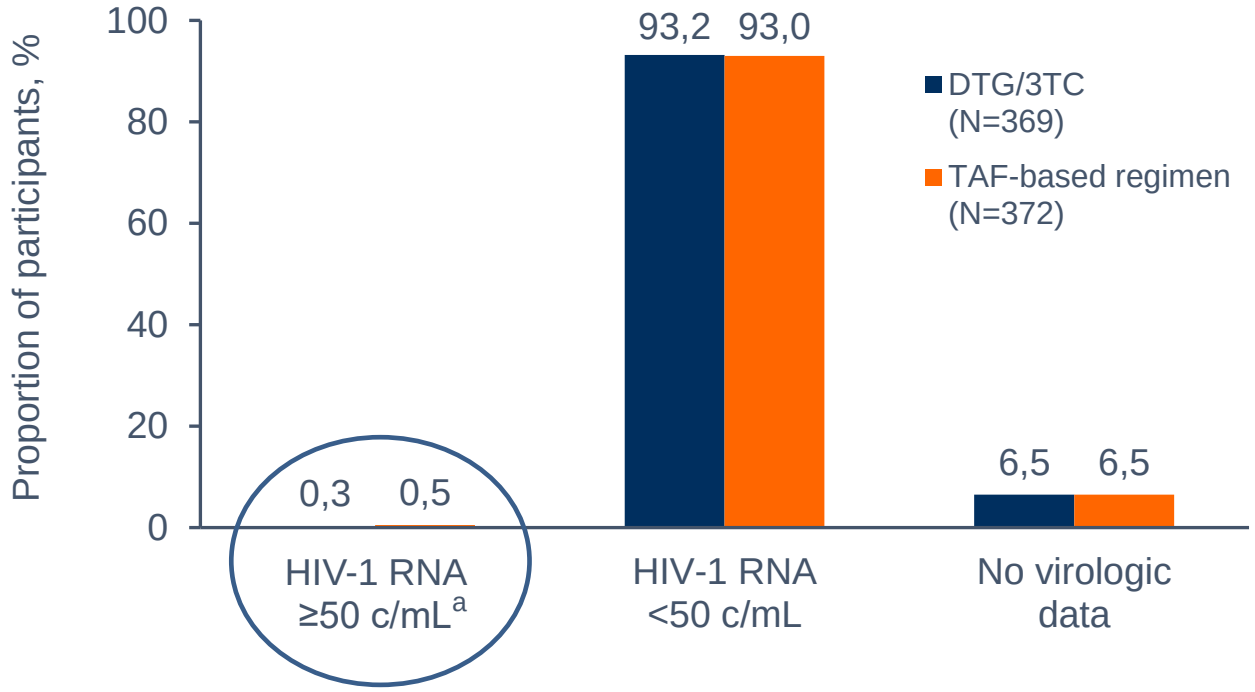


[a]Stratified by baseline third agent class (PI, INI, or NNRTI). [b]Two patients excluded who were randomized but not exposed to study drug. [c]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [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.

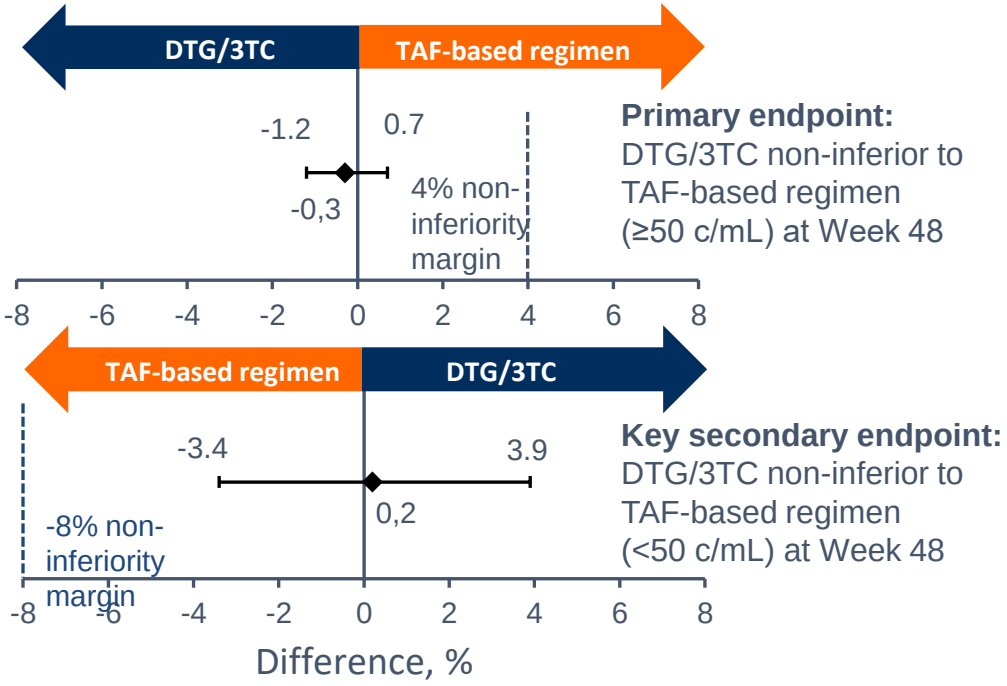
Adapted from van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

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

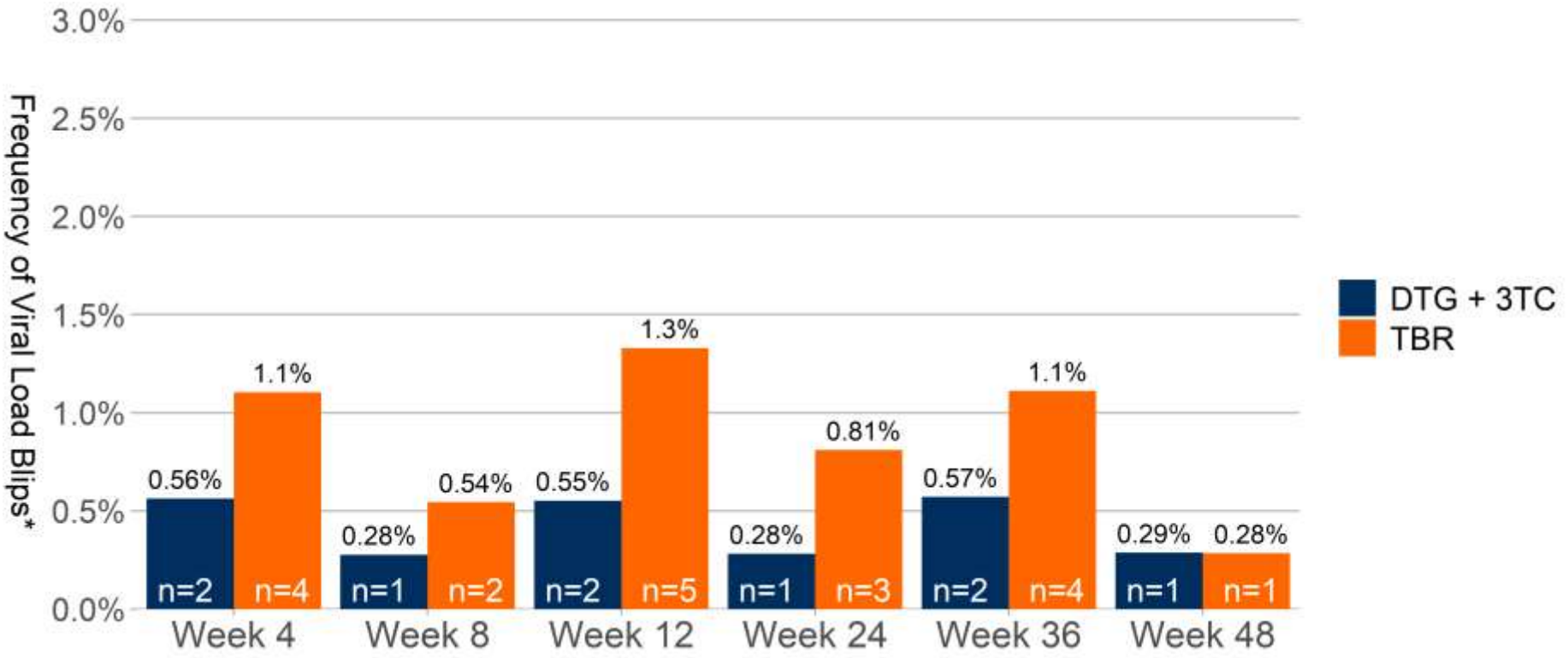
Key secondary endpoint:
DTG/3TC non-inferior to TAF-based regimen (<50 c/mL) at Week 48

- 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

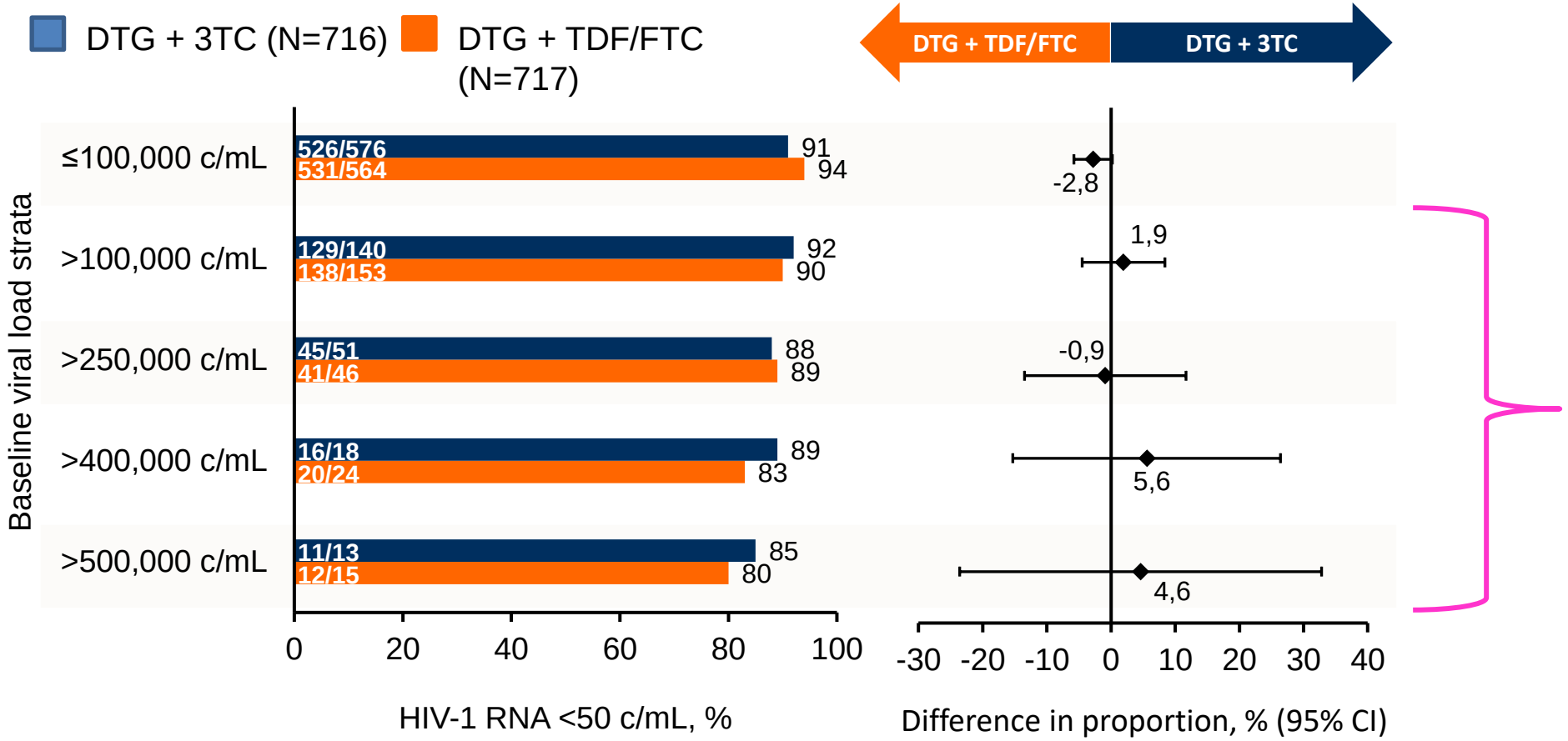


The occurrences of viral blips at each visit by treatment group over 48 weeks were similar

*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.

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



Participants 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.

Cahn et al. Lancet. 2018.

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

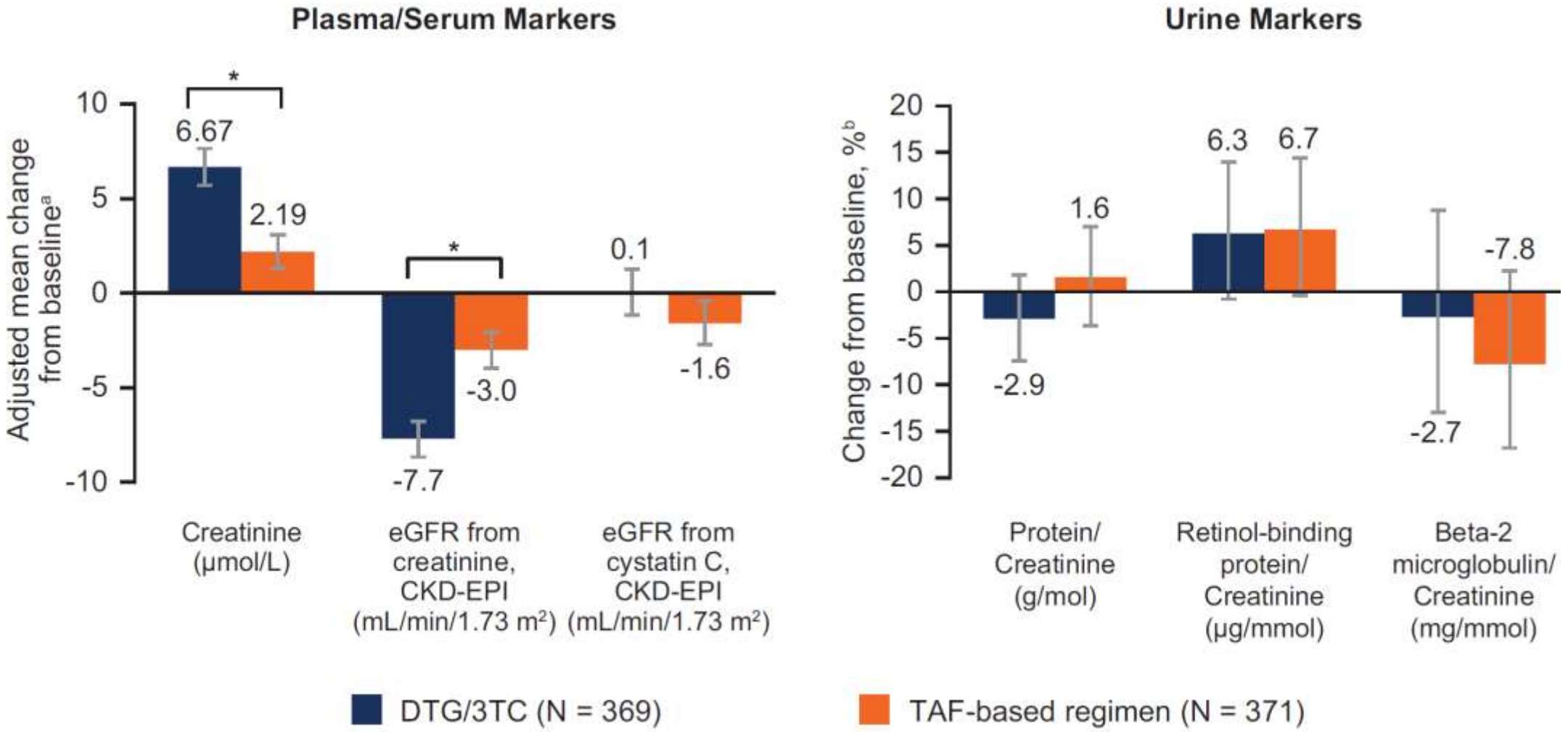
No Confirmed Virologic Withdrawals with DTG/3TC in TANGO through 48 weeks

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.

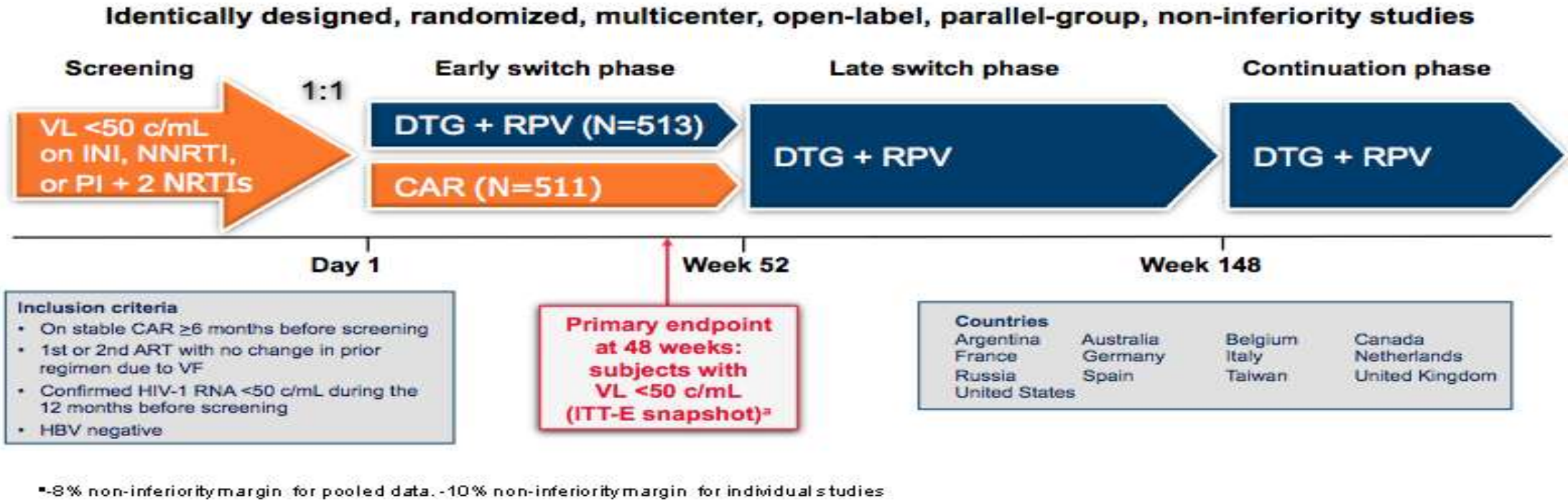
Adapted from van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

Renal abnormalities in TANGO through 48 weeks



van Wyk J et al. CID 2020;71:1920

dolutegravir + rilpivirine: SWORD 1, 2 studies



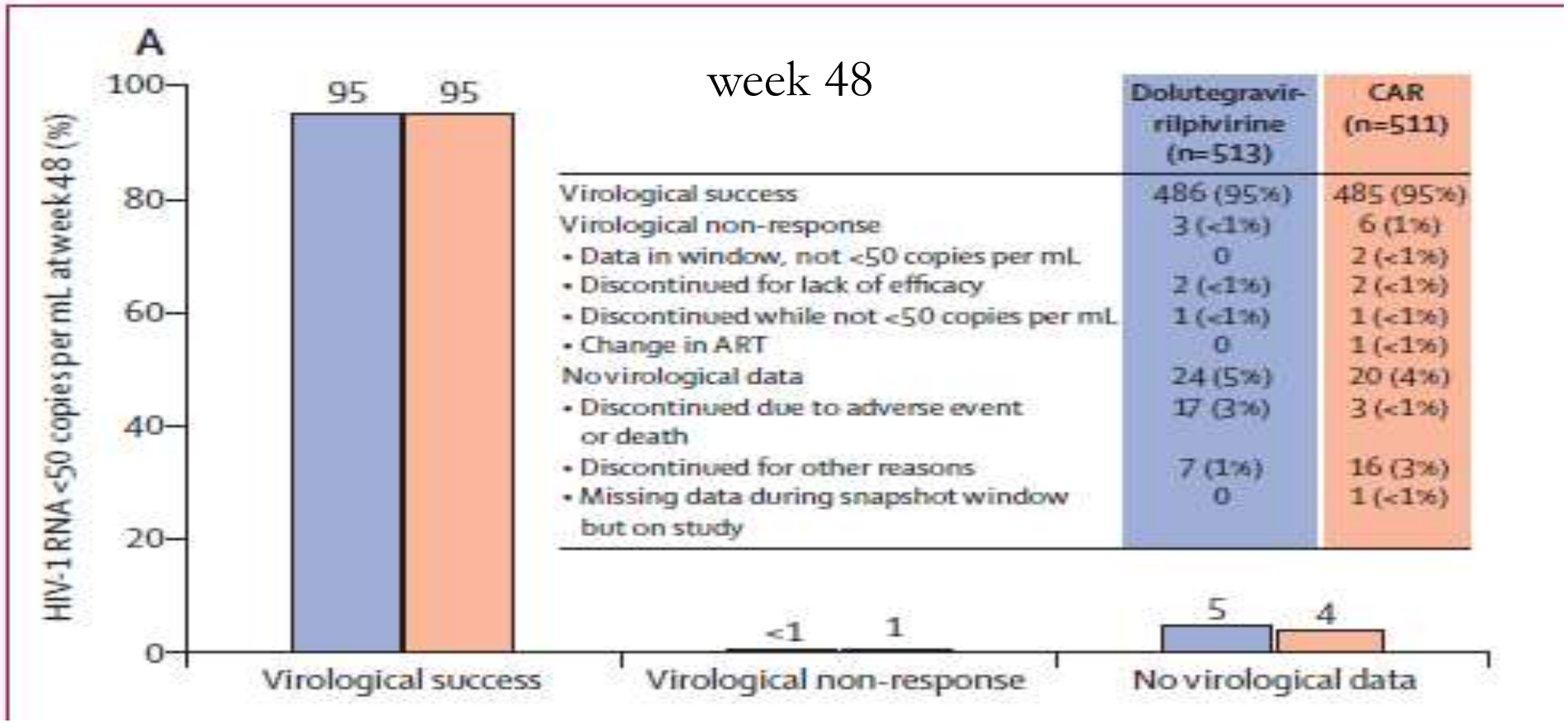
a-8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies

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

SWORD 1, 2 studies: HIV RNA response

HAART at baseline

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



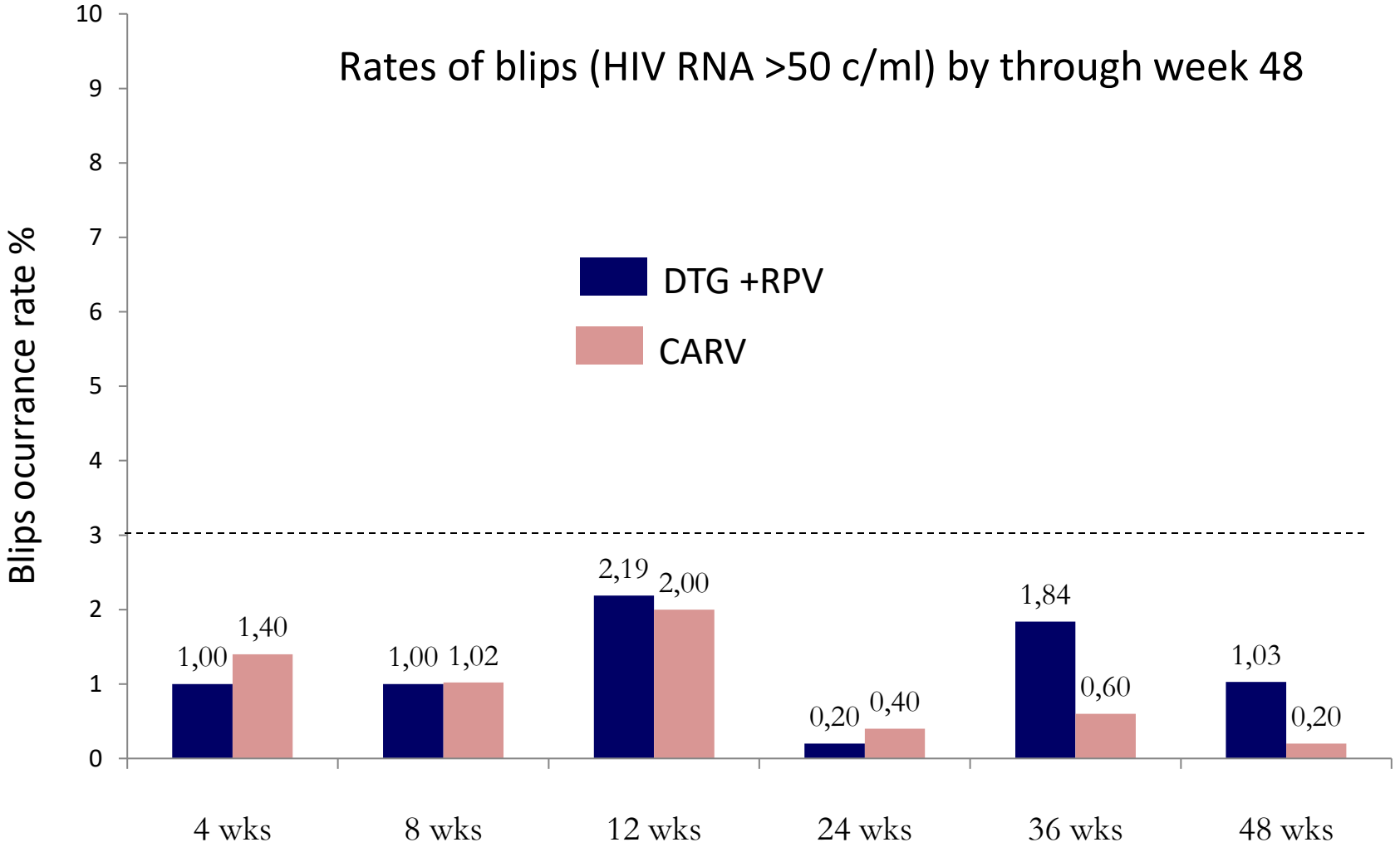
week 48

	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.

SWORD 1, 2 studies: HIV RNA blips



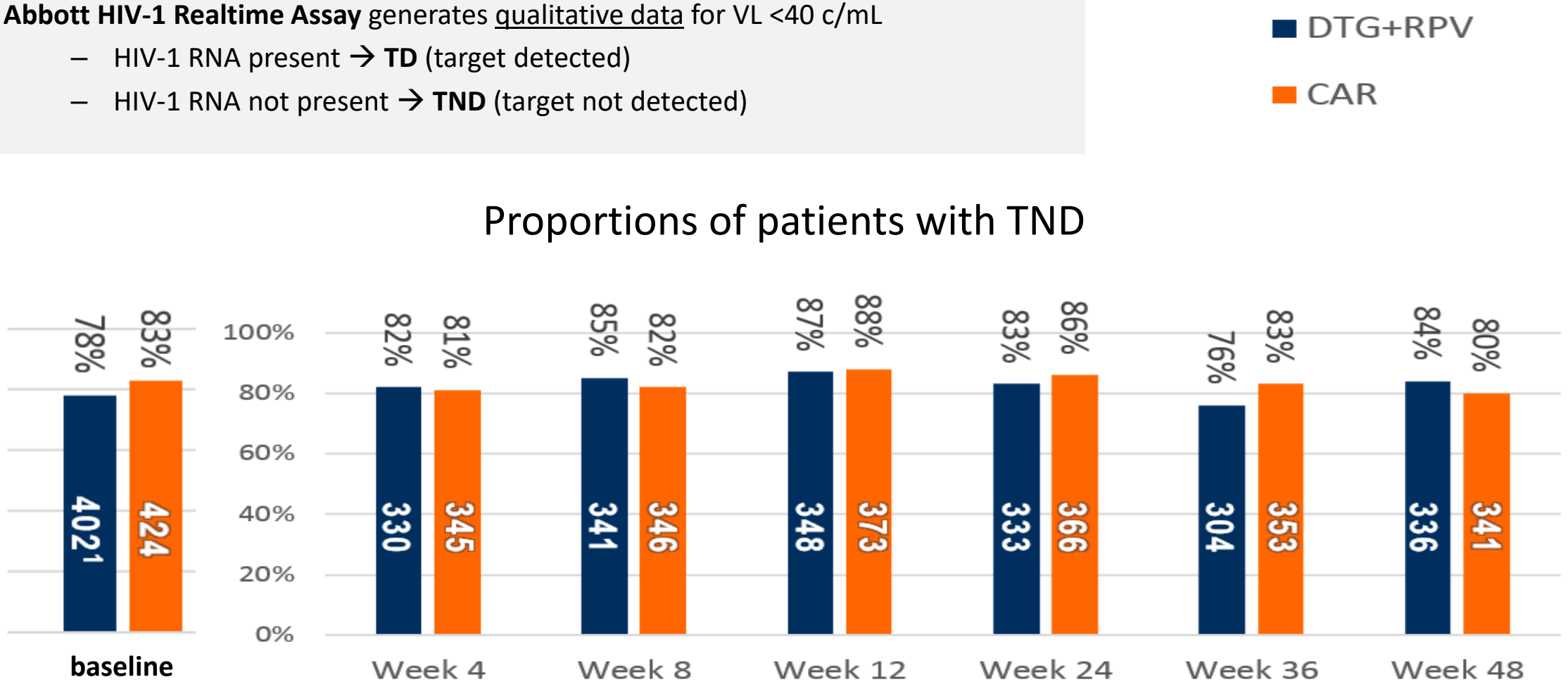
Viral blips were not associated to CVW

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

SWORD 1, 2 studies: TD and TND

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)



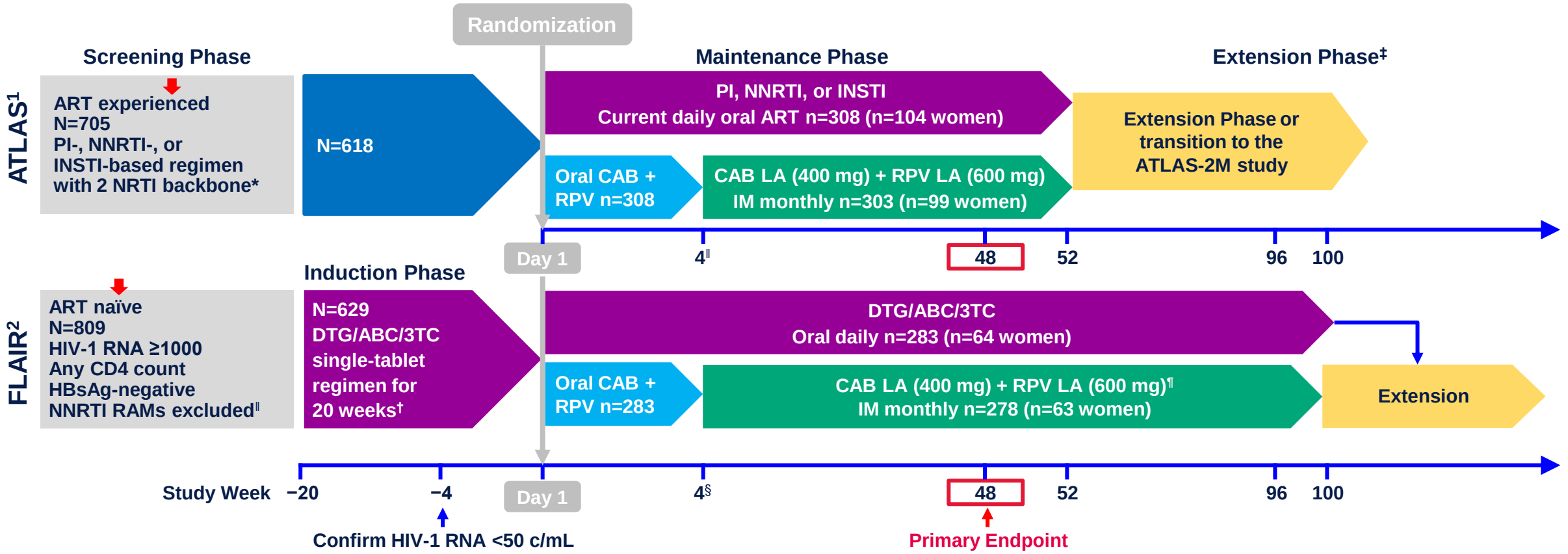
Underwood M et al. HIV Drug Therapy 2018, Glasgow UK; Poster 311.

Cabotegravir + Rilpivirine Long Acting

On 21 December 2020, the combination of long-acting injections of cabotegravir and rilpivirine had been approved for HIV treatment by EMA

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.

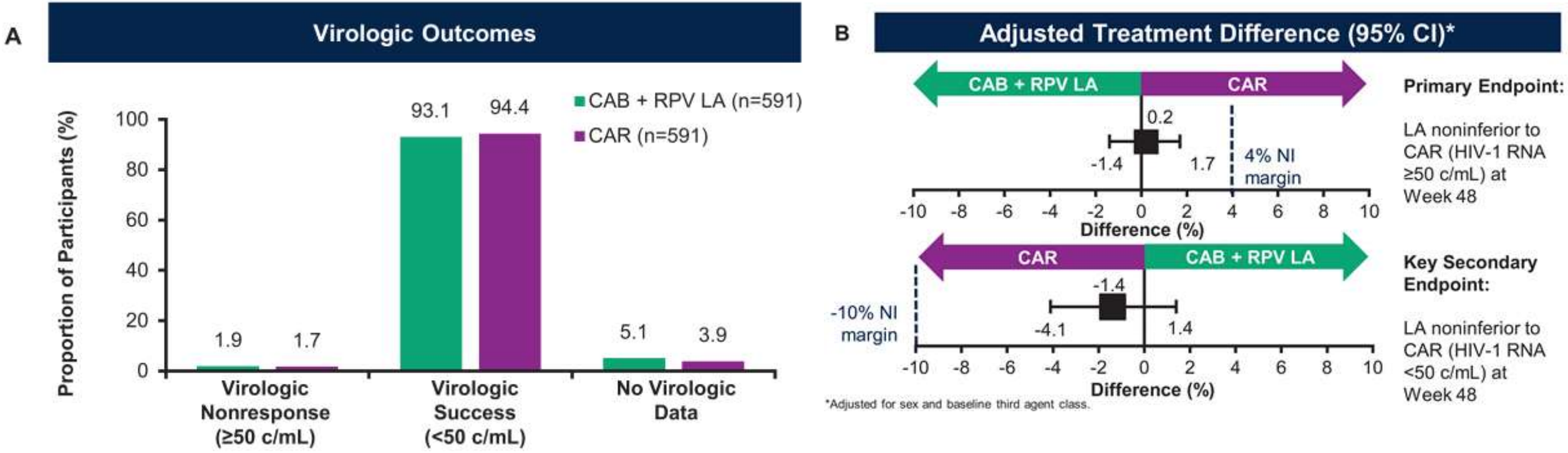
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; DTG, dolutegravir; IM, intramuscular; INSTI, integrase strand transfer inhibitor; HBsAg, hepatitis B surface antigen; HLA, human leukocyte antigen; LA, long-acting; NNRTI, non-nucleoside reverse 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 Study)

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

ATLAS and FLAIR Pooled data at week 48



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

ATLAS and FLAIR Confirmed Virological Failures

Pooled data at week 48

Resistance mutations at failure

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

DUALIS Study: dTG + DRV-r

Pts on bDRV-r
- switch < 50 c/ml
- HBsAg neg

n. 132
DRV-r + 2NRTIs

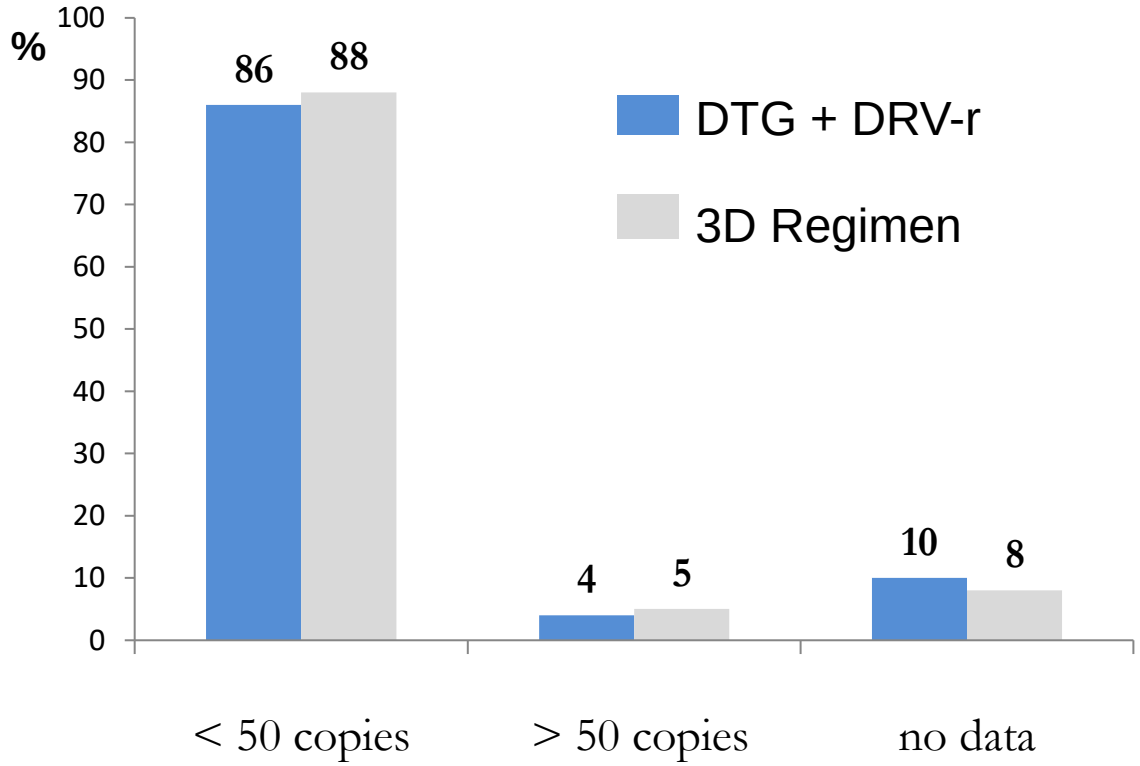
n. 131
DRV-r + DTG

Mean CD4 count at entry: 598 cells

Nadir CD4 count (< 200 cells): 47%

No resistance mutations at failure in this study

HIV RNA < 50 copies/ml, at week 48



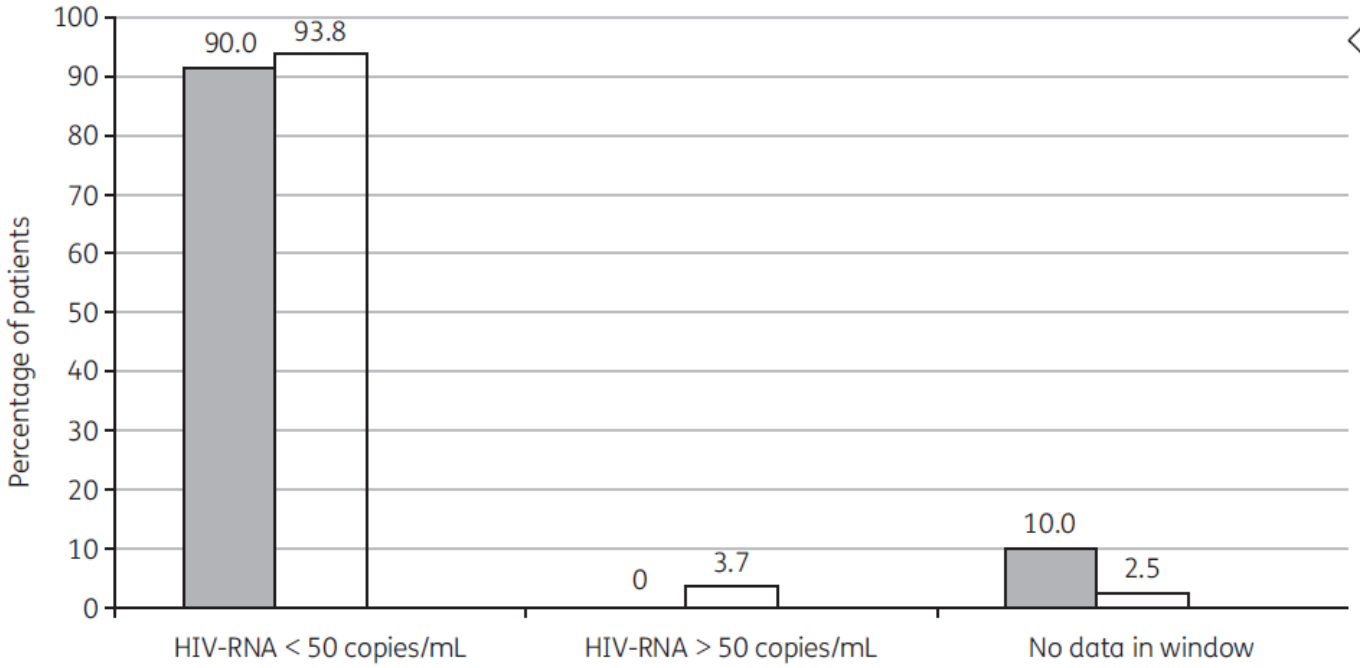
Spinner CD et al. Open Forum Infect Dis 2020

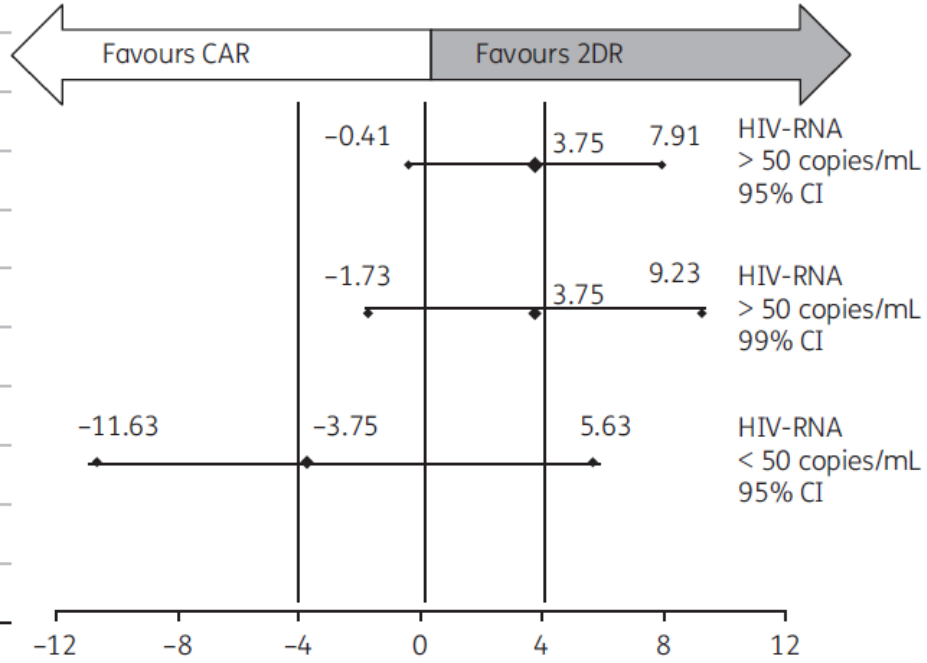
Probe2 Study: RPV + bDRV, 48 weeks data

Pts on cARV
- switch < 50 c/ml
- HBsAg neg

n. 80 — cARV

n. 80 — DRV-r + RPV

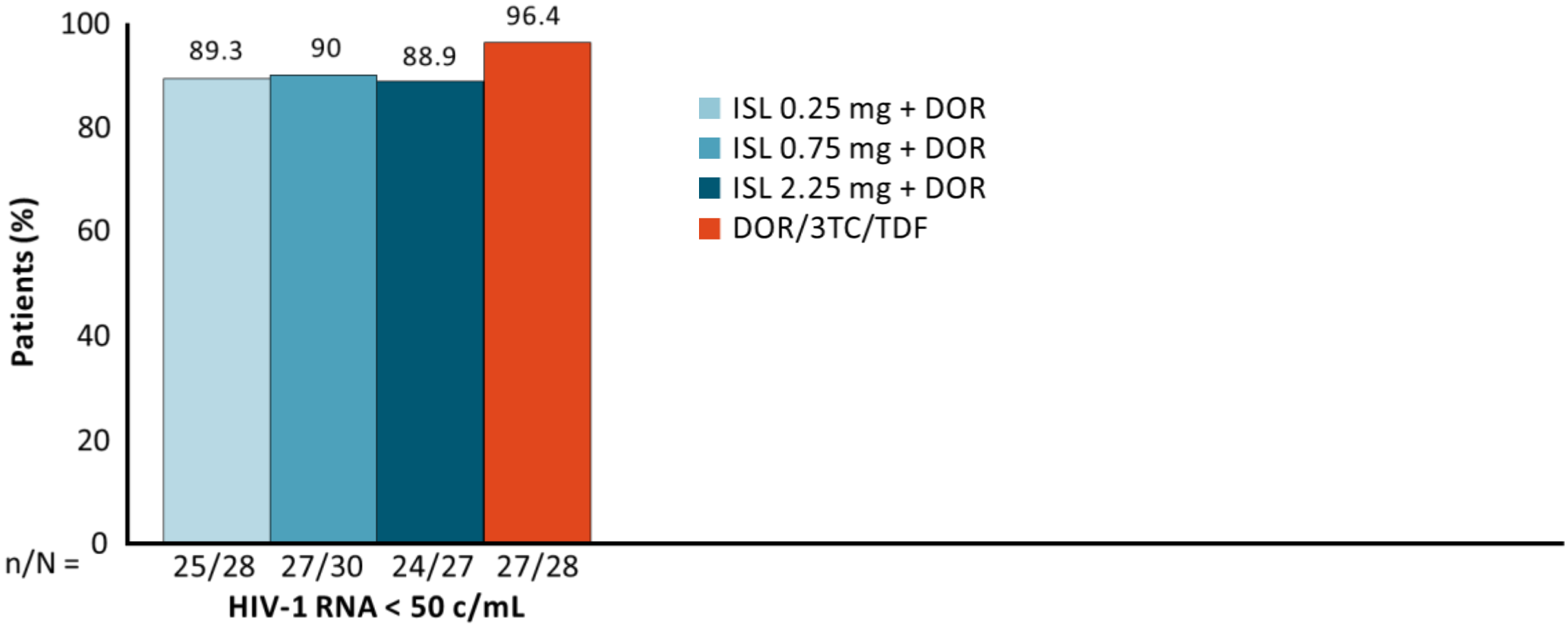




Maggiolo F et al. JAC 2020

DRIVE2Simplify Part 2: Virologic Outcomes

24 weeks after entering Part 2 (phase 2 trial)



Molina. IAS 2019. Abstr WEAB0402LB.

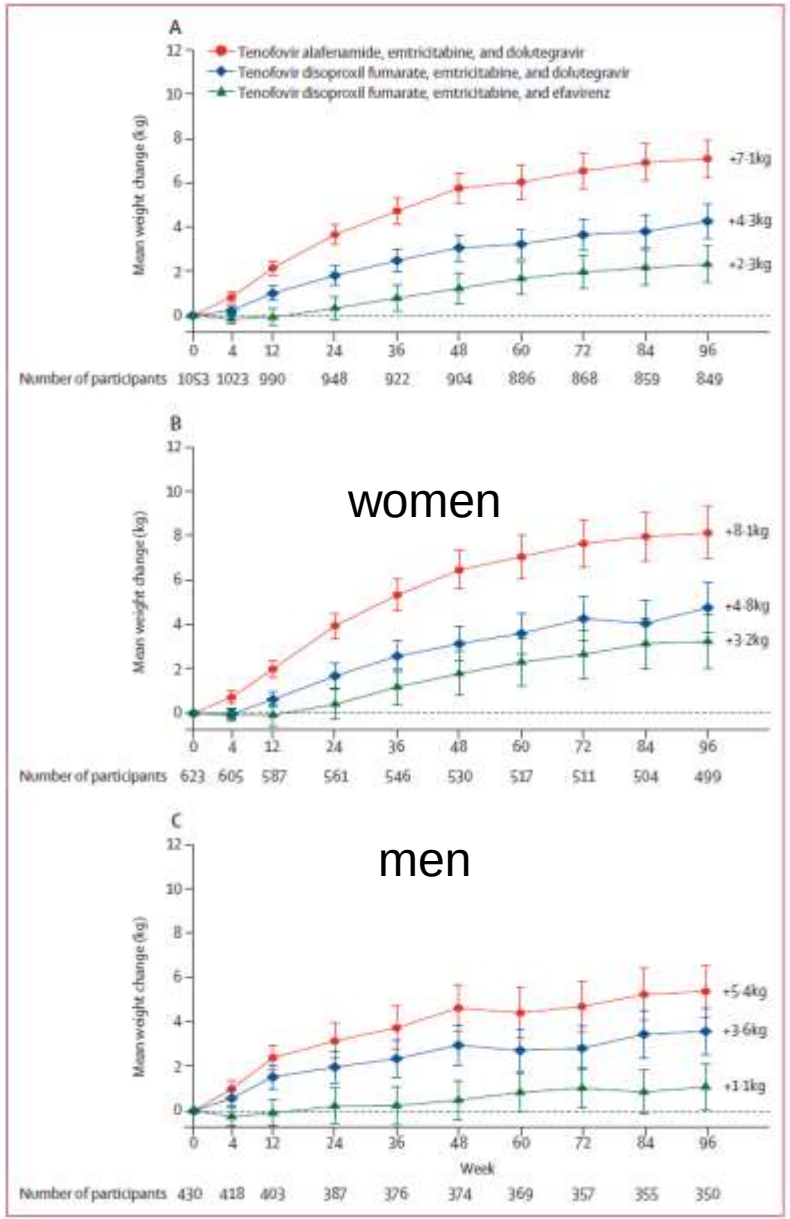
Schürmann D, Rudd DJ. Lancet HIV. 2020 Mar;7(3):e164-e172

Does the control of viral replication tell all the story?

ADVANCE trial (96-week data)

TAF/FTC + DTG
TDF/FTC + DTG
TDF/FTC + EFV

In 1053 naive pts in South Africa
(59% women)



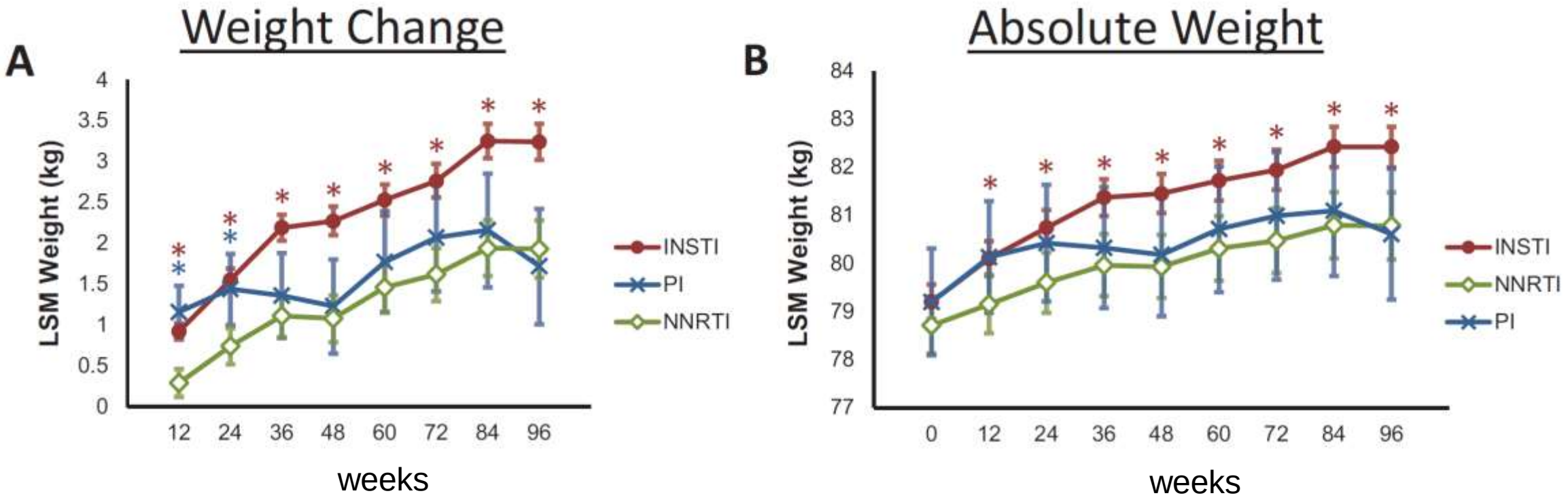
Weight increase
by study regimens
in naive patients

Higher increase when
combining TAF+DTG

Venter WDF et al. Lancet HIV 2020;7:e666-76

Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials

A total 8 randomized CCTs (96-week data) in naïve people initiating ART between 2003 and 2015, comprising > 5,000 participants and 10,000 person-years of follow-up.
Question: Return-to-health effect? Or excessive increases in weight?



8 RCTs including EFV, RPV, **ATV/r**, EGV/c and BIC

Sax P et. CID 2020;71:1379

PROS and CONS

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

HIV Treatment Guidelines 2020

	naive	switch				
	DTG+3TC*	DTG+3TC	DTG+RPV	bPI+3TC	bDRV+RPV	CAB/RPV LA
EACS						
IAS USA					-	
DHHS					-	

* Except for individuals :

- ✓ with pre-treatment HIV RNA >500,000 copies/mL;
- ✓ persons with active hepatitis B virus (HBV) coinfection;
- ✓ who will initiate ART before results of HIV genotype or HBV testing are available.

EACS: https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html
DHHS: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines
IAS USA: https://www.iasusa.org/resources/guidelines

Thanks for the attention