2DR : LESSONS LEARNED, CHALLENGES AHEAD

Professor Chloe Orkin
Queen Mary University of London
Barts Health NHS Trust

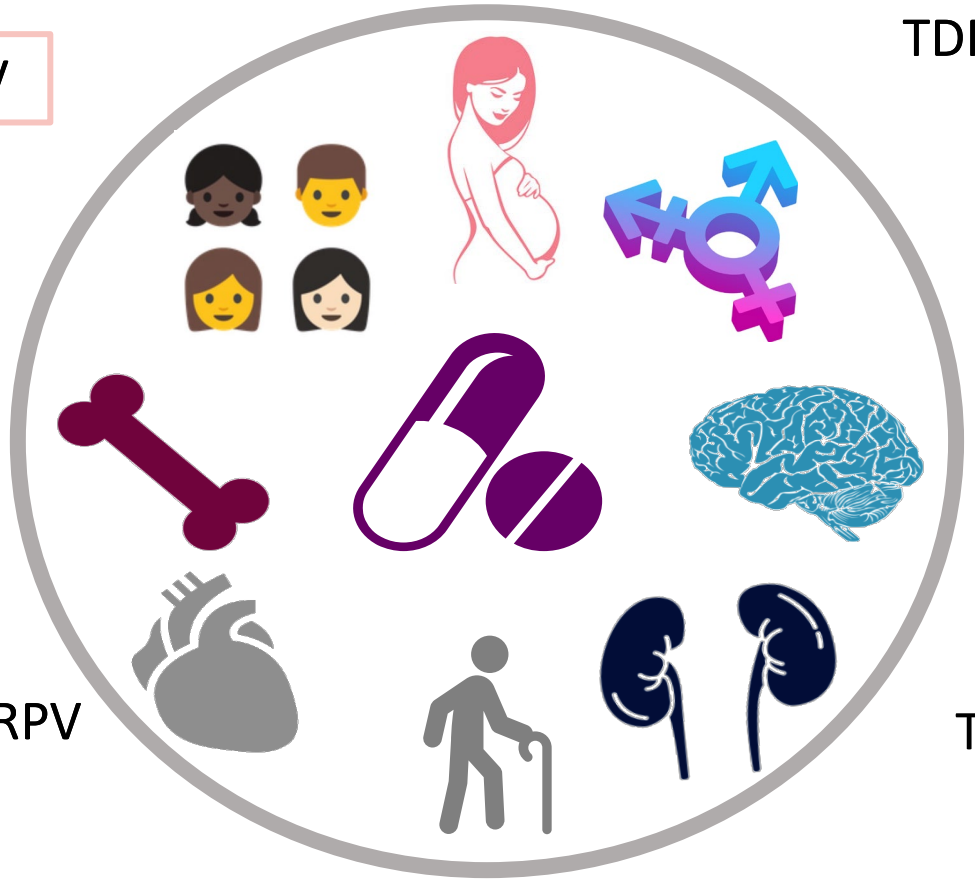
CONFLICTS OF INTEREST – PROF. CHLOE ORKIN

- I have received:
  - Honoraria for lectures and advisory boards
  - Travel grants
  - Research grants to my institution
- From Gilead Sciences, Janssen, MSD and ViiV Healthcare

DO WE NEED 3 DRUGS FOR THE WHOLE OF LIFE?

Age 20 → Age 100

WE NOW HAVE 2DR FIXED DOSE COMBINATIONS



DTG/3TC

TDF/FTC/RFV

DTG/RPV

TDF/FTC/RPV

TAF/FTC/BIC

TDF/FTC/EVG/COBI

TAF/FTC/DRV/COBI

ABC/3TC/DTG

TAF/FTC/RPV

TAF/FTC/EVG/COBI

TDF/3TC/DOR

NO 2DR FOR PEOPLE WITH CHRONIC HEPATITIS B (SAG+)

HIV

CHRONIC HEPATITIS B

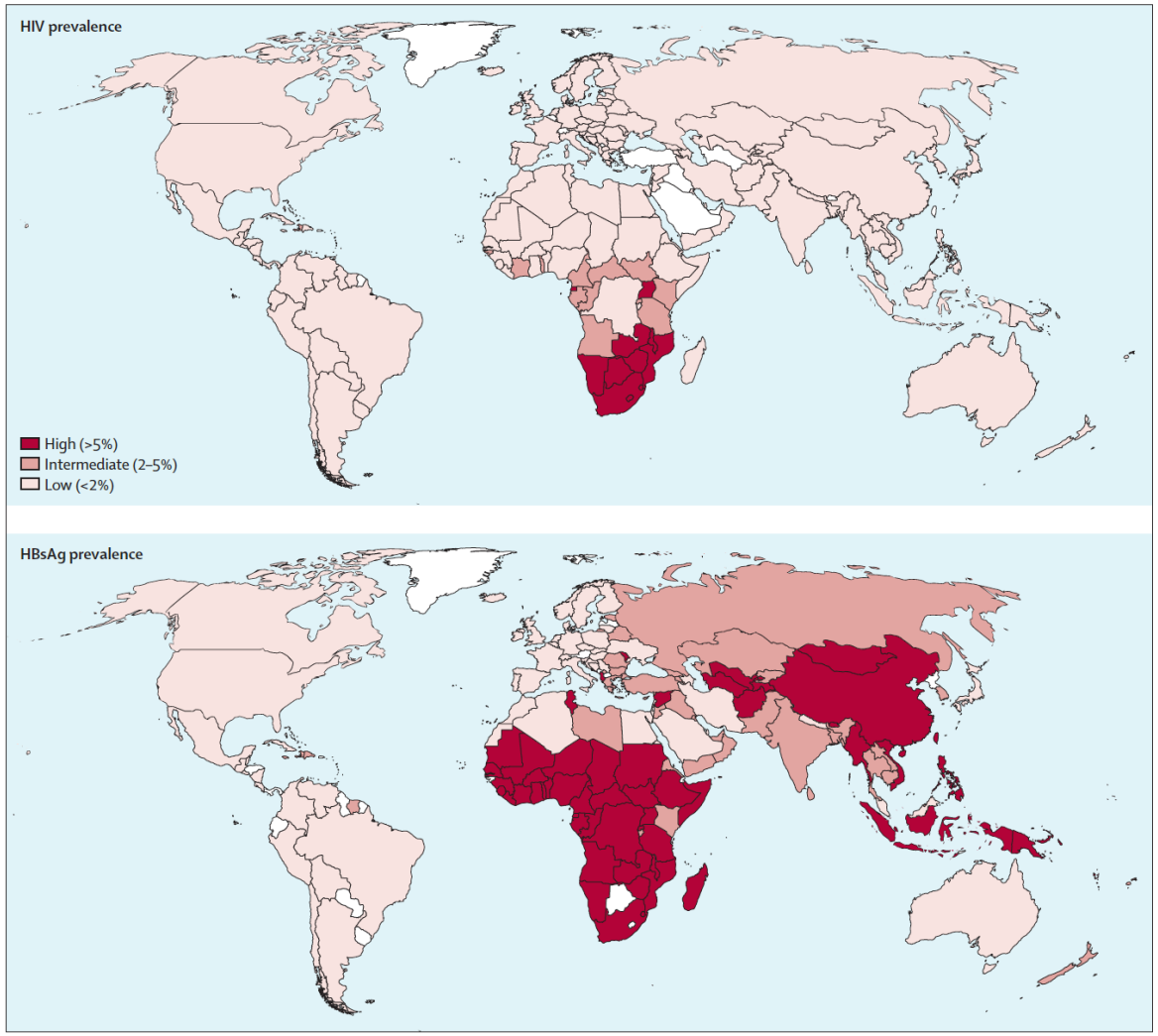


Figure: HIV and chronic hepatitis B virus infection prevalence
Data extracted from multiple sources.[62-70]

Lancet HIV. https://doi.org/10.1016/S2352-3018(19)30342-X

DTG/3TC IN GUIDELINES- FIRST LINE ART

DHHS

- Recommended Initial Regimens for Most People with HIV

EACS

- Recommended regimen

NOT YET IN IAS-USA OR WHO GUIDELINES

DHHS Guidelines. December 2019. EACS Guidelines 10.0 November 2019

DTG/3TC RESTRICTIONS-FIRST LINE ART

	HBsAg+	CD4 < 200	HIV RNA > 500,000	No baseline genotype
DHHS				
EACS				

DHHS Guidelines. December 2019. EACS Guidelines 10.0 November 2019.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211994s000lbl.pdf
https://www.ema.europa.eu/en/documents/product-information/dovato-epar-product-information_en.pdf

EVIDENCE FOR DTG + 3TC IN TREATMENT-NAÏVE PATIENTS…

Efficacy, safety and durability?

What about more sensitive viral markers i.e. **target not detected?**

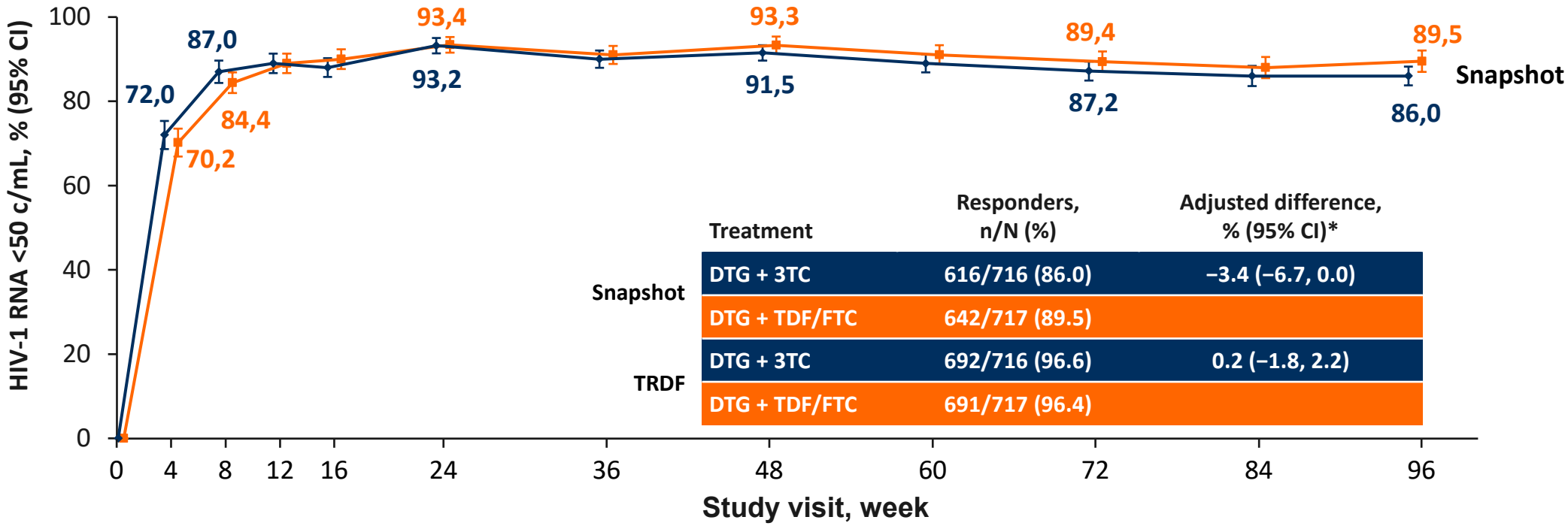
Is the frequency of **blips** the same with DTG + 3TC versus DTG-based 3DR?

Are the **rate of and time to virologic suppression** the same?

Is the **barrier to resistance** of DTG + 3TC high enough?

Safety and **tolerability?**

LONG-TERM DURABILITY: DTG + 3TC IS NON-INFERIOR TO DTG + TDF/FTC IN SNAPSHOT HIV-1 RNA <50 C/ML AT WEEK 96 (GEMINI-1 AND -2)



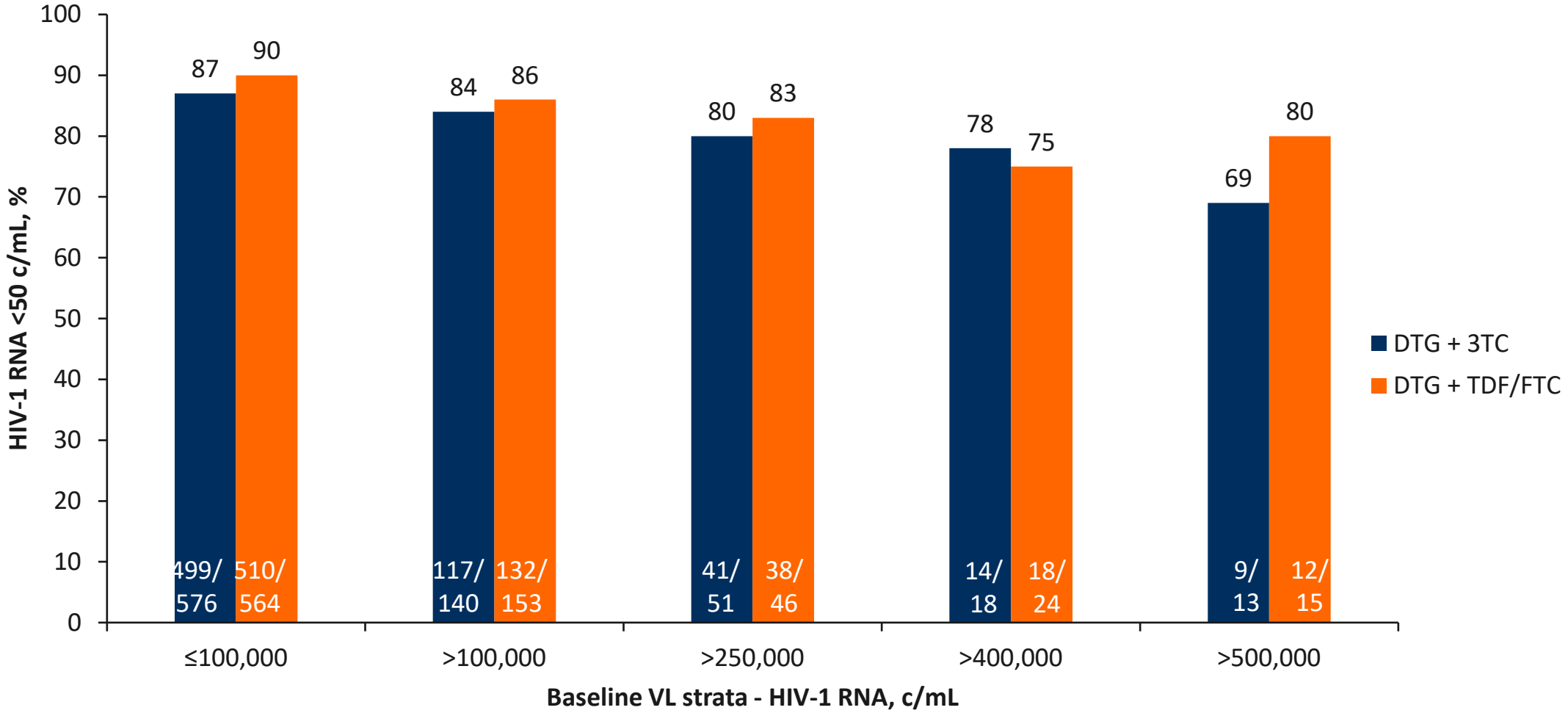
	Treatment	Responders, n/N (%)	Adjusted difference, % (95% CI)*
Snapshot	DTG + 3TC	616/716 (86.0)	−3.4 (−6.7, 0.0)
	DTG + TDF/FTC	642/717 (89.5)	
TRDF	DTG + 3TC	692/716 (96.6)	0.2 (−1.8, 2.2)
	DTG + TDF/FTC	691/717 (96.4)	

- Non-inferiority criteria were met for GEMINI-1, GEMINI-2 and the pooled analysis†
- TRDF population accounts for confirmed virologic withdrawal, withdrawal due to lack of efficacy, withdrawal due to treatment-related AEs and patients who met protocol-defined stopping criteria

*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+ T-cell count (≤200 vs >200 cells/mm3) and study (GEMINI-1 vs GEMINI-2). The upper limit of the 95% CI for the pooled analysis was 0.0007%. TRDF (unadjusted difference) was a pre-planned analysis at Week 96; †In GEMINI-1, HIV-1 RNA <50 c/mL (95% CI) was achieved in 300/356 patients (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])
AE, adverse event; CI, confidence interval; TRDF, treatment related discontinuation=failure

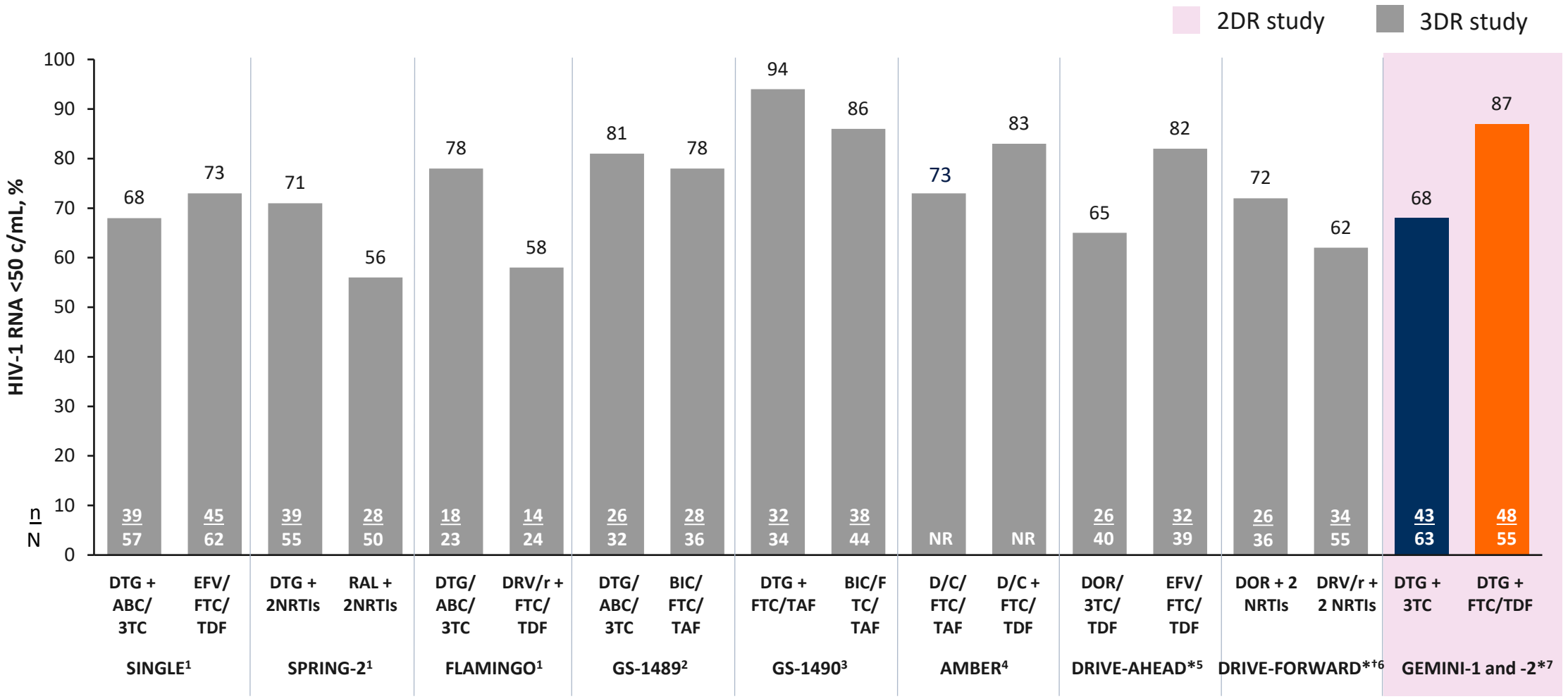
Cahn P, et al. IAS 2019. Oral WEAB0404LB
Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8

GEMINI :HIV-1 RNA <50 C/ML AT WEEK 96 BY BASELINE VL SUBGROUPS



Adapted from van Wyk J, et al. ID Week 2019. Slides 2842
Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8

WEEK 96 SNAPSHOT ANALYSIS - BASELINE CD4+ COUNT <200 CELLS/MM^3

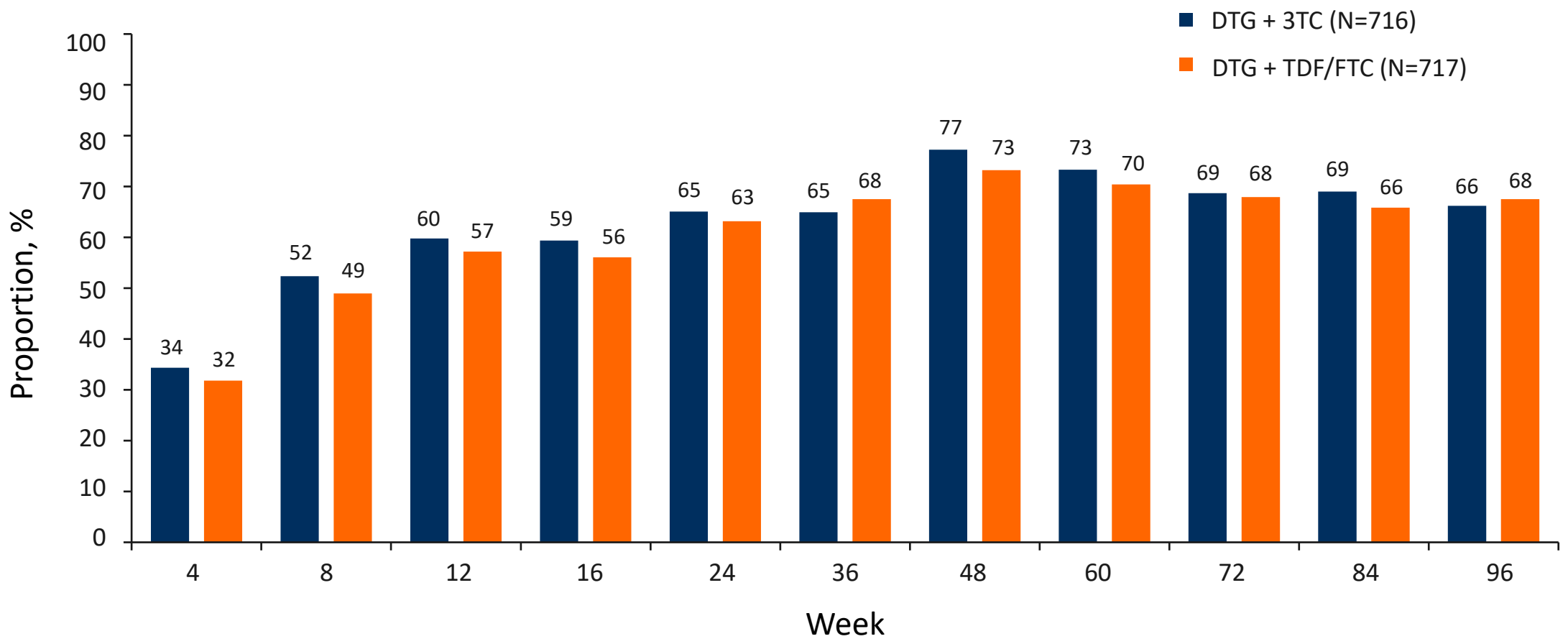


*Studies present ≤200 cells/mm^3 (rather than <200)
†Observed failure approach
NR, not reported

Adapted from: 1. Granier C, et al. CROI 2015. Poster 550; 2. Wohl D, et al. Lancet HIV 2019;6:e355–63 Supplementary Appendix
3. Stellbrink H, et al. Lancet HIV 2019;6:e364–72 Supplementary Appendix; 4. Orkin C, et al. HIV Glasgow 2018. Oral O212
5. Orkin C, et al. ID Week 2018. LB1; 6. Molina JM, et al. IAS 2018; 7. Cahn P, et al. IAS 2019. Oral WEAB0404LB

GEMINI : SENSITIVE VIRAL MARKERS WEEK 96

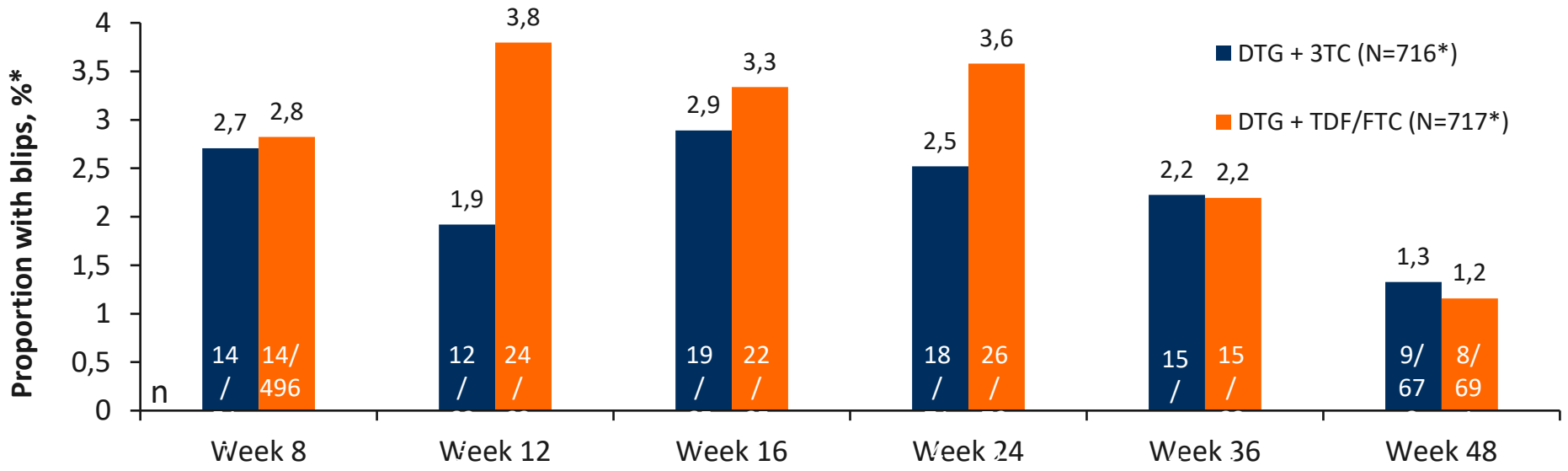
Proportion of participants with TND by visit (Snapshot analysis, ITT-E population)



Number at base of bars is number of participants reaching TND at week visit
ITT-E, intention-to-treat exposed; TD, target detected; TND, target not detected

GEMINI BLIP FREQUENCY WEEK 48

- Similar frequencies of blips were observed across arms by week of visit
- No patients with CVW in either arm had blips prior to CVW
- Cumulative occurrences: DTG + 3TC n=87; DTG + TDF/FTC n=109

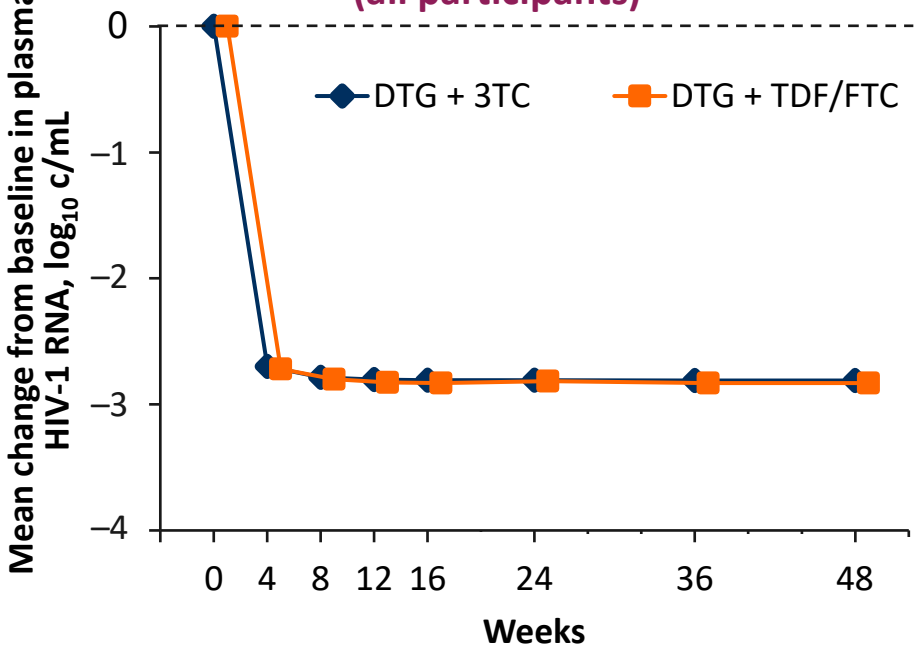


A 'blip' is defined here as VL of 50-<200 c/mL with adjacent values <50 c/mL
*Percentages were calculated from number of blips using previously suppressed (<50 c/mL) patient numbers, respectively, for DTG + 3TC and DTG + TDF/FTC at Week 8 (n=517) and (n=496); Week 12 (n=625) and (n=632); Week 16 (n=657) and (n=659); Week 24 (n=714) and (n=726); Week 36 (n=674) and (n=683); and Week 48 (n=678) and (n=691). Bold numbers on chart are number of blips at given week visits. Individual patients can have had more than one blip
CVW, confirmed virologic withdrawal

Adapted from Underwood M, et al. IAS 2019. MOPEB231

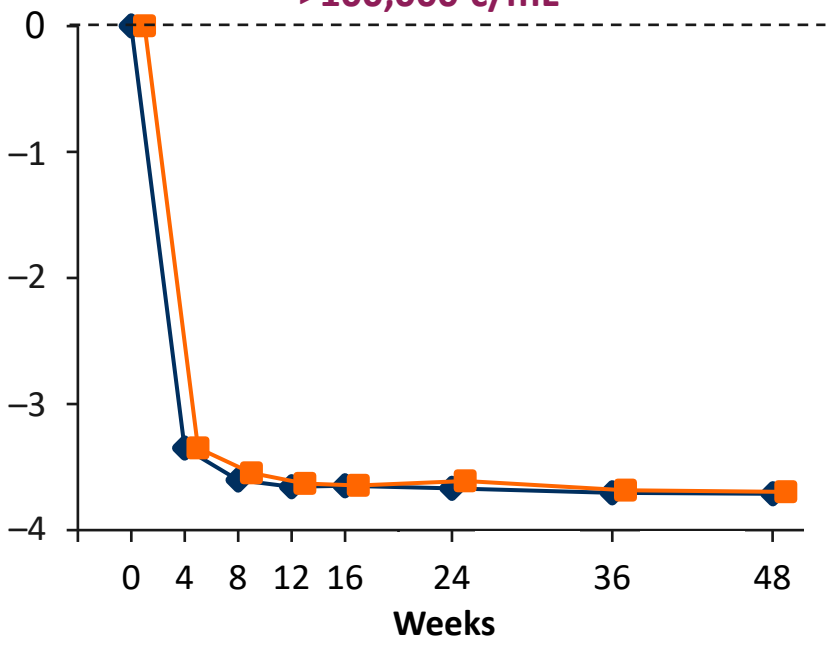
RATE OF, AND TIME TO, VIROLOGIC SUPPRESSION : GEMINI

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]



	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;143–155 Supplementary Appendix
2. Eron J, et al. HIV DART and Emerging Viruses 2018. Oral 7

RESISTANCE BARRIER GEMINI STUDIES

Variable, n (%)		GEMINI-1 DTG + 3TC (N=356)	GEMINI-1 DTG + TDF/FTC (N=358)	GEMINI-2 DTG + 3TC (N=360)	GEMINI-2 DTG + TDF/FTC (N=359)	Pooled DTG + 3TC (N=716)	Pooled 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)*	6 (1.7)	3 (0.8)	11 (1.5)	7 (1.0)*
	Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

*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 P, et al. IAS 2019. Oral WEAB0404LB

GEMINI WEEK 96 - AE PROFILES WERE SIMILAR

LOWER RISK OF DRUG-RELATED AES IN THE DTG + 3TC GROUP AT WEEK 96

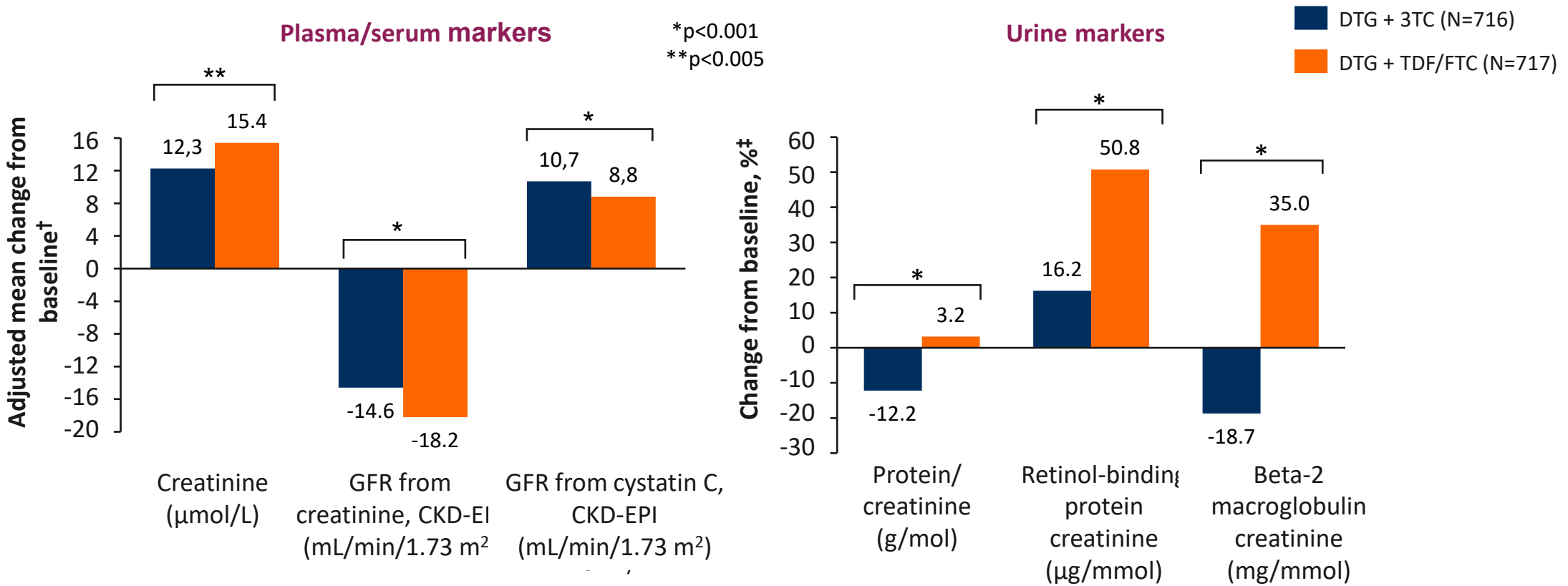
- Increased weight was reported as an AE in 13 (1.8%) patients treated with DTG + 3TC and in 10 (1.4%) treated with DTG + TDF/FTC
  - Overall mean change from baseline was 3.1 kg in the DTG + 3TC group and 2.1 kg in the DTG + TDF/FTC group

n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Any AE	591 (83)	609 (85)
AEs occurring in ≥10% of patients in either group		
Nasopharyngitis	71 (10)	114 (16)
Diarrhoea	89 (12)	93 (13)
Headache	79 (11)	87 (12)
Drug-related AEs*	140 (20)	179 (25)
Any Grade 2–5 drug-related AEs	50 (7)	57 (8)
Grade 2–5 drug-related AEs occurring in ≥1% of patients		
Headache	8 (1)	8 (1)
AEs leading to withdrawal from the study	24 (3)	23 (3)
AEs of interest leading to withdrawal from the study		
Neuropsychiatric	10 (1)	5 (1)
Renal-related	2 (<1)	7 (1)
Osteoporosis	0	2 (<1)
Any serious AE†	64 (9)	67 (9)

*Relative risk (95% CI) for the DTG + 3TC versus DTG + TDF/FTC group was 0.78 (0.64, 0.95)
†3 deaths (acute myocardial infarction, n=1; Burkitt's lymphoma, n=1; coronary artery disease, n=1), 1 in GEMINI-1 and 2 in GEMINI-2; all were in the DTG + 3TC group and were considered unrelated to the study drug regimen

Adapted from Cahn P, et al. IAS 2019. Oral WEAB0404LB
Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8

CHANGE IN RENAL BIOMARKERS AT WEEK 96 FAVOURS DTG + 3TC



- Renal AEs leading to discontinuation were comparable across both arms (DTG + 3TC: n=2, <1%; DTG + TDF/FTC: n=7, 1%)

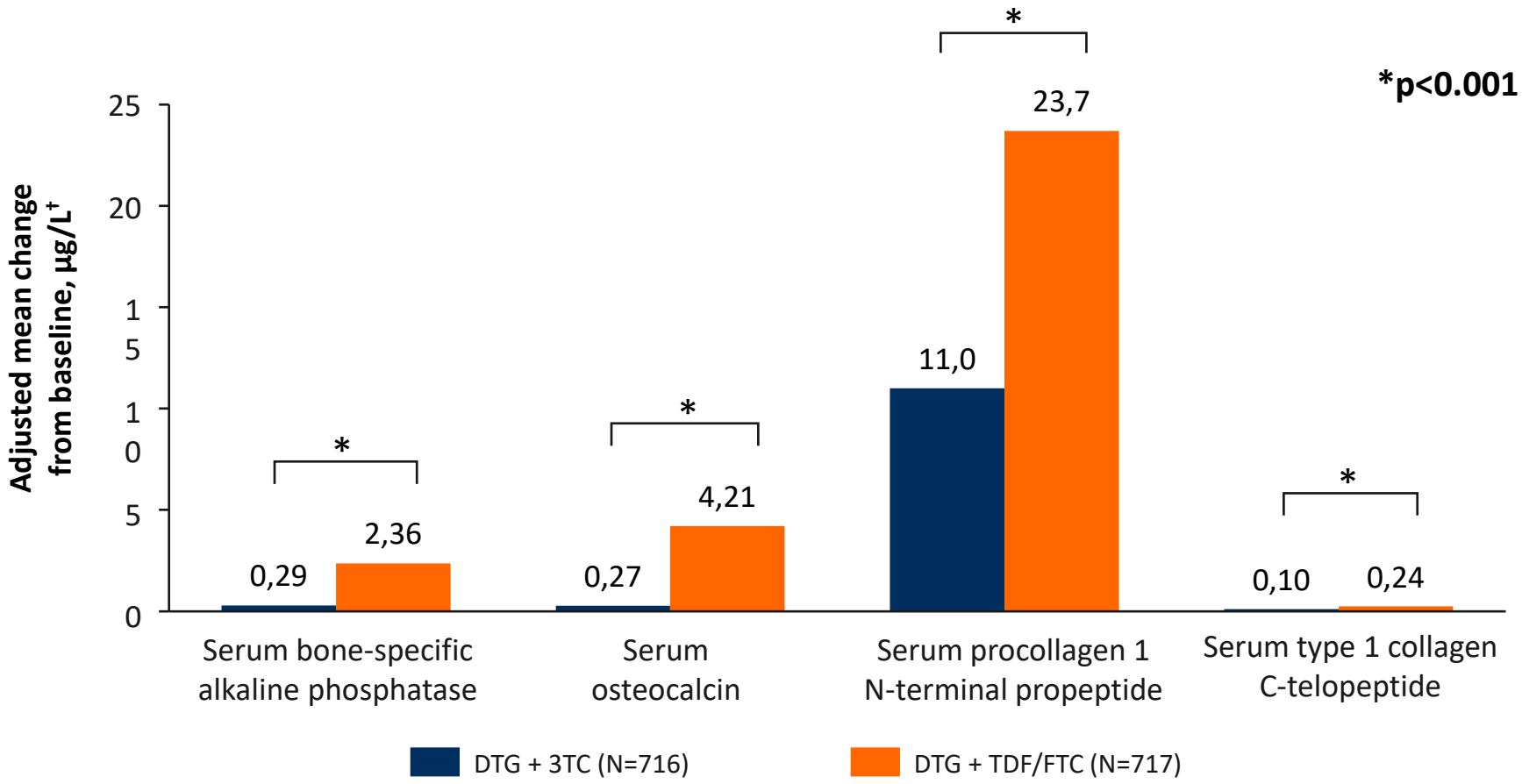
†Estimated mean change from baseline in each group was calculated from a repeated measures model adjusting for study, treatment, visit, baseline plasma HIV-1 RNA, baseline CD4+ T-cell count, age, sex, race, presence of diabetes mellitus, presence of hypertension, baseline biomarker value, treatment and visit interaction, and baseline biomarker value and visit interaction. No assumptions were made about the correlations between participant readings of biomarkers (the correlation matrix for within-participant errors was unstructured)

‡Estimated from geometric means ratio for baseline and Week 96. Based on the same model as plasma/serum markers except adjusting for $\log_e$-transformed baseline biomarker (continuous)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate

Adapted from Cahn P, et al. IAS 2019. Oral WEAB0404LB
Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8

GEMINI CHANGE IN BONE BIOMARKERS AT WEEK 96 FAVOURS DTG + 3TC



†Estimated mean change from baseline in each group was calculated from a repeated measures model adjusting for study, treatment, visit, baseline plasma HIV-1 RNA, baseline CD4+ T-cell count, age, sex, race, BMI, smoking status, current vitamin D use, baseline biomarker value, treatment and visit interaction, and baseline biomarker value and visit interaction. No assumptions were made about the correlations between participant readings of biomarkers (the correlation matrix for within-participant errors was unstructured)

Adapted from Cahn P, et al. IAS 2019. Oral WEAB0404LB
Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8

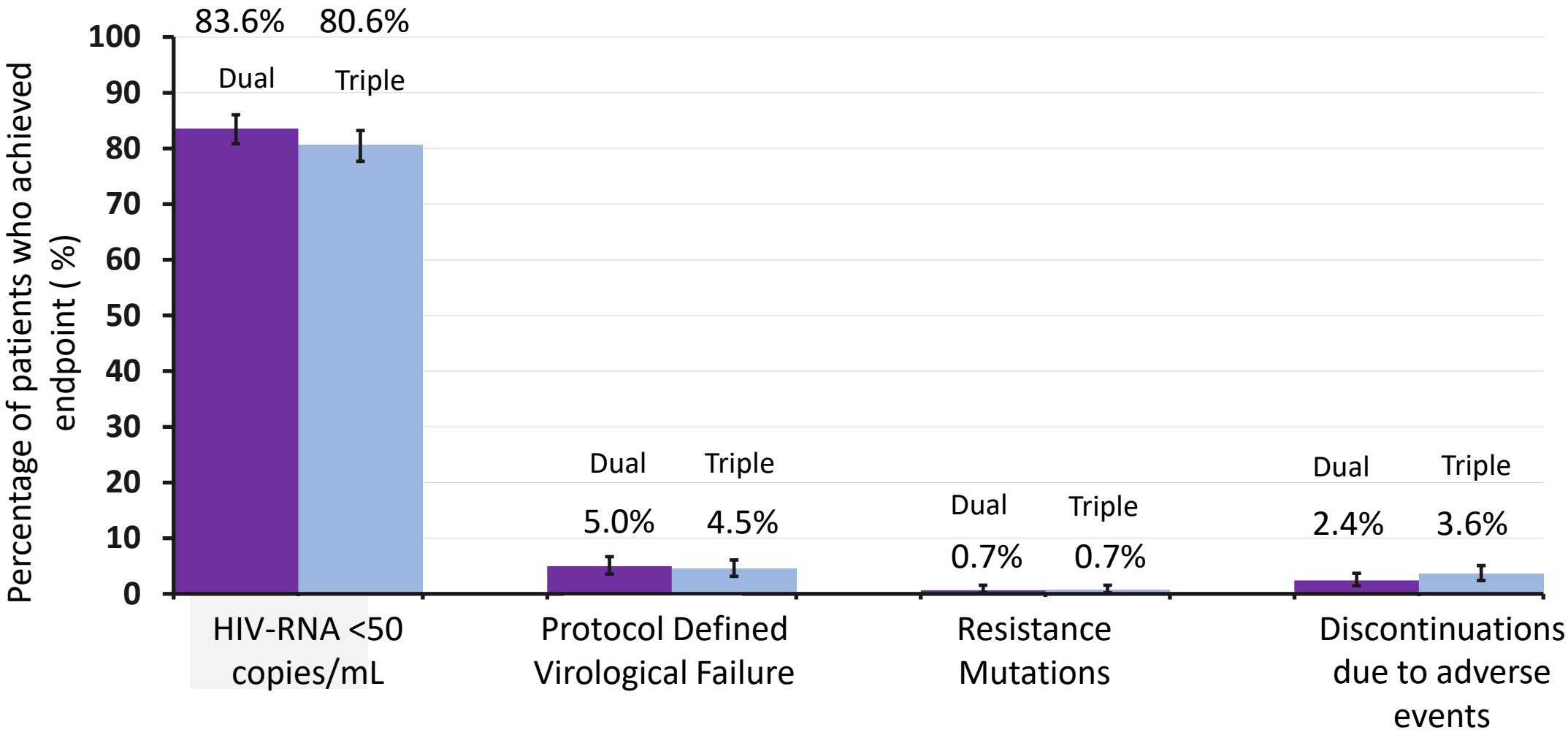
SWITCHING THERAPY: 2-DRUG ART

- DTG/3TC
- DTG/RPV

- LPV/b + 3TC
- ATV/b + 3TC
- DRV/b +3TC
- DRV/b + DTG

Boosted

SUMMARY FINDINGS-BPI 2DR META-ANALYSIS 7 TRIALS (N=~1600)



Liew HIV Glasgow 2018 AbstrO144

DTG/3TC IN GUIDELINES SWITCH

DHHS

- Good option if no resistance to either drug and no HBV coinfection

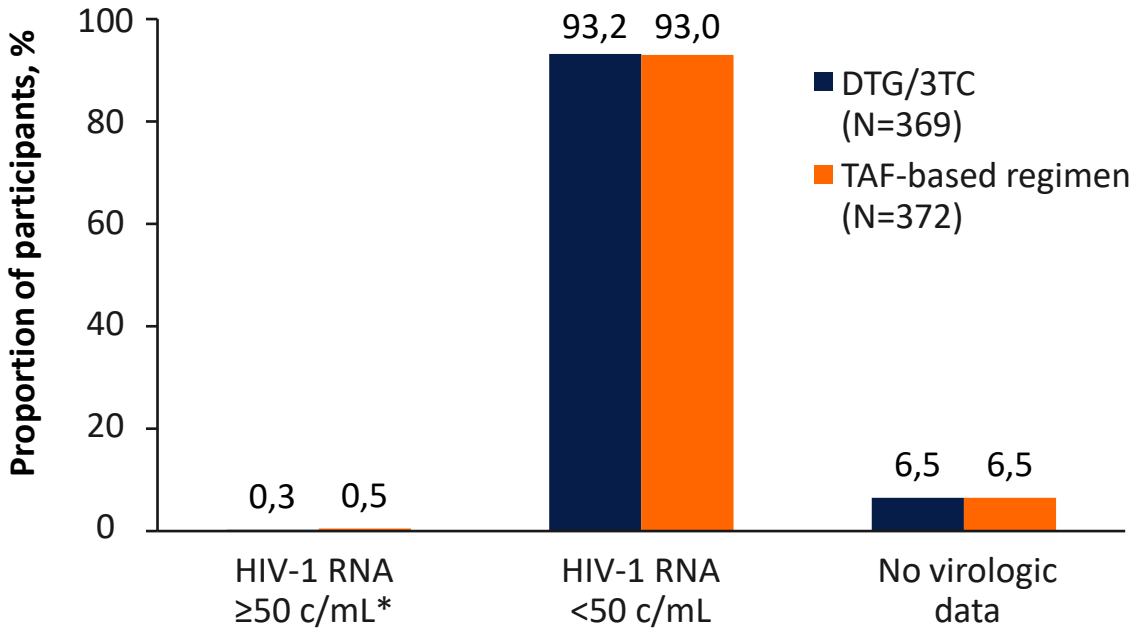
EACS

- Dual therapies supported by large randomized clinical trials or meta-analyses

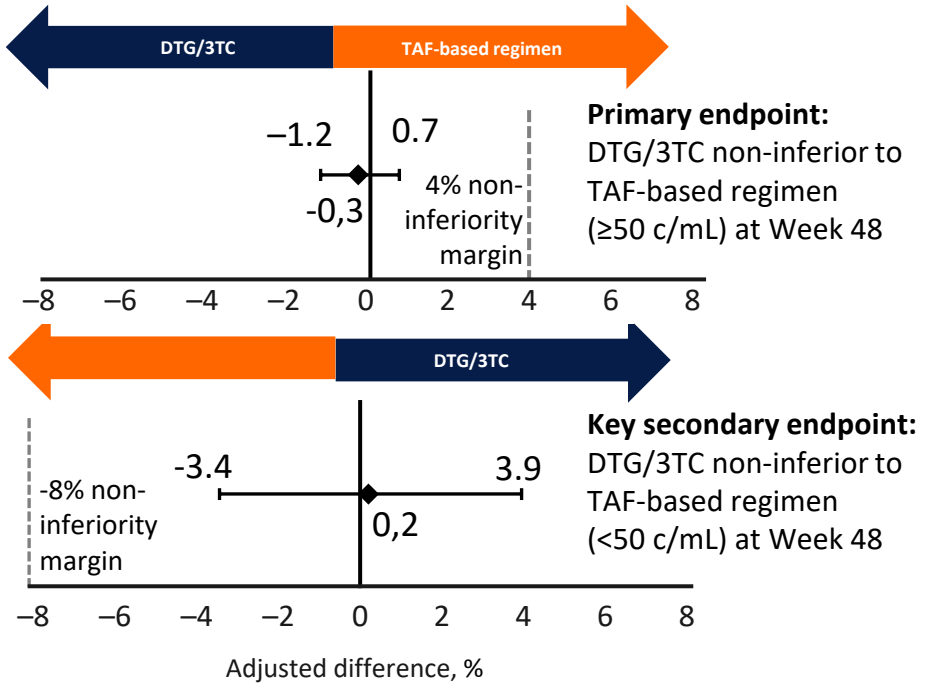
DHHS Guidelines. December 2019. EACS Guidelines 10.0 November 2019

DTG/3TC IS NON-INFERIOR TO TAF-BASED REGIMENS AT WEEK 48

Virologic outcomes



Adjusted treatment difference (95% CI)†



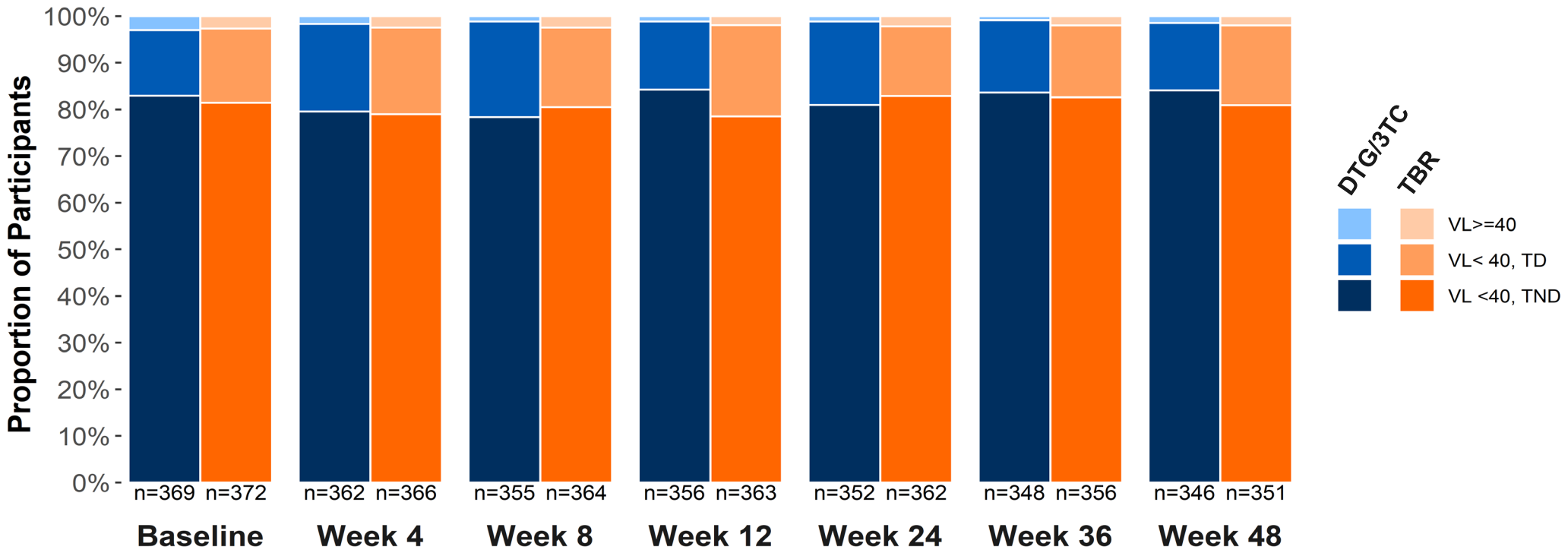
- In the per-protocol population, 0/352 participants in the DTG/3TC group and 2/358 participants in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.6; 95% CI, −1.3 to 0.2)†

*Primary endpoint (Snapshot virologic non-response, ITT-E)
†Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline third agent class
CI, confidence interval

van Wyk J, et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB
van Wyk J, et al. Clin Infect Dis 2020 [Epub ahead of print]

SUMMARY OF PROPORTION OF PARTICIPANTS WITH HIV-1 RNA <40 C/ML AND TND, <40 C/ML AND TD, AND ≥40 C/ML BY VISIT

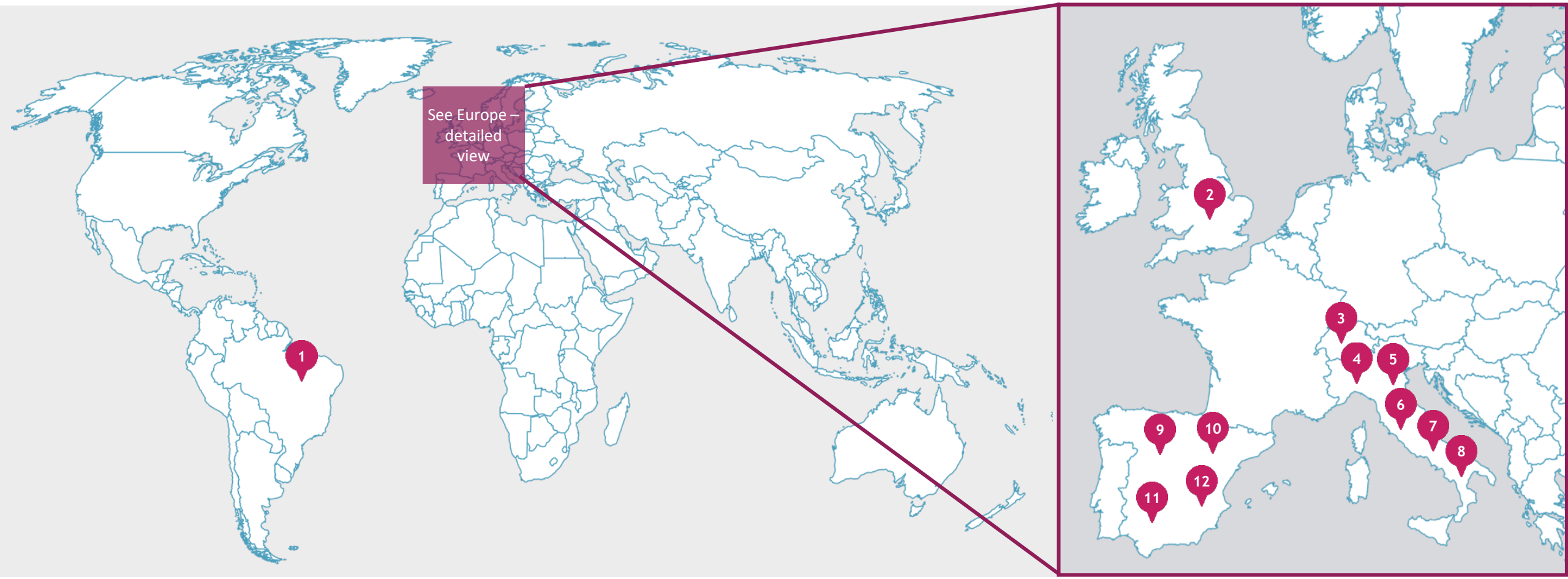
- The proportion of participants with VL <40 c/mL and TND per visit through Week 48 was high
  and



Note: Denominator n at each visit is number of participants with available viral load data within the visit window.

Wang et al. AIDS 2020: Virtual. Slides PEB0238.

>2,000 PLHIV WORLDWIDE HAVE RECEIVED DTG + 3TC* IN REAL-WORLD, SUPPRESSED SWITCH STUDIES†



Numbers correspond to references. Figure is accurate to the level of country of study, placement within country is for visual representation purposes only. Potential overlap between patient cohorts cannot be ruled out

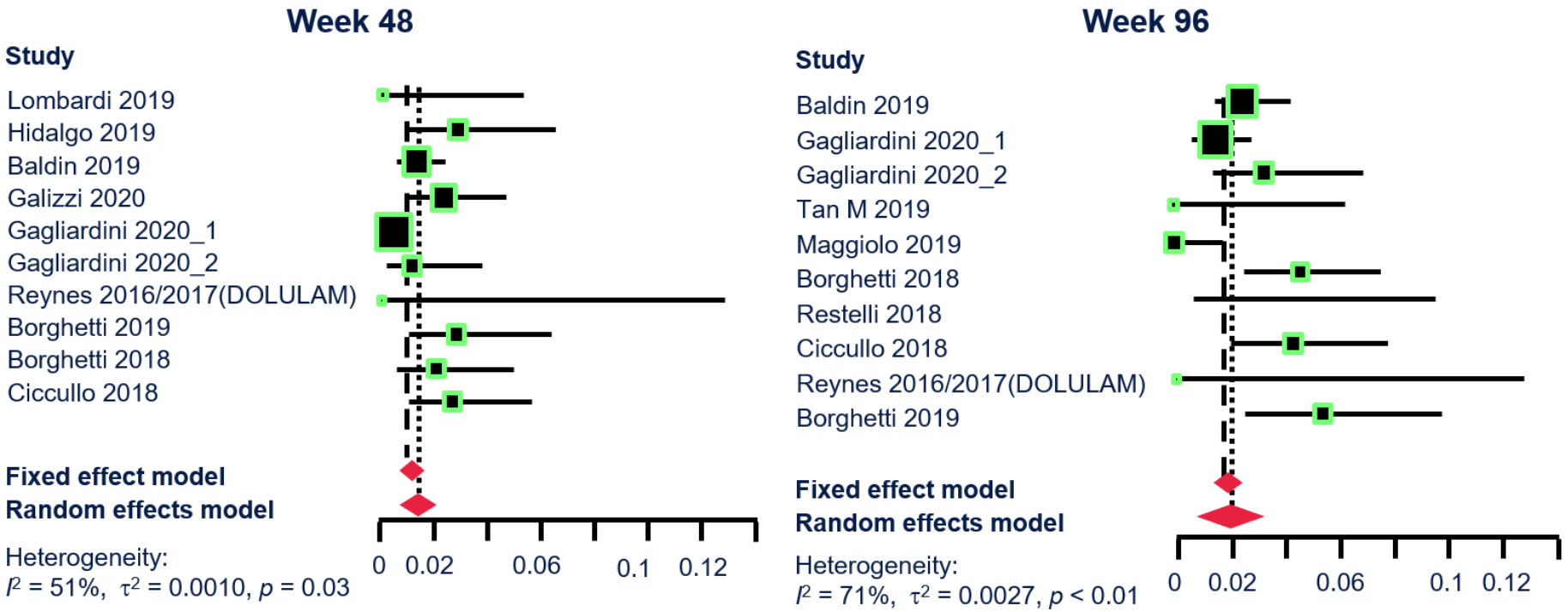
*Includes patients treated with DTG + 3TC in accordance with the DOVATO EU SmPC[13]; †Note that for some studies, a small number of patients were not suppressed at baseline[2,8–12]

SmPC, summary of product characteristics

See slide notes for references

VIRAL FAILURE

- Results showed that, at W48, there were 1.3% (95% CI: 0.6, 2.1) viral failures for DTG+3TC regimen in the random effects model. At W96 analysis, 2.0% (95% CI: 0.9, 3.5) viral failure was reported for the DTG+3TC regimen in random effects analysis
- No study reported presence of treatment emergent resistance



Punekar et al. AIDS 2020: Virtual. Poster PDB0103.

DTG/RPV IN GUIDELINES SWITCH

DHHS

- Reasonable option when the use of nucleoside reverse transcriptase inhibitors is not desirable

EACS

- Dual therapies supported by large randomized clinical trials or meta-analyses

DHHS Guidelines. December 2019. EACS Guidelines 10.0 November 2019

DTG/RPV IN SWITCH

KNOWNS

- Durability (3 years)
- Virological suppression < 50 (TND) = 3DR
- Slightly increased (0.6% of SWORD participants) risk of resistance (NNRTI not ISTI)
- Improvement bone/renal biomarkers (vs TDF)
- No consistent changes in inflammatory biomarkers

UNKNOWNS

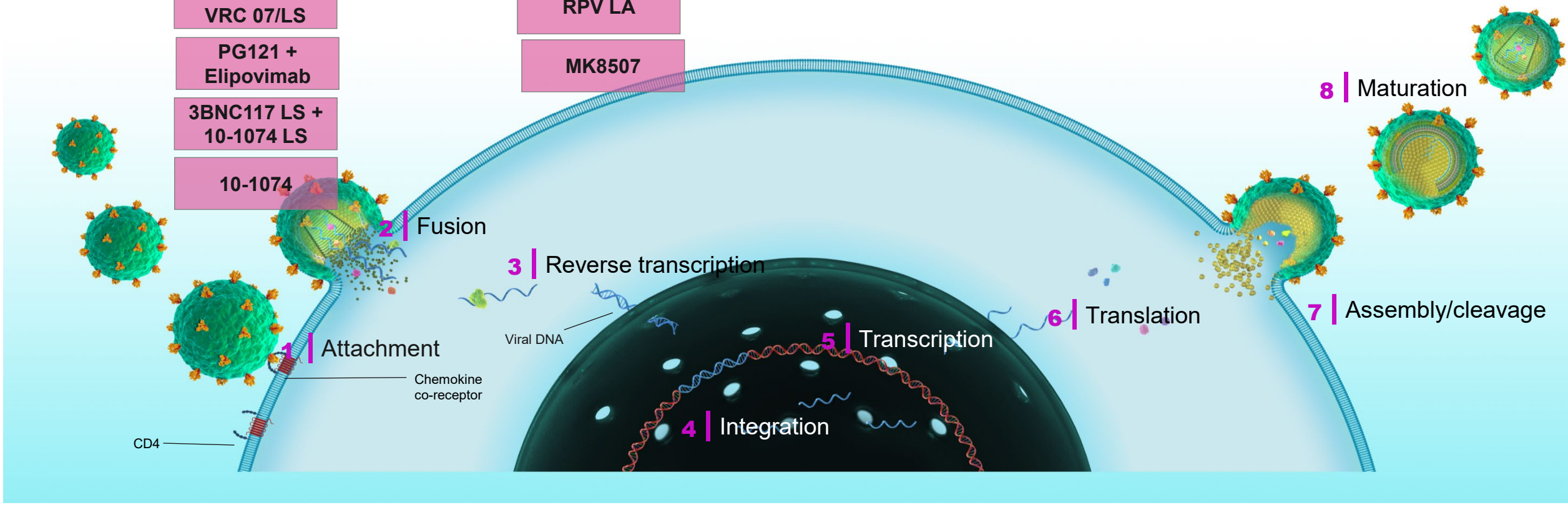
- Impact of archived resistance, especially M184V
- Pregnancy
- Long term weight changes

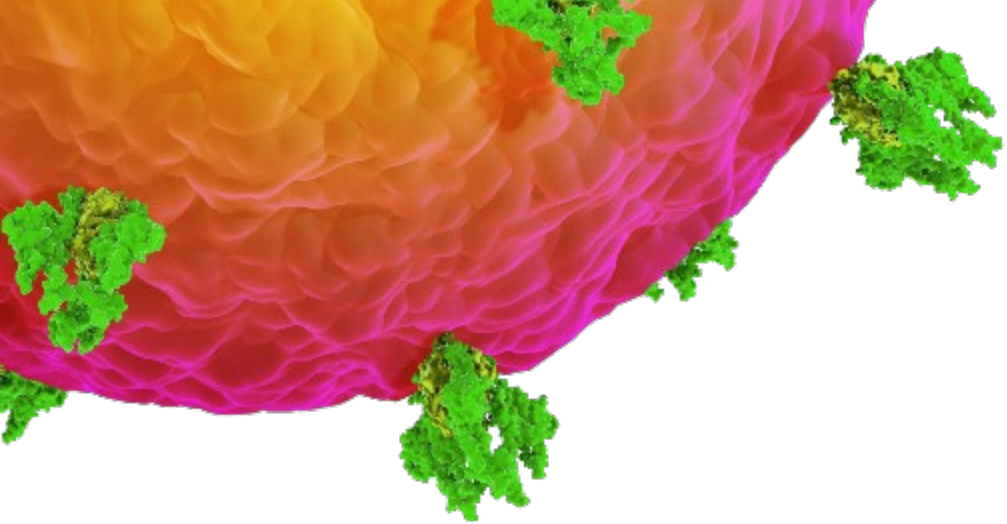
Aboud M et al. The Lancet HIV 2019; 6:e576–e587. Orkin et al C 25th BHIVA P008. Underwood M et al HIV Drug Therapy Glasgow 2018 P311


FUTURE

LA AND 2DR POTENTIAL

Entry fusion inhibitor	bNAb	NRTI/NRTTI	NNRTI	Integrase inhibitor	Protease inhibitor	Capsid inhibitor	Maturation inhibitor	TLR 7 agonist
Albuvirtide	UB-421	Islatravir	Elsulfavirine	RAL LA	ATV LA IM	Lenacapavir	GSK937	Vesatolimod
	Leronlimab PRO-140	TAF implant	ACC007	CAB LA	RTV LA IM			
	VRC 01/LS VRC 07/LS		RPV LA					
	PG121 + Elipovimab		MK8507					
	3BNC117 LS + 10-1074 LS							
	10-1074							





c.m.orkin@qmul.ac.uk

@profchloeorkin