



WORKING ON BEHALF OF
ViiV HEALTHCARE IN HIV

▼ TIVICAY® A NEW TREATMENT OPTION

Els Hollanders
Med Director of Medical Operations and Alliance Countries

Zinc code [LT/DLG/0013/15](#)- Jan 2016





MOST THIRD AGENTS ARE UNABLE TO MEET ALL THE CHALLENGES OF HIV THERAPY

Tolerability of ARVs

- EFV can be associated with CNS AEs, skin rash and hyperlipidaemia
- Boosted PIs are associated with metabolic disorders (dyslipidaemia, insulin resistance, and lipodystrophy)

Convenience

- RAL requires twice-daily dosing
- There are currently few co-formulated fixed-dose combinations, offering one pill, once-daily simple dosing*

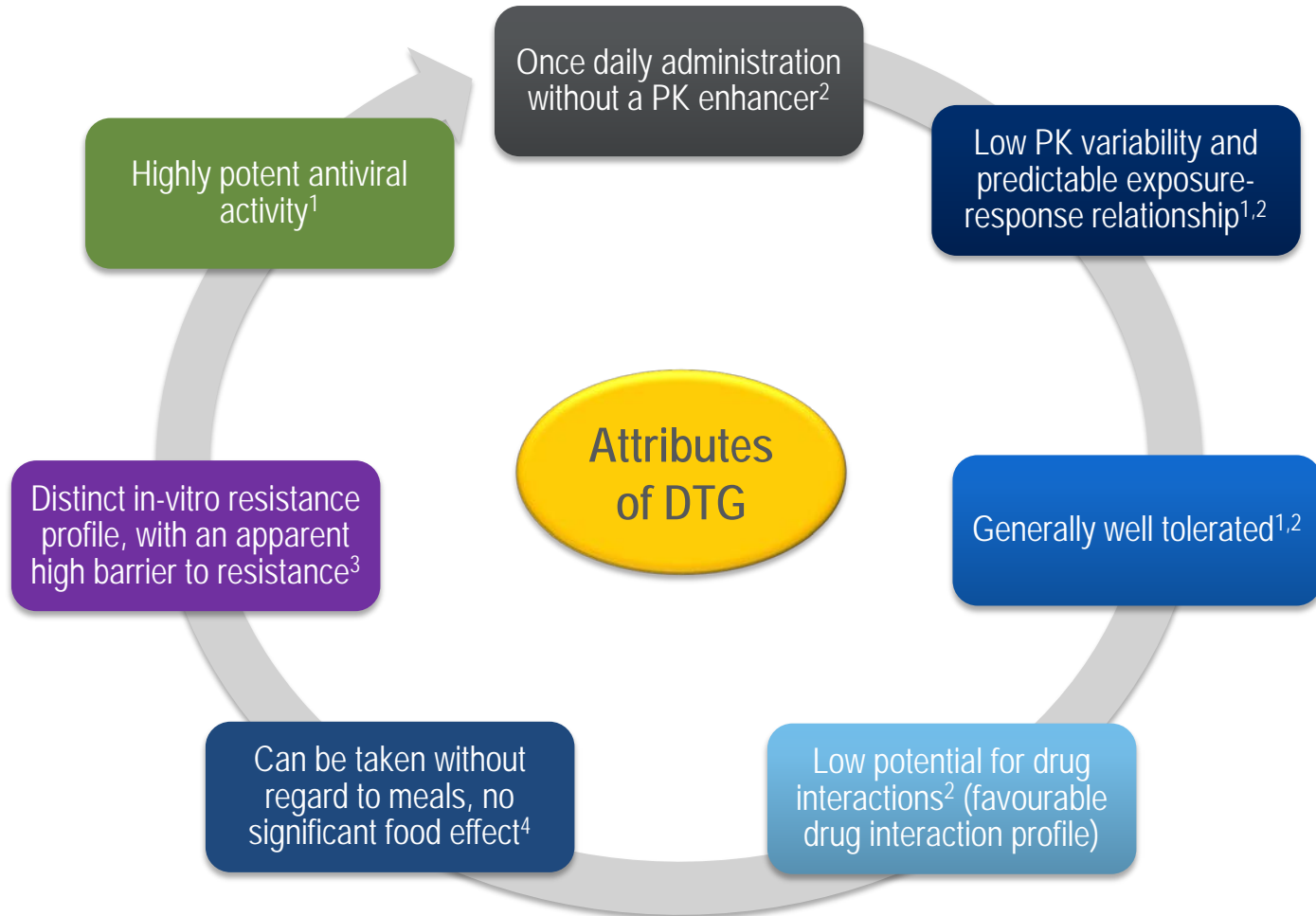
Drug interactions

- Many HIV ARVs (and in particular ARVs boosted with ritonavir or cobicistat) interact with the cytochrome P450 enzymes and are associated with drug interactions

Drug resistance

- EFV, RPV, RAL and EVG appear to be associated with a lower barrier to resistance compared with boosted PIs

ATTRIBUTES OF DTG FOR USE AS A FIRST-LINE TREATMENT



1. Min, S. et al. AIDS 2011;25:1737–45

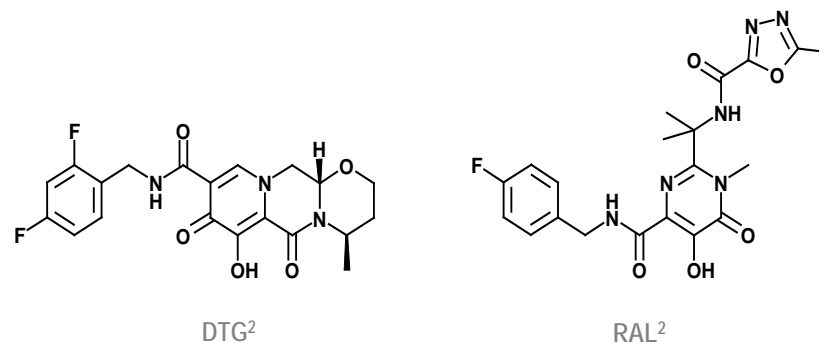
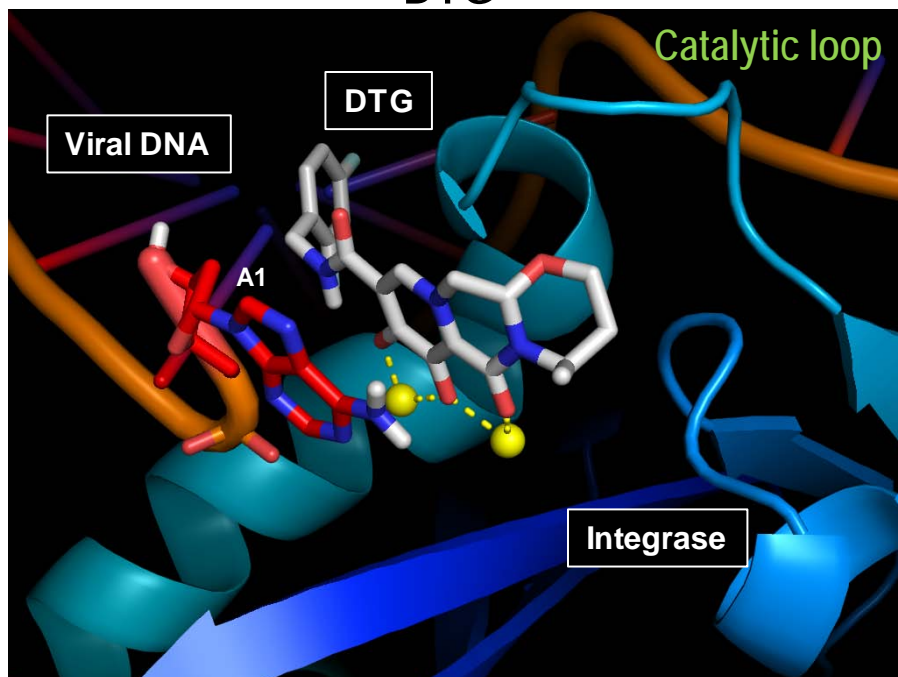
2. Min, S. et al. Antimicrob Agents Chemother. 2010;54:254–8

3. Kobayashi, M. et al. Antimicrob Agents Chemother 2011;55:813–21

4. Song, I. et al. Antimicrob Agents Chemother 2012;56:1627–9

STRUCTURE-BASED RATIONALE FOR DISSOCIATION PROFILES OF DTG AND RAL: WILD TYPE IN

DTG¹



Dissociation $t_{1/2}$ (h) at 37° C²

Integrase	DTG	RAL
Wild type	71	8.8

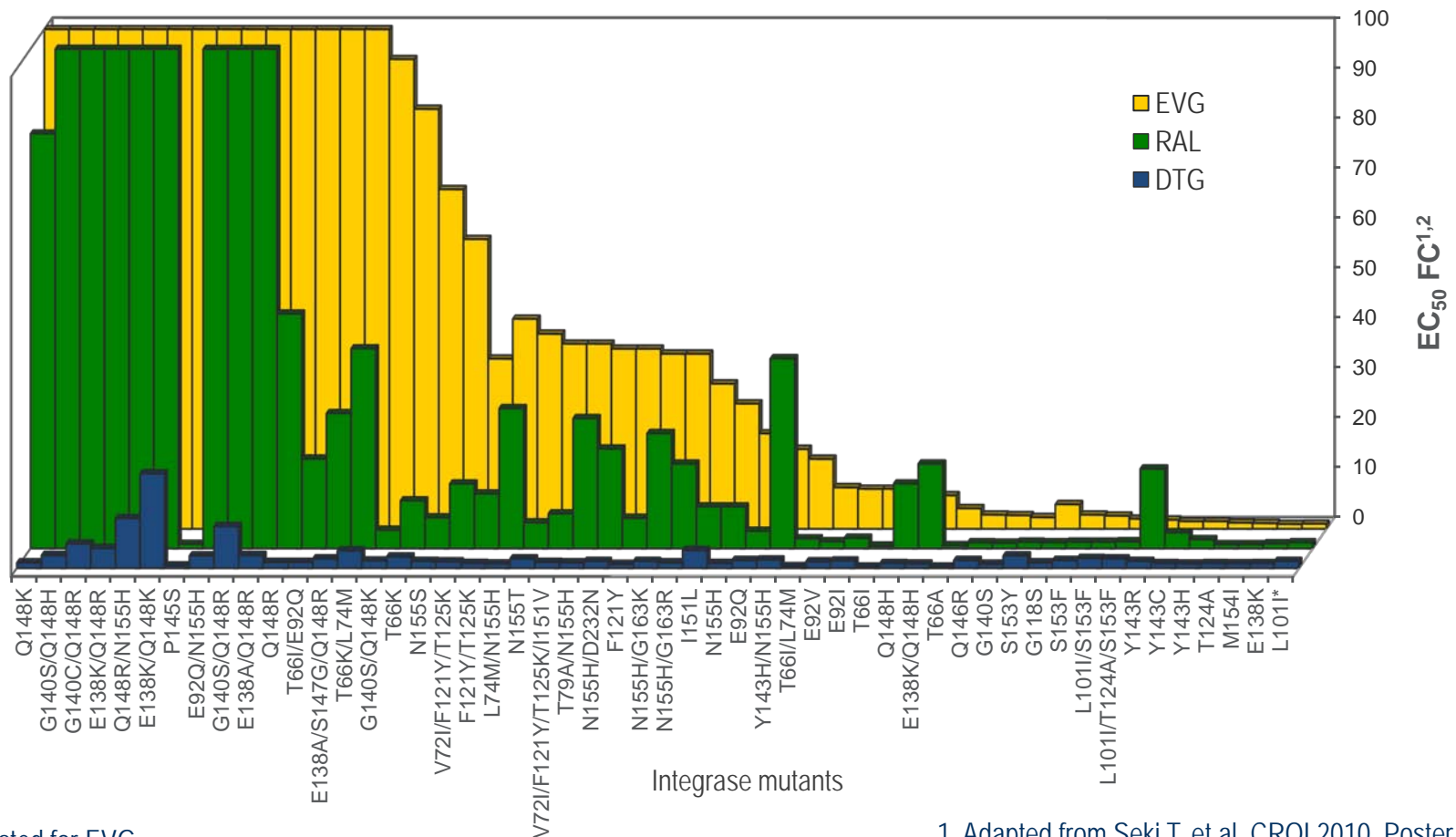
- DTG's larger metal-chelating scaffold may more effectively delocalise positive charge when interacting with the metals¹
- DTG's electron-deficient scaffold may interact favorably with the electron-rich A1¹
- RAL's oxadiazole proximity to Y143 at the top of the catalytic loop increases potential for mutations at Y143, Q148, and N155 to disrupt binding¹
- Together, these properties may increase DTG binding affinity for integrase over RAL¹

$t_{1/2}$, terminal half-life

1. Adapted from DeAnda et al. PLoS ONE 2013;8(10):e77448
2. Adapted from Hightower KE, et al. Antimicrob Agents Chemother 2011;55:4552-9

MOST RAL- AND EVG-RESISTANT MUTANTS ARE SUSCEPTIBLE TO DTG

In contrast to RAL and EVG, single mutations did not confer high level resistance to DTG



*Not tested for EVG

EC₅₀, 50% effective concentration; FC, fold change.

1. Adapted from Seki T, et al. CROI 2010. Poster J-122

2. Adapted from Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21

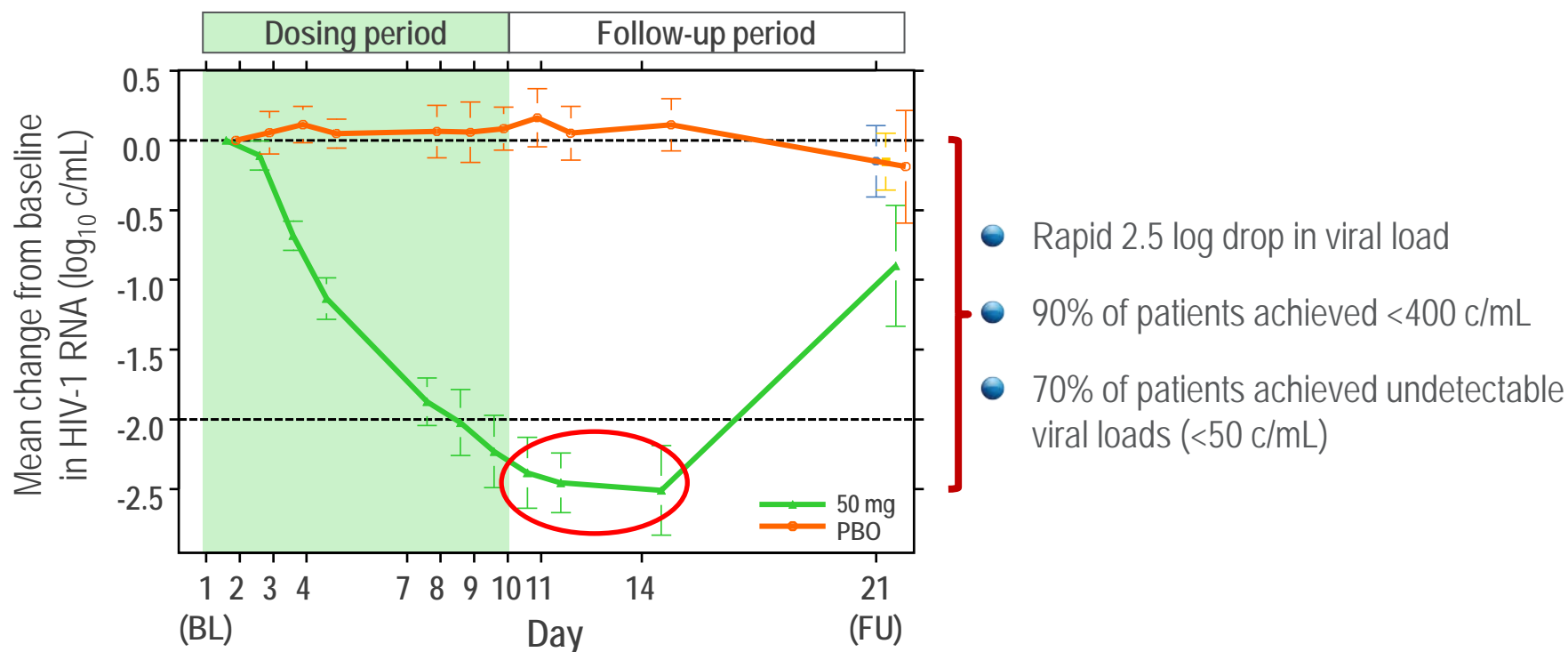
FEWER SUBSTITUTIONS WERE DETECTED DURING PASSAGE WITH DTG COMPARED WITH RAL AND EVG

Raltegravir (84 days)	Elvitegravir (56 days)	DTG (56 days)
T124A Q148K* Q148R E138K/Q148K E138K/Q148R G140S/Q148R N17S/ Q148K /G163R G140C/ Q148K /G163R E138K/Q148K /G163R E92Q/ E138K/Q148K /M154I N155H /I204T V151I/N155H T124A/ V151I/N155H	T66I E92Q T124A P145S Q148K Q148R T66I/T124A T66K/T124A E92V/T124A P145S/T124A Q146L/T124A Q148R/T124A T66I/V72A/A128T T66I/E92Q/T124A T66I/T124A/Q146L	T124A T124A/S153F
		DTG (84 days)
		T124A S153Y T124A/S153Y L101I/T124A/S153F
		DTG (112 days)
		T124A S153Y T124A/S153Y L101I/T124A/S153F

- *Red text indicates substitutions seen in clinical trials
- Maximum ~4 FC for DTG mutants selected *in vitro*
- T124A and L101I are polymorphic and do not confer resistance to DTG or RAL
- Preclinical data suggested DTG had potential for a higher barrier to resistance

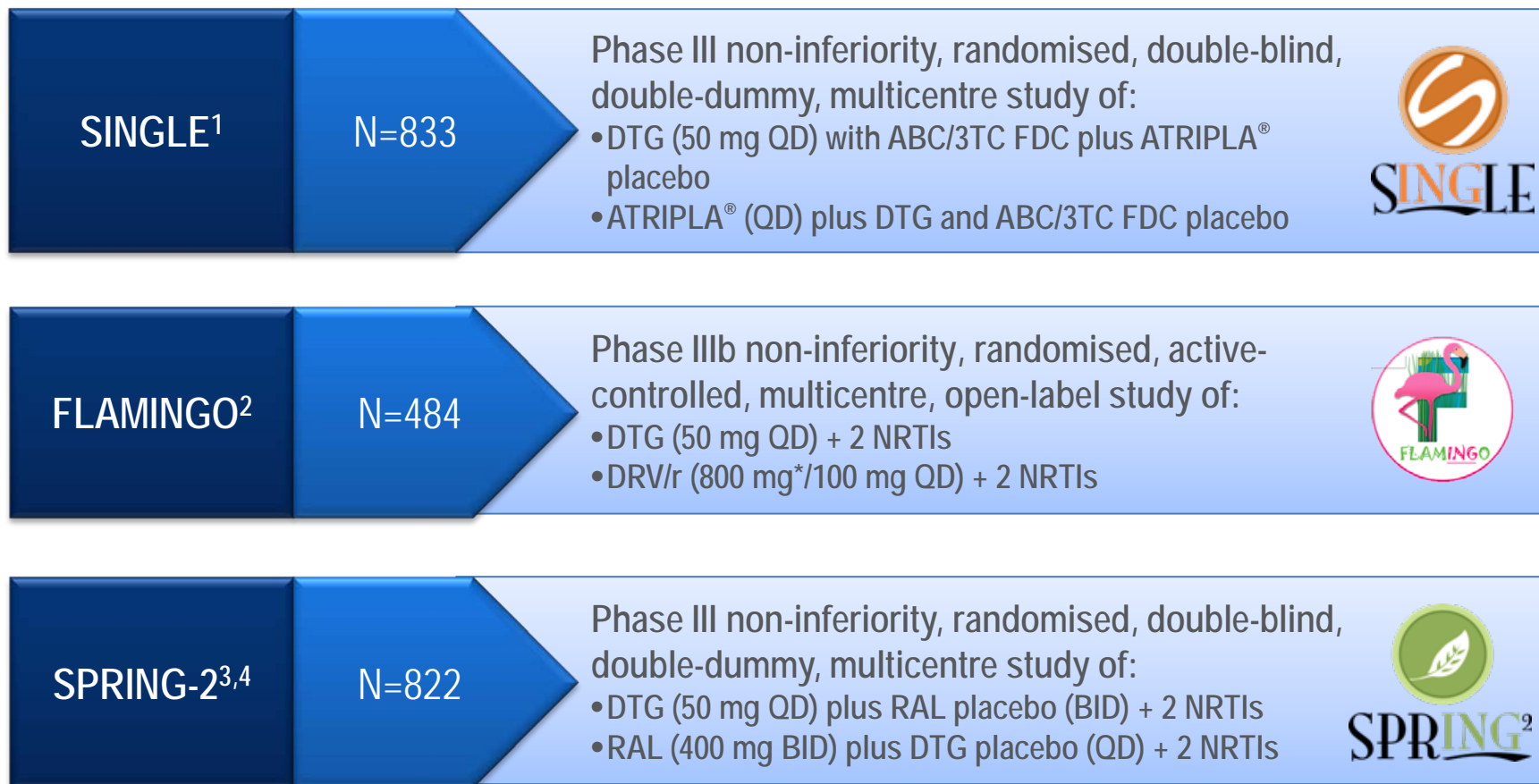
DTG CONFERRED RAPID AND POTENT ANTIVIRAL EFFICACY

10 day monotherapy with DTG 50 mg QD



EFFICACY IN NAIVE PATIENTS

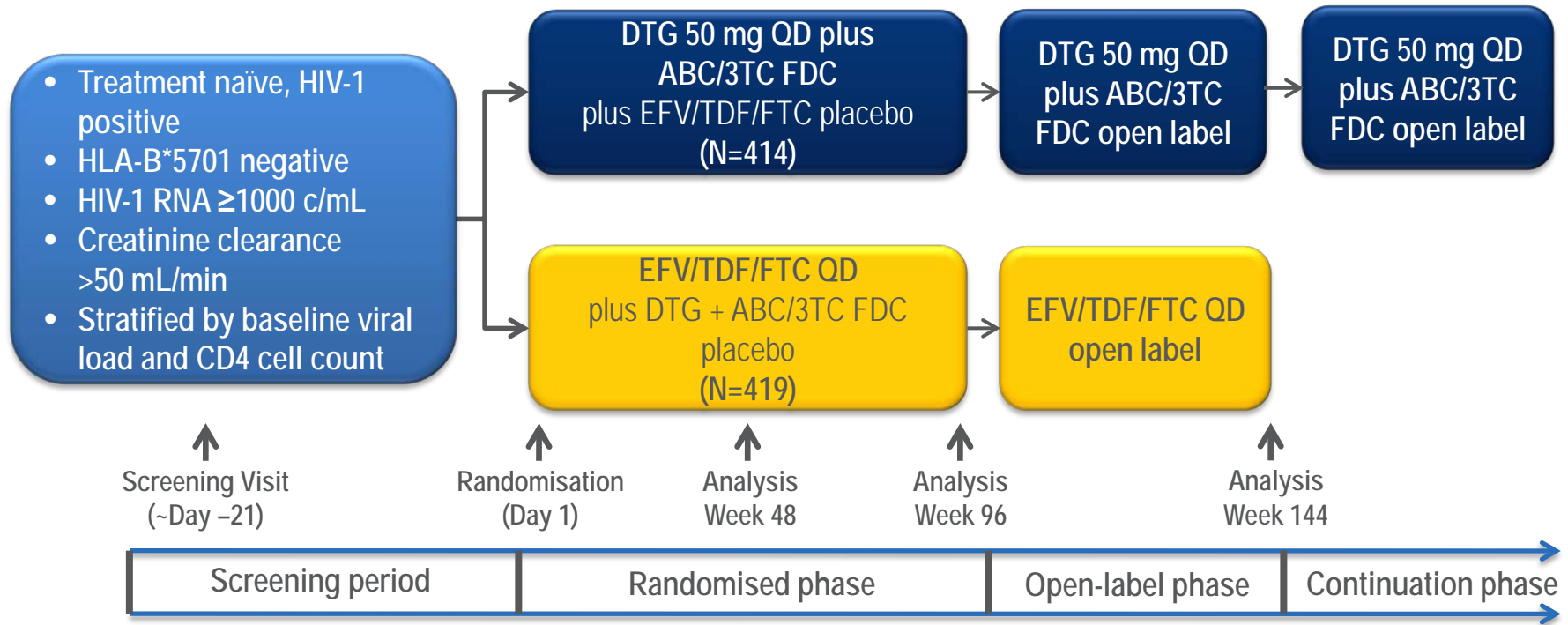
PHASE III DTG TRIALS IN TREATMENT-NAÏVE ADULT SUBJECTS WITH HIV



NRTI, nucleoside reverse transcriptase inhibitor
QD, once daily; BID, twice daily; FDC, fixed-dose combination

1. Walmsley S, et al. N Engl J Med 2013;369:1807-18
2. Clotet B, et al. Lancet 2014 March 31 & Molina Lancet 2014
3. Raffi F et al. Lancet 2013;381:735-43
4. Raffi F, et al. Lancet Infect Dis 2013; 13:927-35

SINGLE STUDY DESIGN^{1,2}



Primary endpoint: Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis (10% non-inferiority margin with pre-specified tests for superiority)

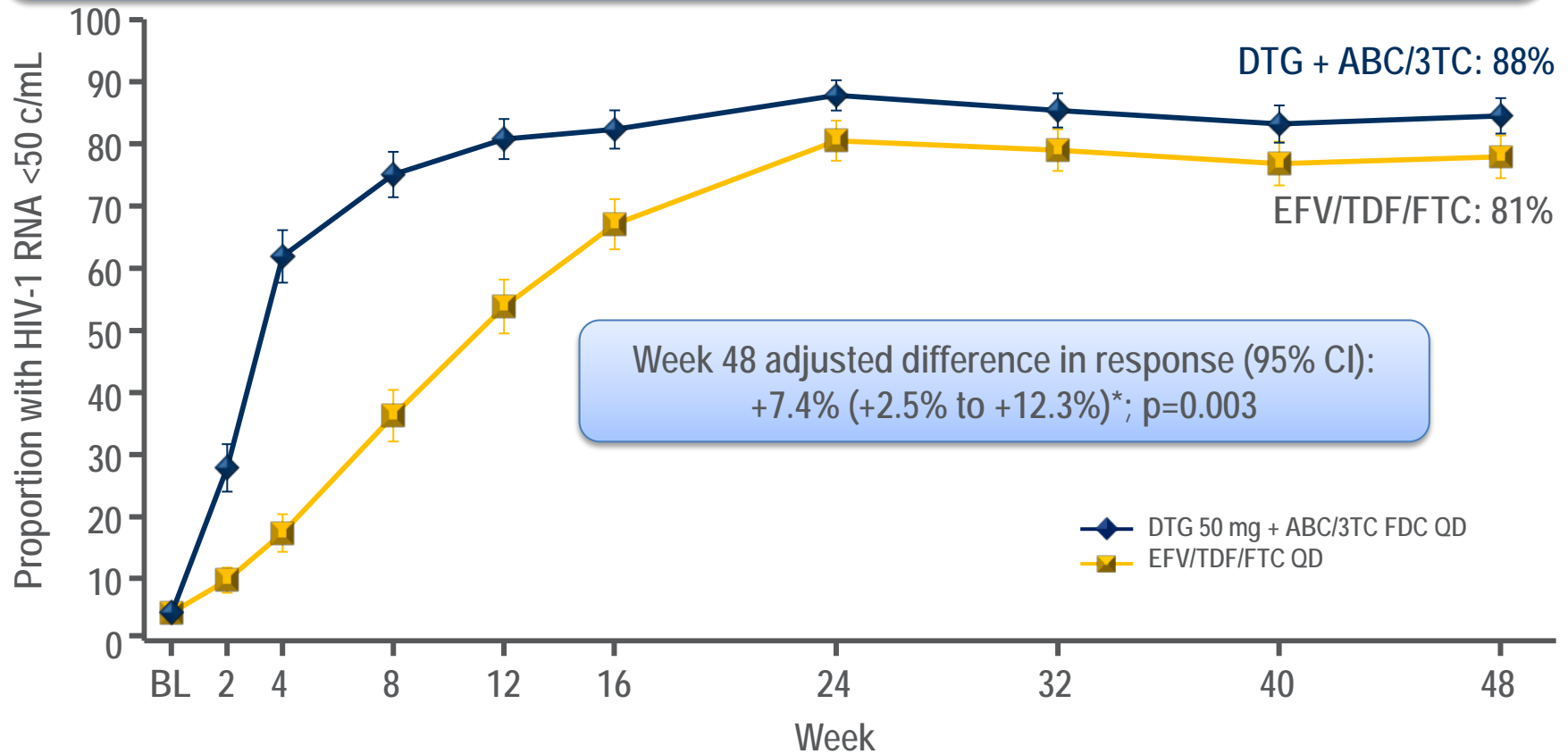


BASELINE CHARACTERISTICS

Characteristic	DTG 50 mg + ABC/3TC QD (N=414)	EFV/TDF/FTC QD (N=419)
Median age, years	36	35
Female, %	16	15
African American / African Heritage, %	24	24
CDC class C, %	4	4
Baseline HIV-1 RNA		
Median (log ₁₀ c/mL)	4.67	4.70
>100,000 c/mL, %	32	31
Median CD4 cell count, cells/mm ³	335	339
<200, %	14	14
200 to <350, %	39	38
350 to <500, %	32	31
≥500, %	15	17

VIROLOGIC RESPONSE AT WEEK 48

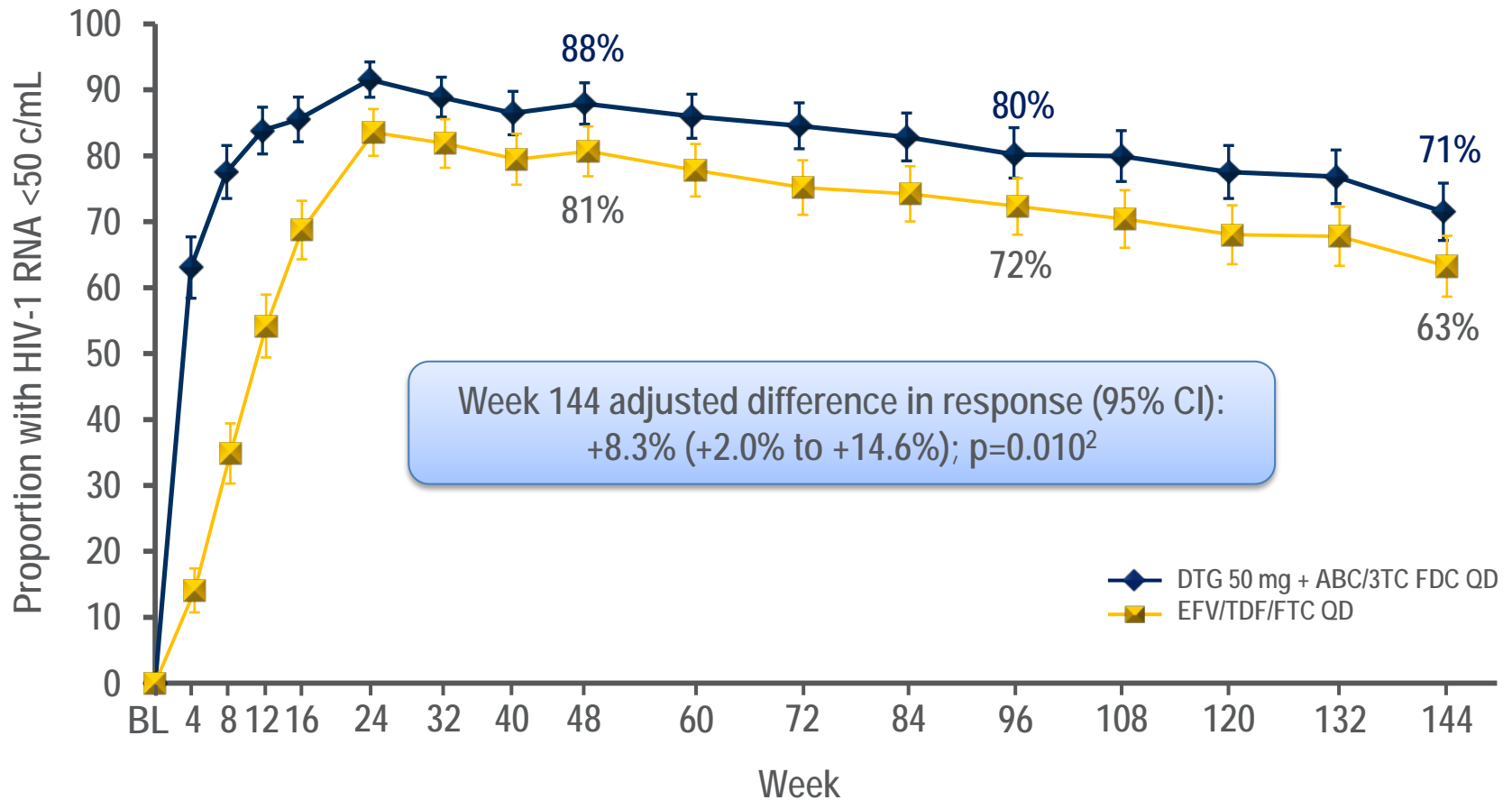
DTG + ABC/3TC was statistically superior to EFV/TDF/FTC at Week 48
 Subjects receiving DTG + ABC/3TC achieved faster virologic suppression than EFV/TDF/FTC
 ($p < 0.001$)



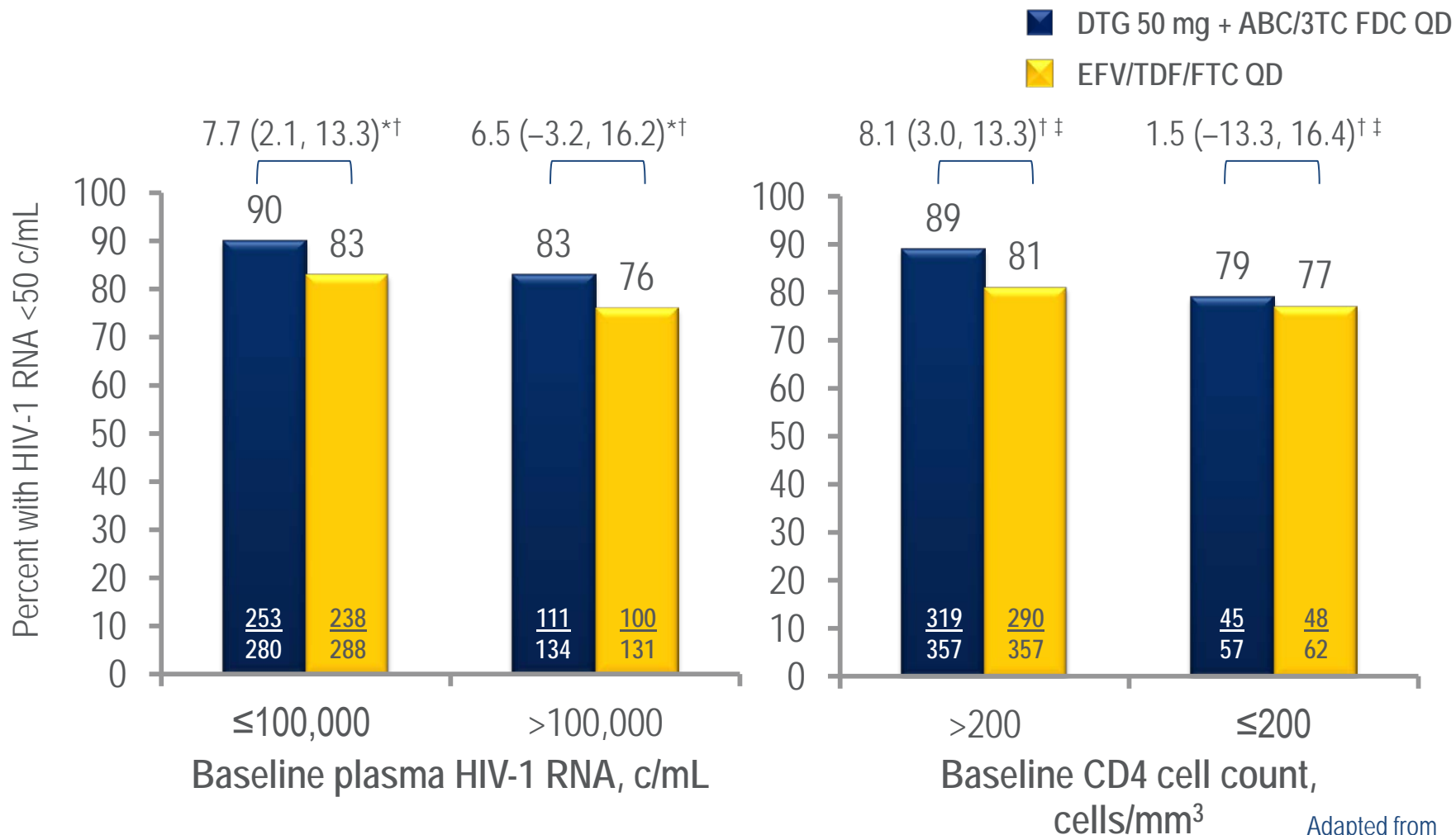
*-10% non-inferiority margin with pre-specified tests for superiority

VIROLOGIC RESPONSE THROUGH TO WEEK 144

DTG + ABC/3TC remained statistically superior to EFV/TDF/FTC through to Weeks 96¹ and 144²



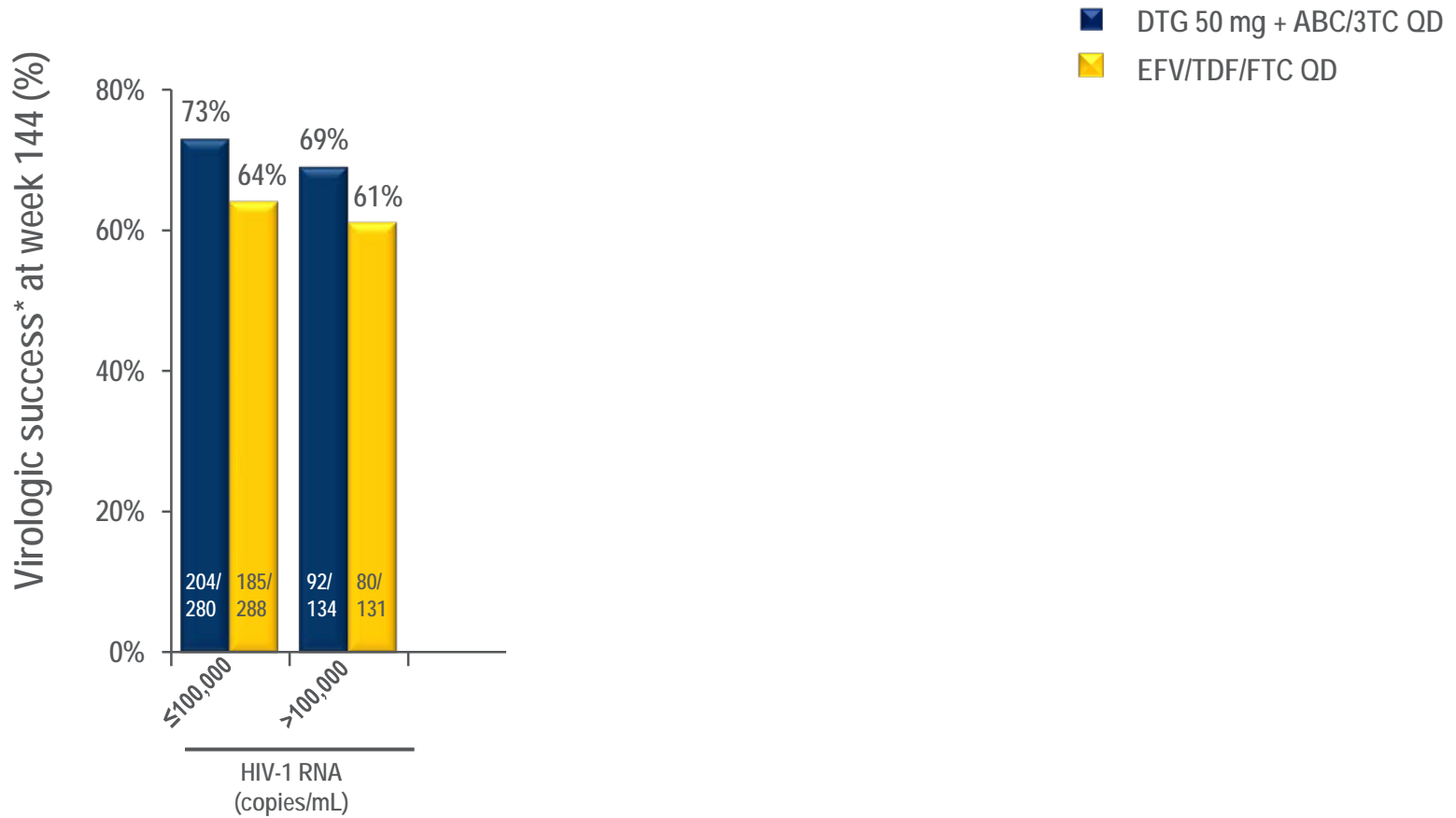
VIROLOGIC RESPONSE BY BASELINE VIRAL LOAD AND CD4 CELL COUNT AT WEEK 48¹



*p=0.831; †test for homogeneity; ‡p=0.414: p value confirms that there is no evidence of heterogeneity in treatment difference across the baseline stratification factors

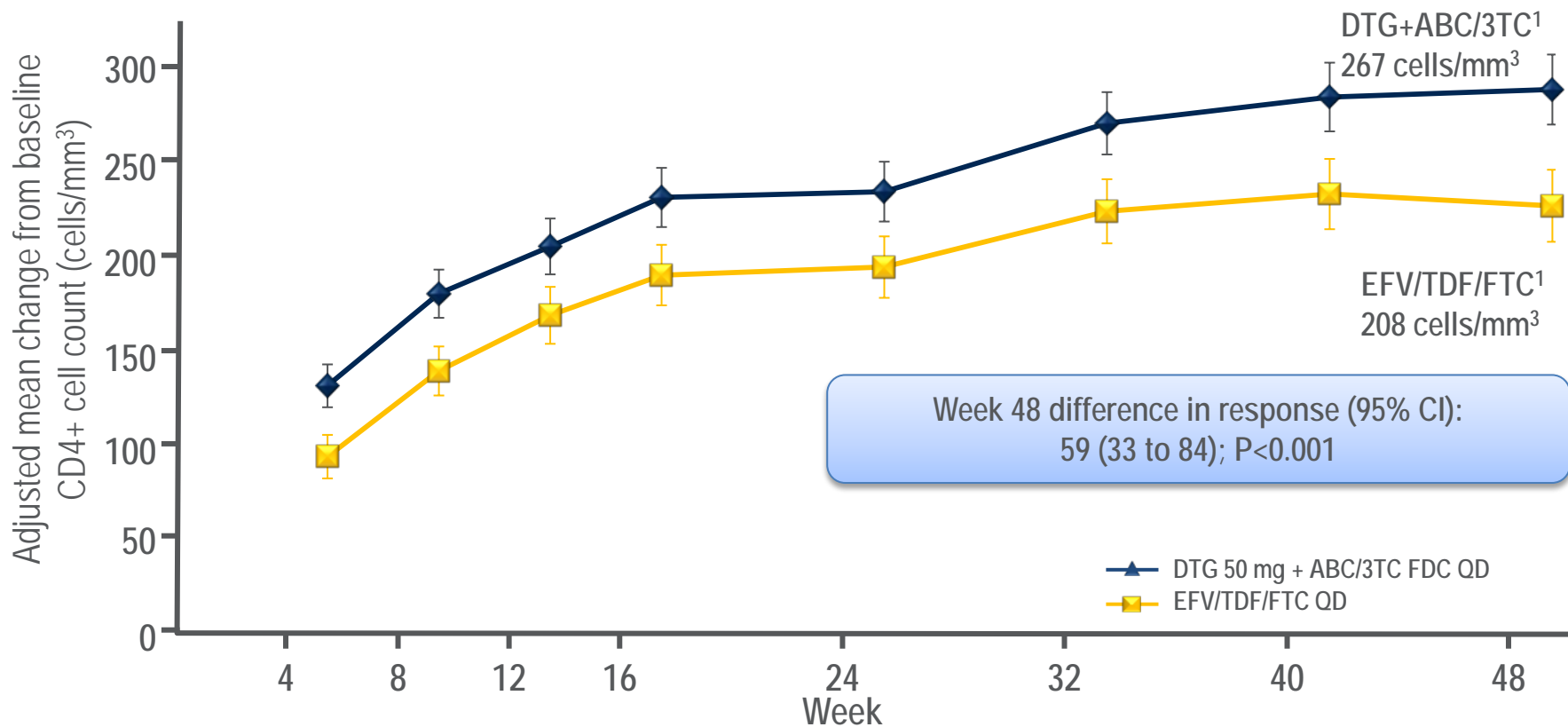
Adapted from
Walmsley S, et al. N Engl J Med 2013;369:1807-18
And supplementary index

EFFICACY SUBGROUPS VL AT WEEK 144



*HIV-1 RNA <50 c/mL

MEAN CHANGE IN CD4+ CELL COUNT AT WEEK 48, WEEK 96 AND WEEK 144



- At Week 96, mean change from baseline was +325.3 cells/mm³ versus +281.4 cells/mm³; p=0.004)²
- At Week 144, mean change from baseline was +378 cells/mm³ versus +332 cells/mm³; p=0.003)³

Adapted from 1. Walmsley S, et al. N Engl J Med 2013;369:1807-18

2. Walmsley S, et al. CROI 2014. Abstract 543

3. Pappa K, et al. ICAAC 2014. Abstract H-647a

144 WEEKS SAFETY RESULTS

AE LEADING TO WITHDRAWAL BY SYSTEM ORGAN CLASS

Body system ($\geq 2\%$ in either arm*), n (%)	DTG 50 mg + ABC/3TC QD (N=414)	EFV/TDF/FTC QD (N=419)
Overall	16 (4)	58 (14)
Psychiatric disorders	4 (<1)	24 (6)
Nervous system disorders	1 (<1)	17 (4)
Skin and subcutaneous tissue disorders	2 (<1)	10 (2)
General disorders and administration site conditions	0	11 (3)
Gastrointestinal disorders	0	8 (2)

*individual may have had an AE in ≥ 1 body system

SINGLE: CONCLUSIONS

Virologic suppression was statistically superior with DTG 50 mg + ABC/3TC QD vs EFV/TDF/FTC in the proportion of subjects achieving HIV-1 RNA <50 c/mL (FDA snapshot) at Week 48 (p=0.003)¹ and maintained to Week 96 (p=0.006)² and Week 144 (p=0.010)³

- DTG + ABC/3TC was statistically superior to EFV/TDF/FTC with respect to the proportion of subjects achieving HIV-1 RNA <50 c/mL over 48 weeks (88% vs 81%, respectively)¹ and maintained to Week 96 (80% vs 72%)² and Week 144 (71% vs 63%)³
 - differences in efficacy were driven by a lower rate of discontinuations due to AEs for the DTG + ABC/3TC arm, which was independent of baseline viral load²
- Over 144 weeks, CD4+ change from baseline was statistically significantly higher in the DTG 50 mg QD + ABC/3TC arm than in the EFV/TDF/FTC arm (p=0.003)³
- DTG + ABC/3TC safety and tolerability was generally favourable compared with EFV/TDF/FTC
 - lower rate of CNS and rash events / fewer discontinuations due to AEs at 144 weeks³
 - lower rate of liver chemistry elevations at 48 weeks¹
 - smaller increases in bone-turnover markers at 48 weeks⁴
- No treatment-emergent major INI or NRTI mutations were detected through 144 weeks on DTG + ABC/3TC;³ major NNRTI and NRTI mutations were detected in the EFV/TDF/FTC arm³

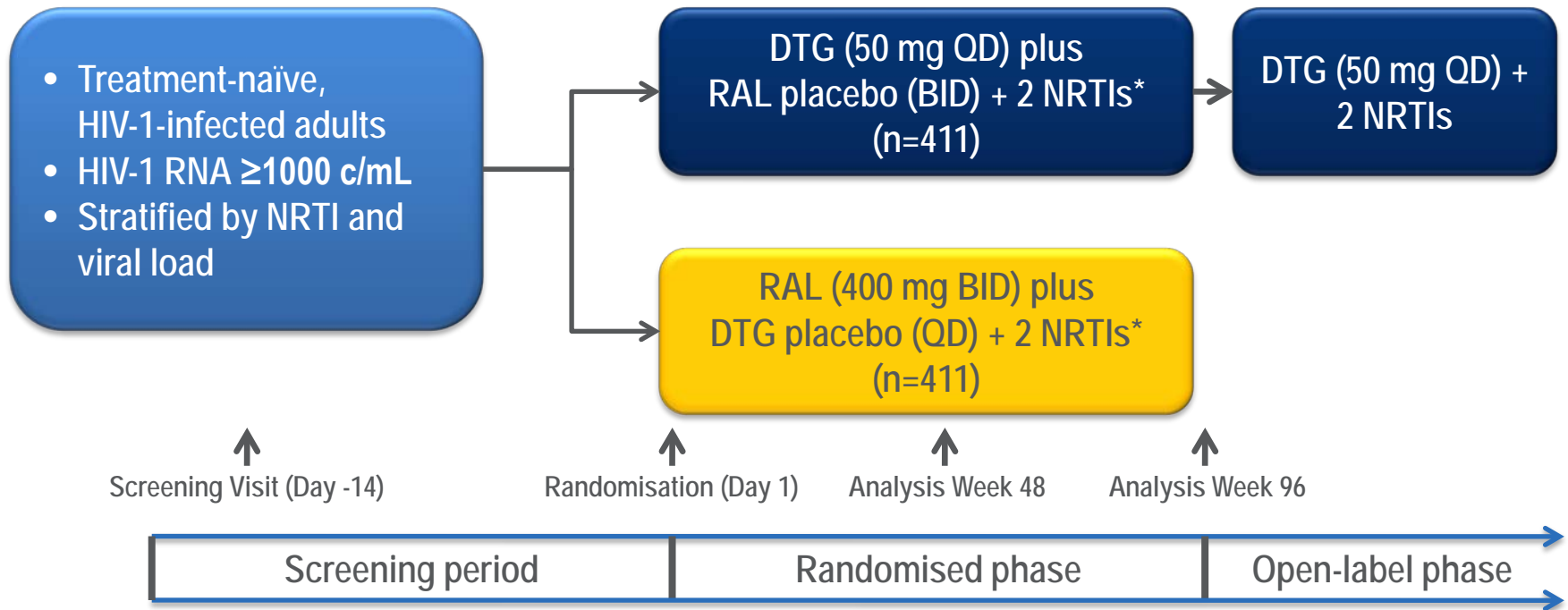
Adapted from 1. Walmsley S, et al. N Engl J Med 2013;369:1807–18

2. Walmsley S, et al. CROI 2014. Abstract 543

3. Pappa K, et al. ICAAC 2014. Abstract H-647a

4. Tebas P, et al. ICAAC 2013. Abstract H-1461

SPRING-2: STUDY DESIGN

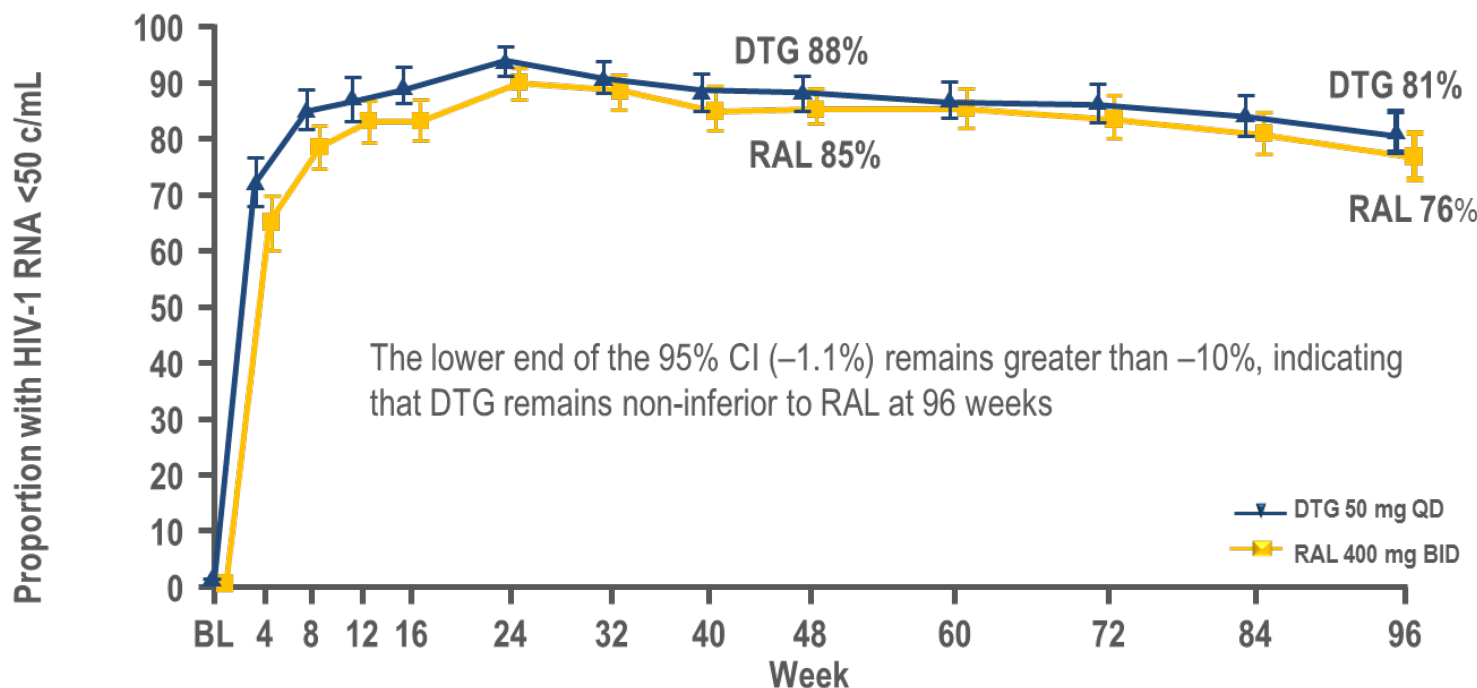


Primary endpoint: proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot), with a -10% non-inferiority margin

BASELINE CHARACTERISTICS

Characteristic	DTG 50 mg OD (n=411)	RAL 400 mg BID (n=411)
Median age, years (range)	37 (18–68)	35 (18–75)
Male gender, n (%)	348 (85)	355 (86)
Race, %		
White	346 (84)	352 (86)
African American/African heritage	49 (12)	39 (9)
Other	16 (4)	20 (5)
Baseline HIV-1 RNA		
Median (log ₁₀ c/mL)	4.5	4.6
>100,000 c/mL, n (%)	114 (28)	116 (28)
Baseline CD4⁺		
Median (cells/mm ³)	359	362
<200 cells/mm ³ , n (%)	55 (13)	50 (12)
Hepatitis co-infection, n (%)		
Hepatitis B	7 (2)	8 (2)
Hepatitis C	41 (10)	35 (9)
Investigator-selected dual NRTIs, n (%)		
TDF/FTC	242 (59)	247 (60)
ABC/3TC	169 (41)	164 (40)

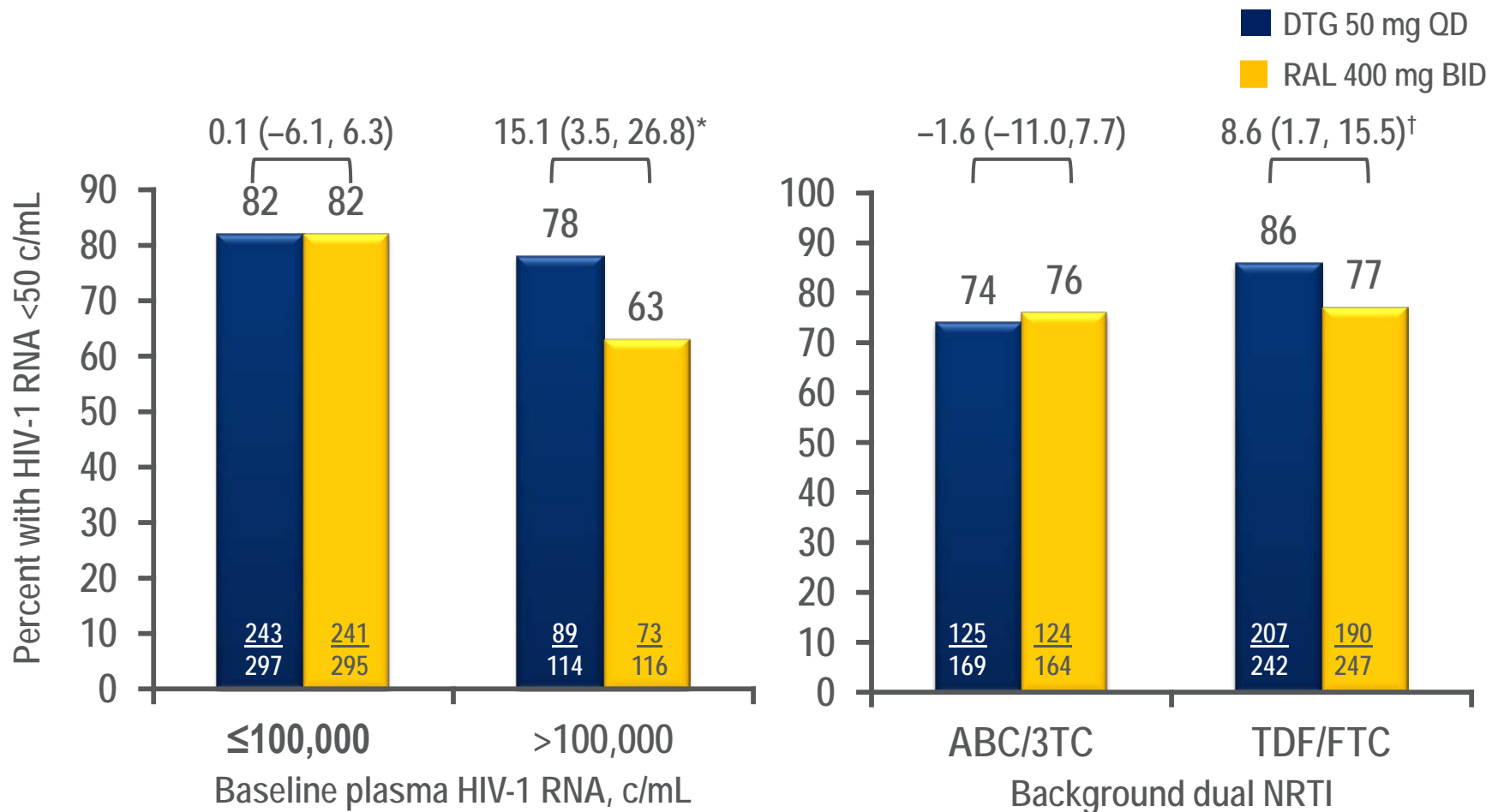
IN TREATMENT-NAÏVE PATIENTS, DTG WAS NON-INFERIOR TO RAL AT 96 WEEKS



Treatment	Number of responders/ total assessed, n (%)	Difference in proportion (95% CI) (DTG - RAL)	Adjusted difference in proportion (95% CI) (DTG - RAL)
DTG 50 mg QD	332/411 (81)	4.4% (-1.2%, 10.0%)	4.5% (-1.1%, 10.0%)
RAL 400 mg BID	314/411 (76)		

DTG and RAL were associated with similar increases in CD4+ cell count from baseline over time.^{1,2}

DTG EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD OR BACKGROUND REGIMEN (WEEK 96)



*P=0.026; †P=0.083; p-values evaluated using a test for homogeneity



CHANGES IN CD4+ CELL COUNT TO WEEK 96

Change from baseline in CD4 ⁺ cell count (cells/mm ³), median (IQR)	DTG 50 mg QD (N=411)	RAL 400 mg BID (N=411)
Week 4 ¹	87 (26, 149)	88 (32, 163)
Week 24 ¹	183 (100, 295)	182 (94, 296)
Week 48 ^{1,2}	230 (128, 338)	230 (139, 354)
Week 96 ^{3,4}	276 (159, 402)	264 (155, 396)

1. Adapted from Raffi F, et al. IAS 2012. Abstract THLB04
2. Adapted from Raffi F, et al. Lancet 2013;381:735–43
3. Adapted from Raffi F, et al. IAS 2013. Abstract TULBPE17
4. Raffi F, et al. Lancet Infect Dis 2013;13:927–35



MOST COMMON CLINICAL ADVERSE EVENTS TO WEEK 96

AEs, n (%)	DTG 50 mg QD (N=411)	RAL 400 mg BID (N=411)
WEEK 48^{1,2}		
Any event	339 (82)	340 (83)
Nausea	59 (14)	53 (13)
Headache	51 (12)	48 (12)
Nasopharyngitis	46 (11)	48 (12)
Diarrhoea	47 (11)	47 (11)
WEEK 96³		
Any event	349 (85)	349 (85)
Nausea	60 (15)	56 (14)
Nasopharyngitis	55 (13)	58 (14)
Diarrhoea	57 (14)	55 (13)
Headache	56 (14)	55 (13)

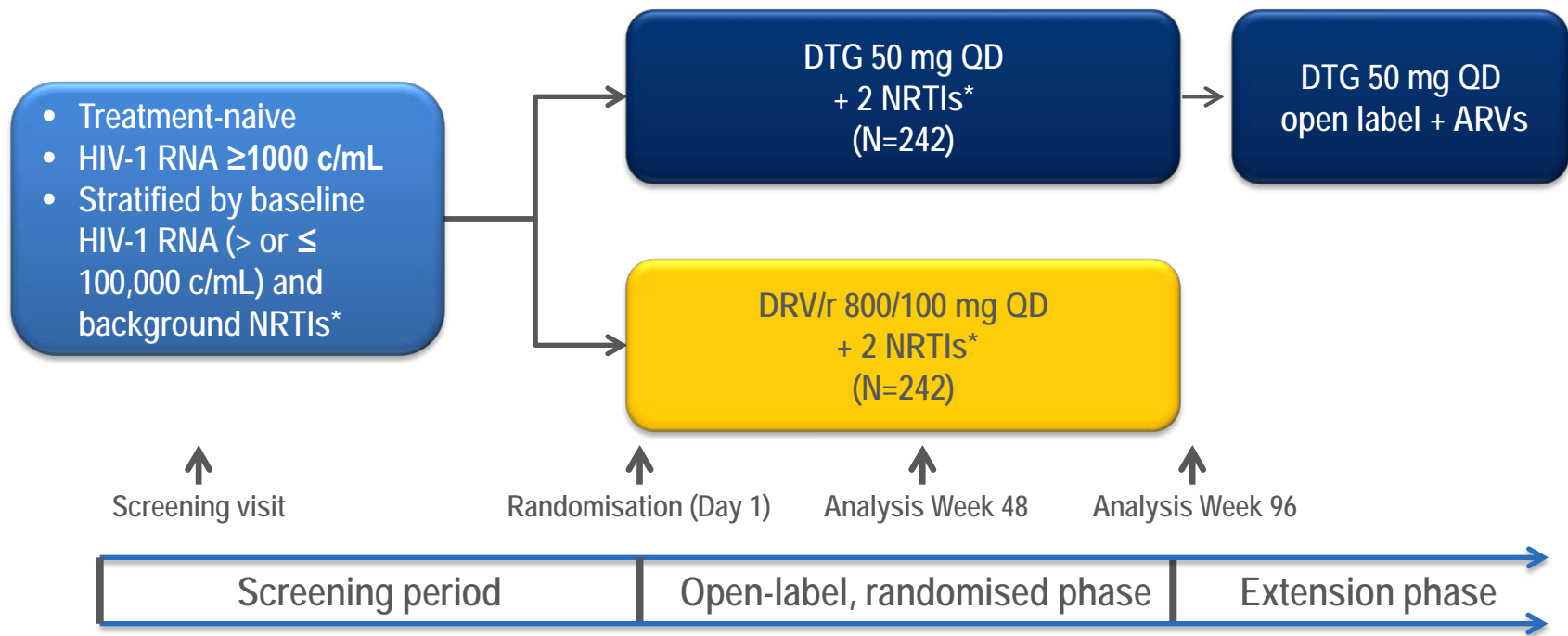
1. Adapted from Raffi F, et al. IAS 2012. Abstract THLB04

2. Adapted from Raffi F, et al. Lancet 2013;381:735–43

3. Adapted from Raffi F, et al. Lancet Infect Dis 2013;13:927–35; Supplementary appendix



FLAMINGO STUDY DESIGN^{1,2}



Primary endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48
(FDA Snapshot with a 12% non-inferiority margin and pre-specified tests for superiority)

*Stratified by HIV-1 RNA $> 100,000$ or $\leq 100,000$ c/mL and ABC/3TC or TDF/FTC

Adapted from 1. Clotet B, et al. Lancet 2014;383:2222–31, and 2. Molina JM et al. Lancet HIV 2015; 2: e127-e136

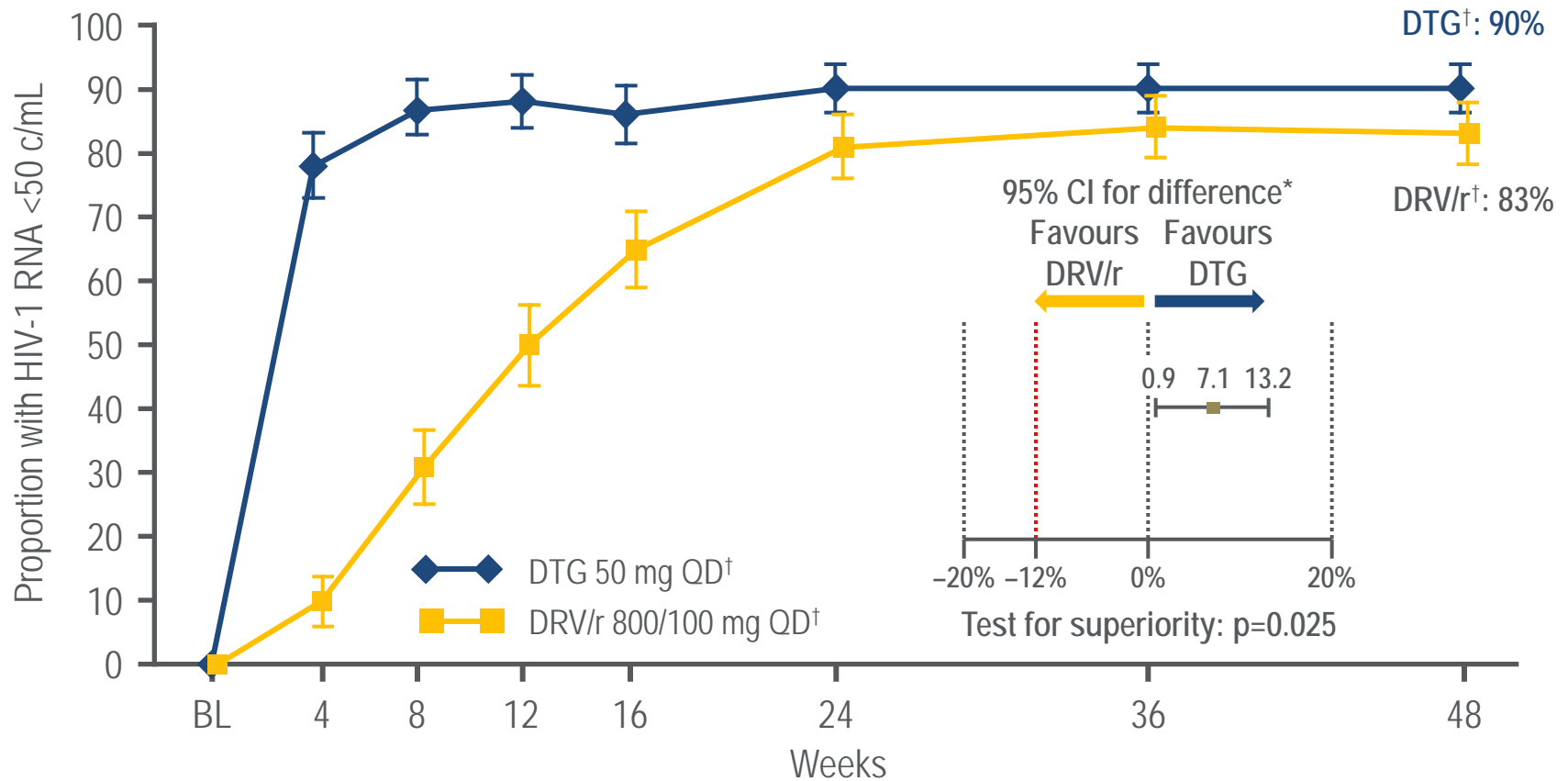


BASELINE CHARACTERISTICS

	DTG 50 mg QD (N=242)	DRV/r 800/100 mg QD (N=242)
Age (years), median	34	34
Female, %	13	17
African American/African heritage, %	25	22
HBV/HCV positive, %	4/7	2/6
Baseline HIV-1 RNA		
Median (log ₁₀ c/mL)	4.49	4.48
>100,000 c/mL, %	25	25
Baseline CD4 cell count		
Median (cells/mm ³)	390	400
<200 cells/mm ³ , %	10	10
Investigator-selected ABC/3TC, %	33	33



VIROLOGIC RESPONSE AT WEEK 48^{1,2}



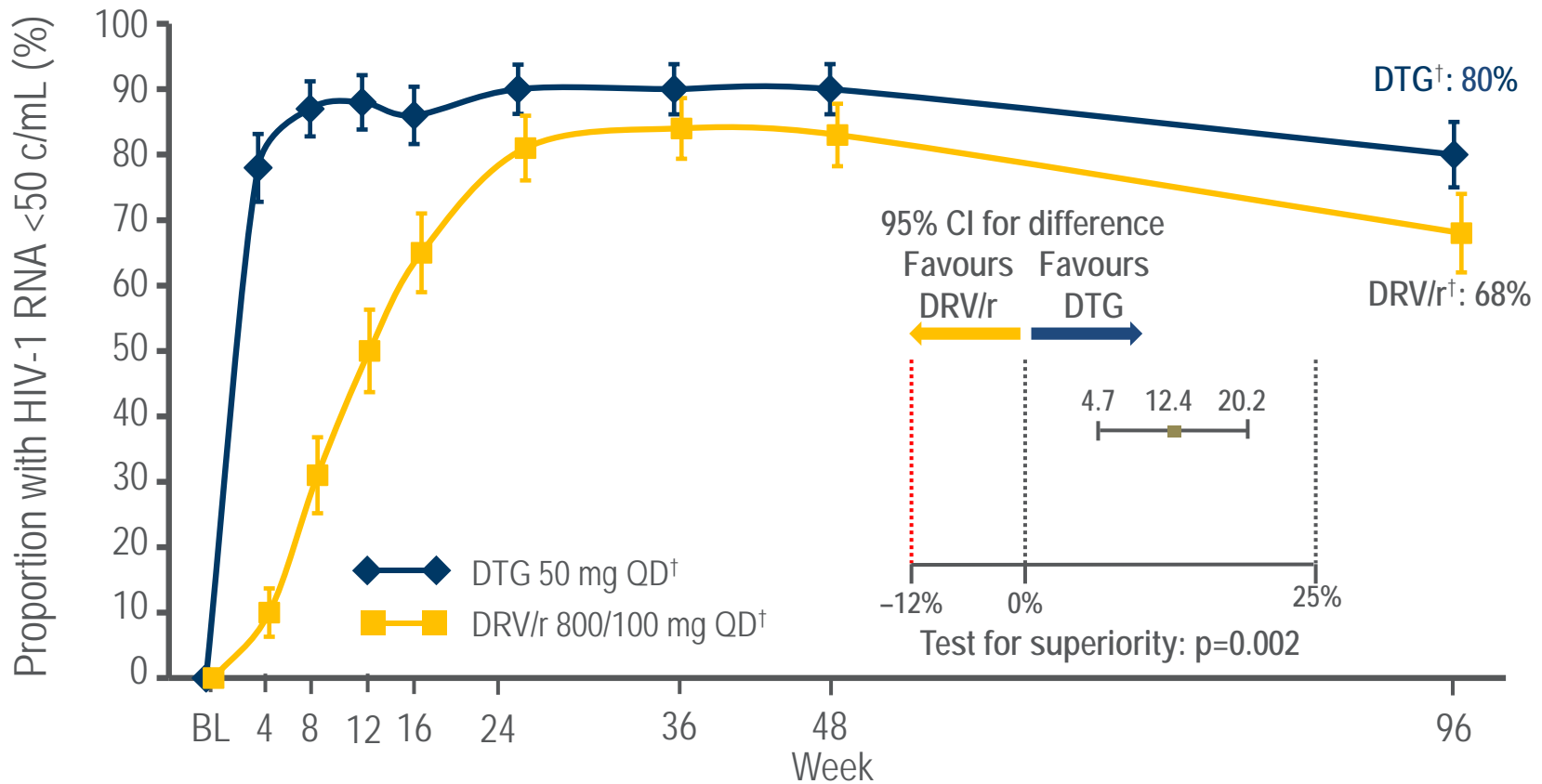
- Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r (difference [95% CI]: 7.4% [1.4–13.3])²

*Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy; [†]plus 2 NRTIs

. Adapted from 1. Clotet B, et al. Lancet 2014;383:2222–31
2. Clotet B, et al. Lancet 2014;383:2222–31. Supplementary appendix



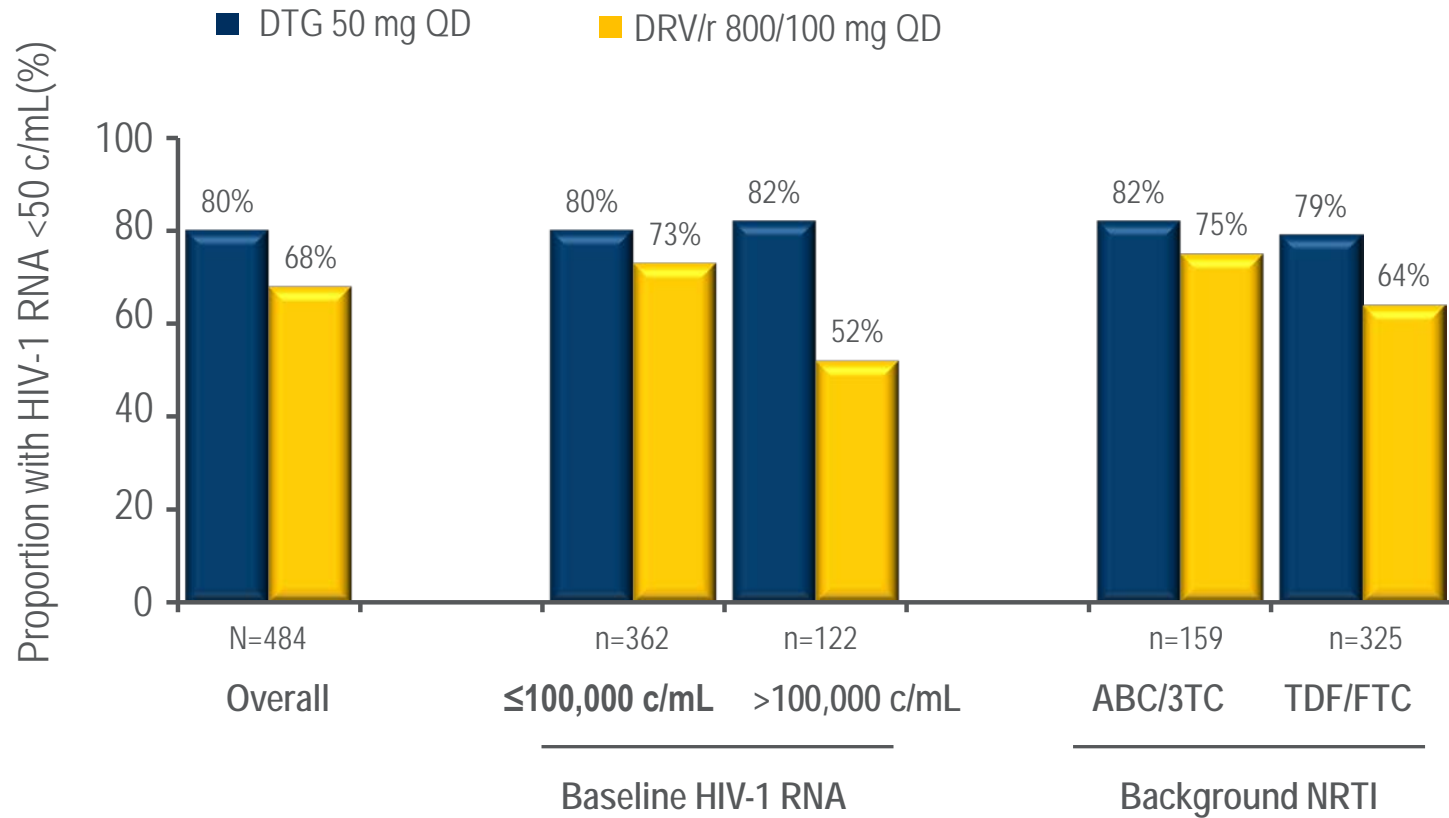
VIROLOGIC RESPONSE AT WEEK 96



- Differences largely driven by lower virologic failure rate and fewer withdrawals protocol deviation, loss to follow-up and withdrawal of consent in the DTG arm



VIROLOGIC RESPONSE BY BASELINE VIRAL LOAD AND DUAL NRTI THERAPY AT WEEK 96





MEDIAN (IQR) CHANGE FROM BASELINE TO WEEK 48&96 IN CD4+ CELL COUNT (CELLS/MM³)^{1,2}

At 48W : CD4 cell counts increased from baseline to week 48 by a median of 210 cells per microL in both group

At 96W : median change in CD4: 260 (DTG) vs 250 (DRV/r)

Adapted from

1. Clotet B, et al. Lancet 2014;383:2222–31
2. Molina JM et al. Lancet HIV 2015; 2: e127-e136



ADVERSE EVENTS OVER 96 WEEKS

n (%)	Week 48 DTG 50 mg QD (N=242)	Week 96 DTG 50 mg QD (N=242)	Week 48 DRV/r 800/100 mg QD (N=242)	Week 96 DRV/r 800/100 mg QD (N=242)
Overall	206 (85)	222 (92)	205 (85)	217 (90)
Common AEs (≥15% in either arm)				
Diarrhoea	41 (17)	44 (18)	70 (29)	74 (31)
Nausea	39 (16)	40 (17)	43 (18)	48 (20)
Headache	37 (15)	40 (17)	24 (10)	26 (11)
Discont due to AE/death	3(1)	5 (2)*	9 (4)	13 (5)†

*Suicide, acute hepatitis C, nephrolithiasis

†Hepatitis C, diarrhoea/nausea, dysgeusia, renal colic, substance abuse



FLAMINGO: CONCLUSIONS

DTG 50 mg QD demonstrated non-inferiority and statistical superiority to DRV/r 800/100 mg QD (both co-administered with 2 NRTIs) in the proportion of subjects achieving HIV-1 RNA <50 c/mL (FDA Snapshot) at Week 48 (p=0.025)¹ and Week 96 (p=0.002)²

- Non-inferiority was demonstrated between the DTG- and DRV/r-based regimens, with statistical superiority for the DTG arm concluded using a pre-specified testing procedure at Week 48 (90% vs 83%, respectively)¹ and Week 96 (80% vs 68%)²
- Overall statistical superiority (Snapshot analysis) was driven by:
 - a lower number of withdrawals due to AEs and other reasons in the DTG arm^{1,2}
 - fewer virologic non-responders (HIV-1 RNA >50 c/mL, FDA Snapshot), particularly among subjects with baseline HIV-1 RNA >100,000 c/mL, in the DTG arm^{1,2}
- No emergent primary INI, PI or NRTI mutations were seen in either arm over 96 weeks^{1,2}
- DTG was generally well tolerated in this treatment-naive population
 - there were few discontinuations due to AEs, with no significant differences in AEs leading to withdrawal by subgroup over 96 weeks^{1,2}
 - small nonprogressive increases in serum creatinine were observed in the DTG arm due to inhibition of OCT2^{1,2}
 - more favourable lipid parameters in the DTG arm^{1,2}
- Satisfaction questionnaires showed improvements in treatment satisfaction with DTG over DRV/r at Week 96

TREATMENT-EMERGENT RESISTANCE IN TREATMENT-NAIVE PATIENTS

	Spring-2 (96 weeks) ¹		Single (144 weeks) ²		Flamingo (96 weeks) ⁴	
	DTG 50 mg QD (n=411)	RAL 400 mg BID (N=411)	DTG 50 mg QD + ABC/3TC (N=414)	TDF/FTC/EFV QD (N=419)	DTG 50 mg QD (N=242)	DRV/r 800/100 mg QD (N=242)
Subjects with PDVF	22 (5)	29 (7)	39 (9)	22 (8)	2 (<1)	2 (<1)
TE INI-resistance	0	1	0 [†]	–	0	–
TE NRTI resistance	0	4*	0	1 (K65R)	0	0
TE NNRTI resistance	–	–	–	6 (K101E, K103N, G190A) [‡]	–	–
TE PI resistance	–	–	–	–	–	0

*INI mutations T97T/A + E138E/D + V151V/I + N155H, plus NRTI mutations A62A/V + K65R + K70K/E + M184V (n=1); A62A/V (n=1); M184M/I (n=1); M184M/V (n=1)

[†]E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

[‡]K101E (n=1); K103N (n=1); K103K/N (n=2); G190A (n=1); K103N + G190A (n=1)

No treatment-emergent INI or NRTI resistance was seen through up to 96 weeks amongst treatment-naive patients receiving DTG + 2 NRTIs in Phase III clinical studies

3TC, lamivudine; ABC, abacavir; BID, twice daily; EFV, efavirenz; FTC, emtricitabine; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI nucleoside-analogue reverse transcriptase inhibitor; PDVF, protocol-defined virological failure; PI, protease inhibitor; QD once daily; TE treatment-emergent

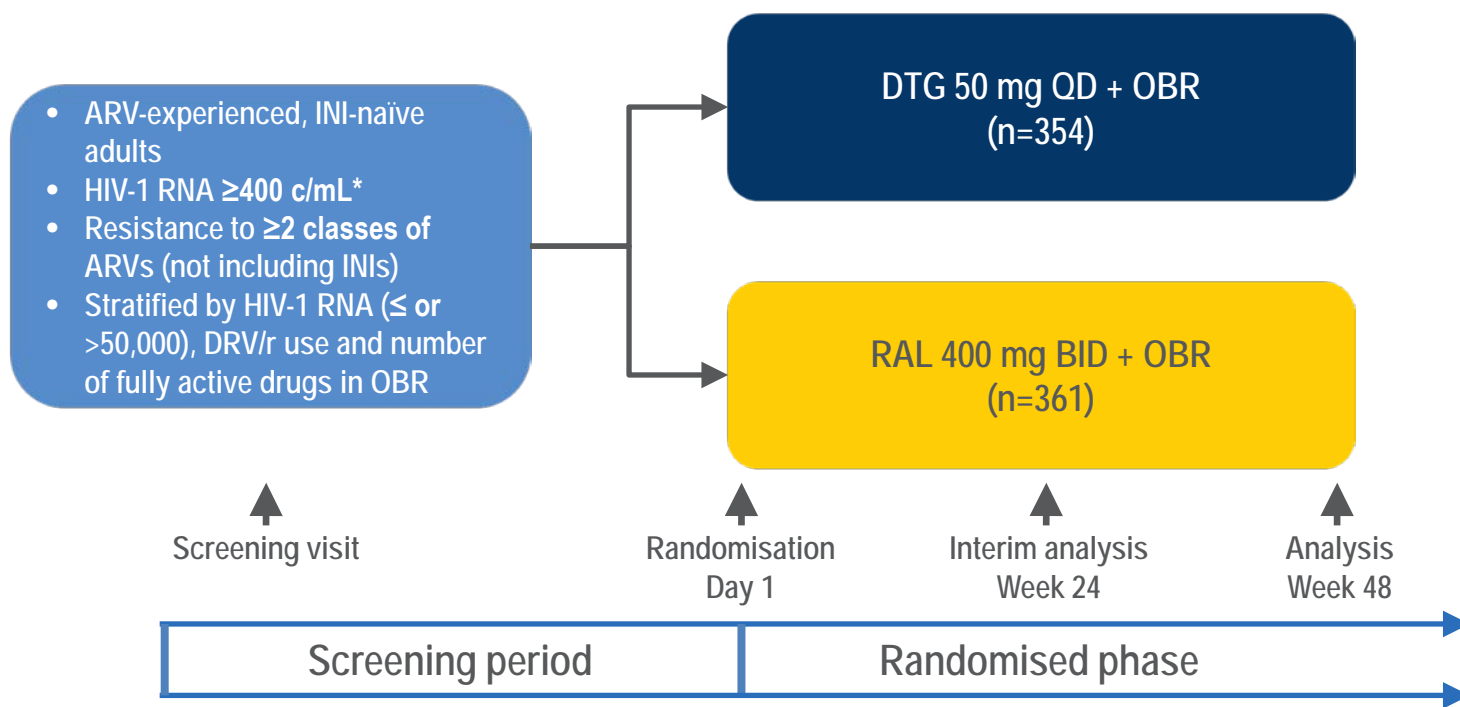
1. Raffi F, et al. Lancet Infect Dis 2013;13:927-35;

2.Pappa et al ICAAC Washington USA Sept 2014;

3. Clotet B, et al. Lancet 2014 March 31 [Epub]

4. Molina JM, et al. Lancet 2015

SAILING: PHASE III TRIAL IN TREATMENT-EXPERIENCED, INI-NAÏVE SUBJECTS



Primary endpoint: proportion of subjects with HIV-1 RNA <50 c/mL at Week 48

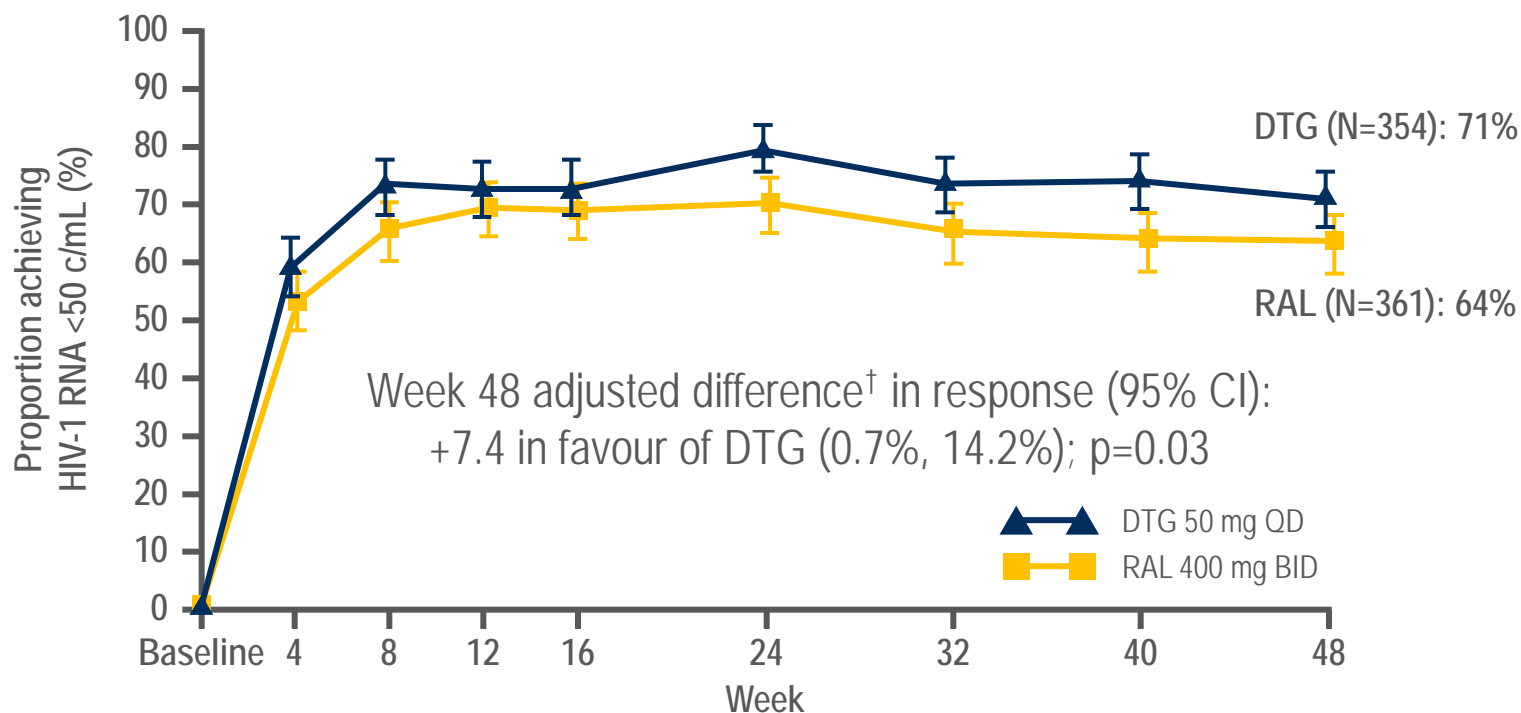
*With two consecutive HIV-1 RNA ≥ 400 c/mL, unless screening HIV-1 RNA $>1,000$ c/mL

ARV, antiretroviral; INI integrase inhibitor; OBR, optimised background regimen.

Adapted from: Cahn P, et al. Lancet 2013;382:700–8

PROPORTION OF SUBJECTS WITH HIV-1 RNA <50 C/ML (SNAPSHOT*)

DTG 50 mg QD was statistically superior to RAL 400 mg BID at Week 48



Mean (SD) CD4+ change from baseline to Week 48 was similar between arms: DTG: +162 (151) cells/mm³; RAL: +153 (144) cells/mm³

*Analysis based on all subjects randomised who received ≥ 1 dose of study drug, excluding four subjects at one site with violations of good clinical practice

[†]Adjusted difference based on stratified analysis adjusting for BL HIV-1 RNA ($\leq 50,000$ c/mL vs $> 50,000$ c/mL), DRV/r use without primary PI mutations and baseline PSS (2 vs <2)

CI, confidence interval; PI, protease inhibitor; PSS, phenotypic sensitivity score; SD, standard deviation

PDVF SUBJECTS WITH TREATMENT-EMERGENT INTEGRASE SUBSTITUTIONS FROM BASELINE

n (%)	Week 24		Week 48	
	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
PDVF (defined as 2 consecutive HIV-1 RNA values >400 c/mL, on or after Week 24)	14 (4)	34 (9)	21 (6)	45 (12)
INI mutations present for patients with determinable genotype/phenotype, n (%)	2/9 (22) [†]	9/27 (33)	4/17 (24) [‡]	16/38 (42)

[†]Mutation(s), DTG FC: R263R/K, FC=1.12; R263K, FC=1.93

[‡]Mutation(s), DTG FC: R263R/K, FC=1.1; R263K, FC=1.9; E138T/A and T97A, DTG FC > maximum (baseline sample testing showed this patient enrolled with pre-existing RAL resistance [Q148] and FC > maximum for RAL and DTG); V151V/I, DTG FC=0.92

Adapted from
Cahn P, et al. Lancet 2013;382:700-8
(supplementary appendix)

VIROLOGY

The proportion of subjects with evidence of INI genotypic or phenotypic resistance was significantly lower in the DTG arm than in the RAL arm¹

- DTG 50 mg QD was statistically superior in proportion of subjects harbouring virus with evidence of INI resistance by Week 48 (DTG: 4/354 [1%]; RAL: 17/361 [5%]; adjusted difference: 3.7%, P=0.003)¹
- Regarding genotypic resistance
 - Two subjects on DTG harboured virus with K substitutions at position R263 at PDVF (in each case, fold change IC₅₀ for both DTG and RAL was <2). Two other subjects on DTG were found to have additional mutations. One subject harboured virus with mutations E138T/A and T97A; the second subject harboured virus with V151V/I mutations²
 - Sixteen subjects on RAL had genotypic resistance consistent with prior RAL studies; in these subjects, high-level phenotypic resistance was present but cross-resistance to DTG was limited¹
- The difference in treatment-emergent resistance to background regimen was also statistically significant*¹
 - DTG 1% vs RAL 3%, adjusted difference (95% CI) of -2.2% (-4.3%, -0.1%)²

*This analysis was pre-specified but was unadjusted for multiple testing¹

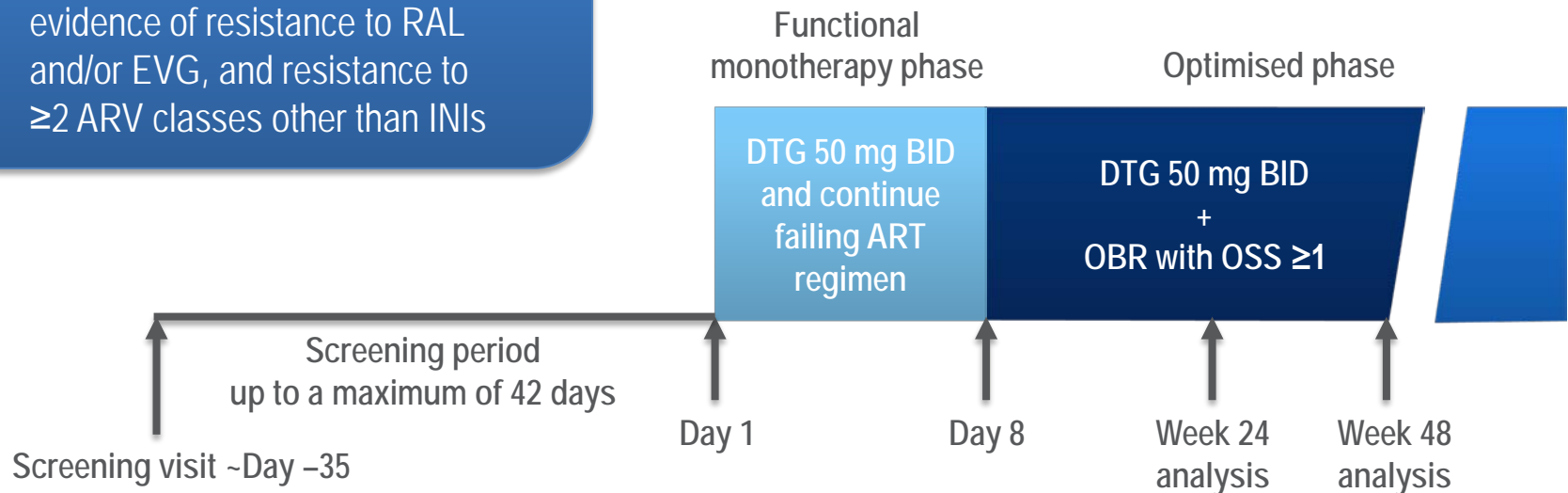
1. Cahn P, et al. Lancet 2013;382:700-8

2. Cahn P, et al. Lancet 2013;382:700-8. Supplementary appendix

VIKING-3: STUDY DESIGN (N=183)

Main eligibility criteria

- HIV-1 RNA ≥ 500 c/mL
- Screening or documented historical evidence of resistance to RAL and/or EVG, and resistance to ≥ 2 ARV classes other than INIs



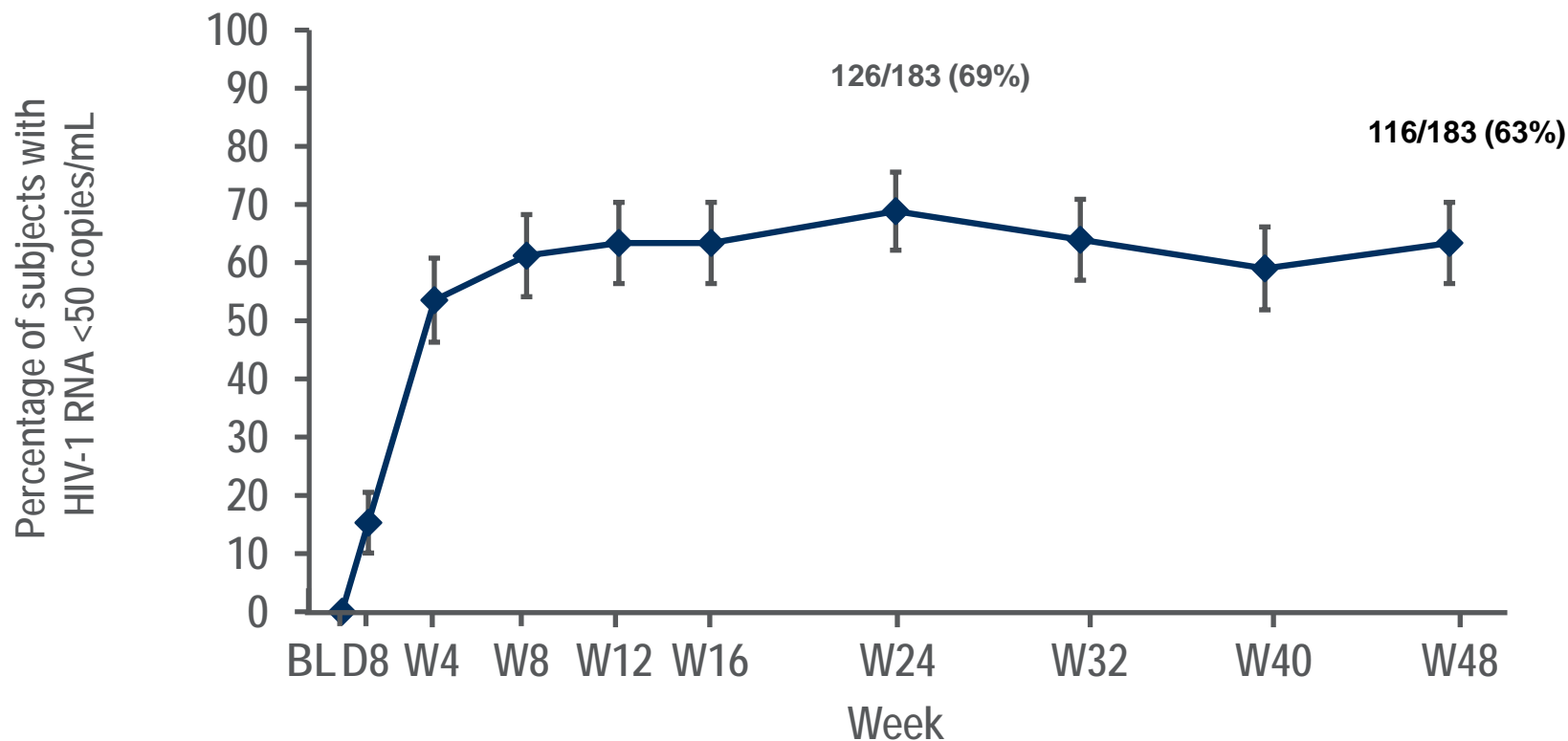
OSS, overall susceptibility score, determined by Monogram Biosciences net assessment



BASELINE CHARACTERISTICS

Characteristic, n (%) [*]	DTG 50 mg BID (N=183)
Male gender	141 (77)
African American/African heritage	49 (27)
CD4 ⁺ cells/mm ³ , median (IQR)	140 (40–330)
CDC class C, n (%)	102 (56)
Hepatitis B and/or hepatitis C positive, n (%)	38 (21)

EFFICACY OF DTG OVER TIME (SNAPSHOT, ITT-E)



Day 8 efficacy: DTG was associated with significant reductions from baseline in HIV-1 RNA; change from baseline: $-1.43 \log_{10}$ c/mL HIV-1 RNA (95% CI: -1.52 to -1.34 ; $p < 0.001$)¹



WEEK 24 AND WEEK 48 RESPONSE BY BASELINE INI MUTATIONS (ITT-E, SNAPSHOT ALGORITHM)

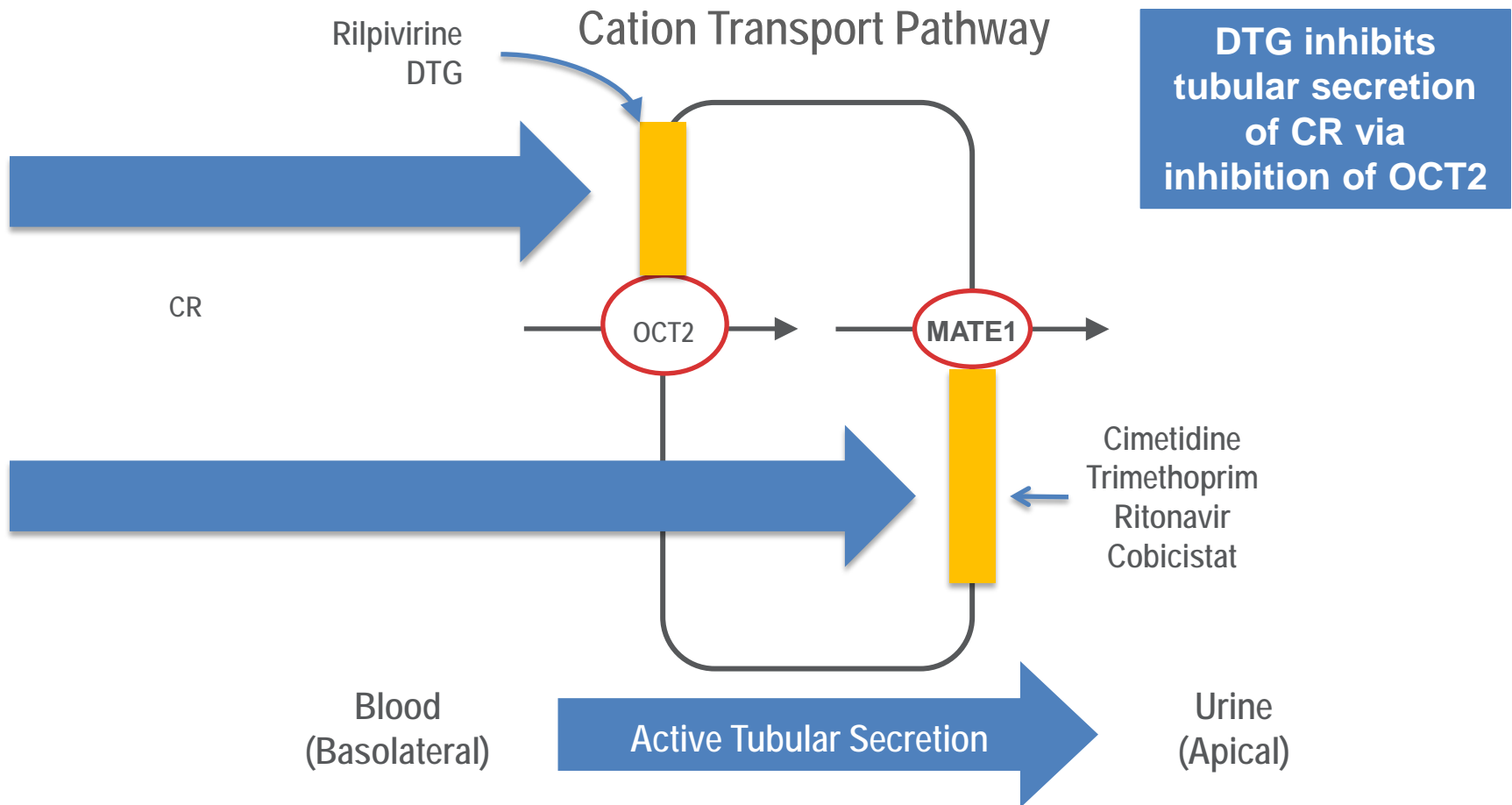
Derived INI Mutation Group at BL	N	% With <50 c/mL HIV-1 RNA at Week 24	% With <50 c/mL HIV-1 RNA at Week 48
Total	183	69%	63%
No Q148	126	79%	71%
Q148 + 1 secondary mutation*	36	58%	56%
Q148 + ≥ 2 secondary mutations*	21	24%	29%

*Key secondary mutations were G140A/C/S, L74I and E138A/K/T

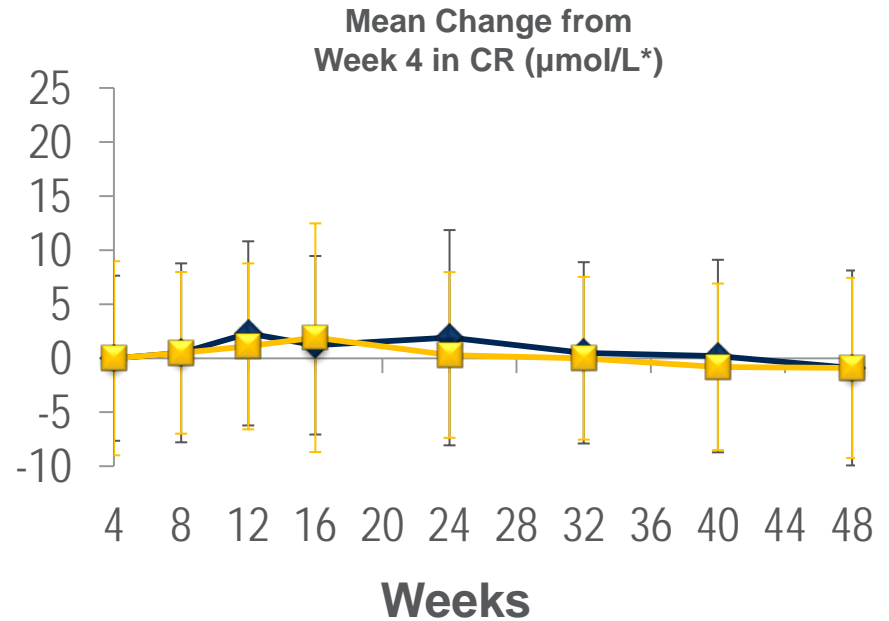
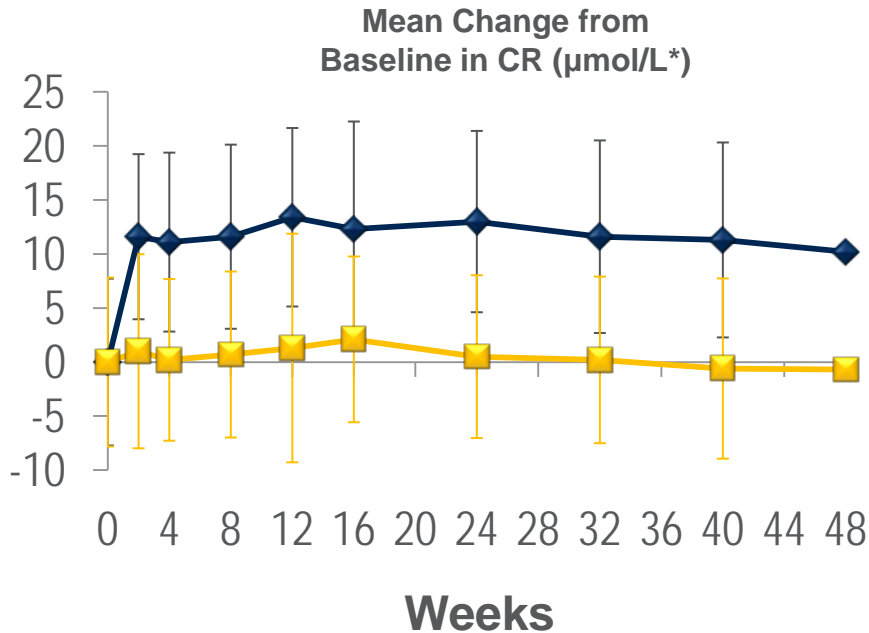
- Antiviral response was sustained through Week 48
- Difference in response rates between Week 24 and Week 48 was primarily for non-virological reasons

RENAL

DOLUTEGRAVIR LEADS TO INHIBITION OF RENAL OCT2 AND TUBULAR CREATININE ELIMINATION



RENAL SAFETY OVER 48 WEEKS



Urine albumin/creatinine (mg/mmol CR)

DTG 50 mg+ABC/3TC QD

EFV/TDF/FTC QD

Median change (IQR) from baseline to Week 48

0.00 (-0.30, 0.30)

+0.05 (-0.20, 0.30)

Mean change from baseline in creatinine at Week 48:

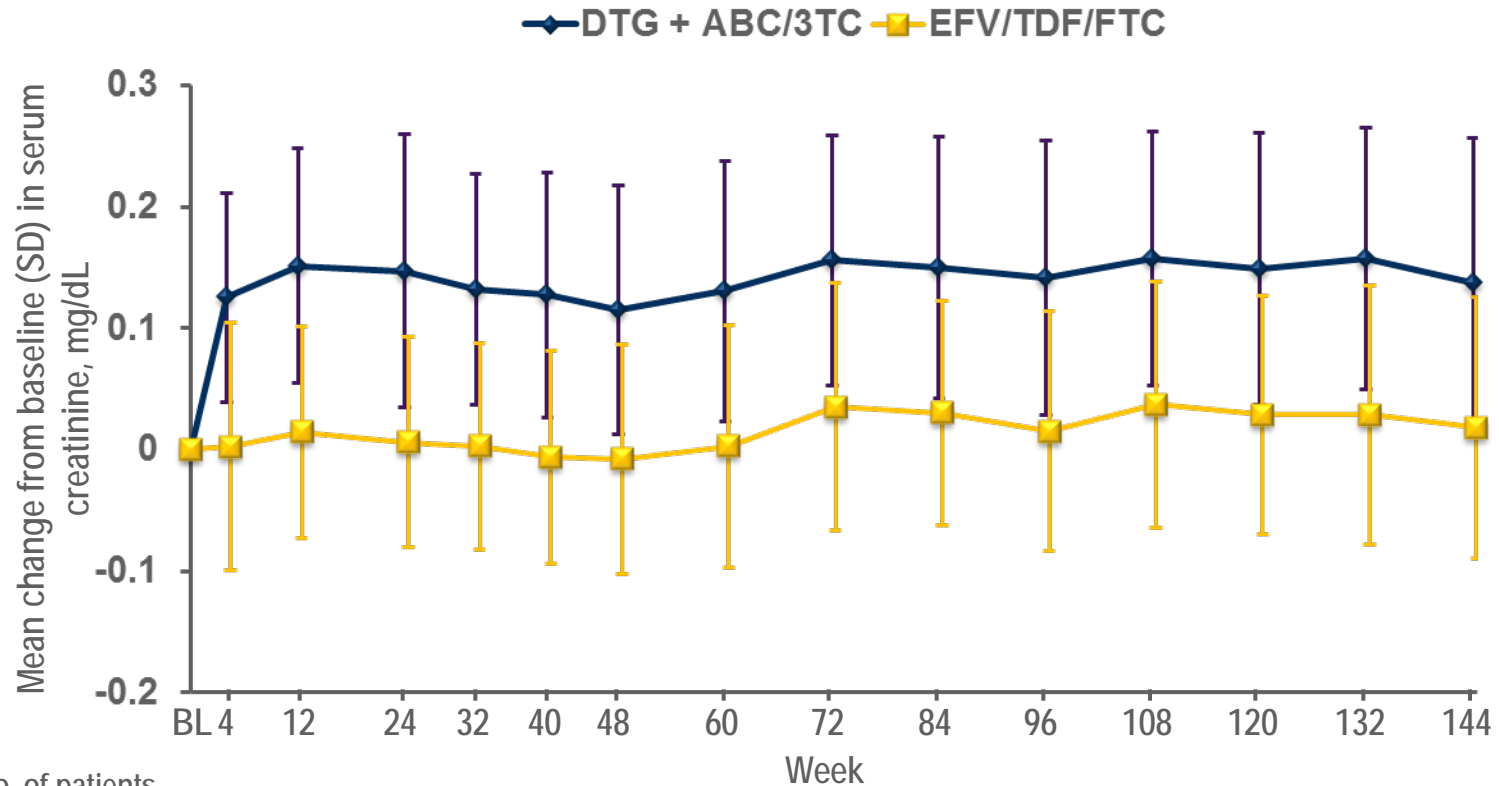
DTG+ABC/3TC: +0.11mg/dL (+9.27 $\mu\text{mol/L}$);

EFV/TDF/FTC: -0.01 mg/dL (-0.88 $\mu\text{mol/L}$)

*10 $\mu\text{mol/L}$ =0.11mg/dL

Adapted from Walmsley S, et al. N Engl J Med 2013;369:1807-18

CREATININE PROFILE OVER TIME



	No. of patients															
	BL	4	12	24	32	40	48	60	72	84	96	108	120	132	144	
DTG + ABC/3TC	399	399	391	387	379	367	369	359	355	350	344	336	332	322	312	
EFV/TDF/FTC	390	390	375	363	352	345	342	330	317	311	308	300	288	282	267	

Parameter	DTG + ABC/3TC QD			EFV/TDF/FTC QD		
	Week 48	Week 96	Week 144	Week 48	Week 96	Week 144
Urine albumin/creatinine ratio (mg/mmol)	0	0	0	0.05	0.05	0.10
Median change (IQR)	(-0.3, 0.3)	(-0.3, 0.2)	(-0.4, 0.2)	(-0.2, 0.3)	(-0.2, 0.3)	(-0.2, 0.4)

Clin Drug Investig
DOI 10.1007/s40261-014-0266-2

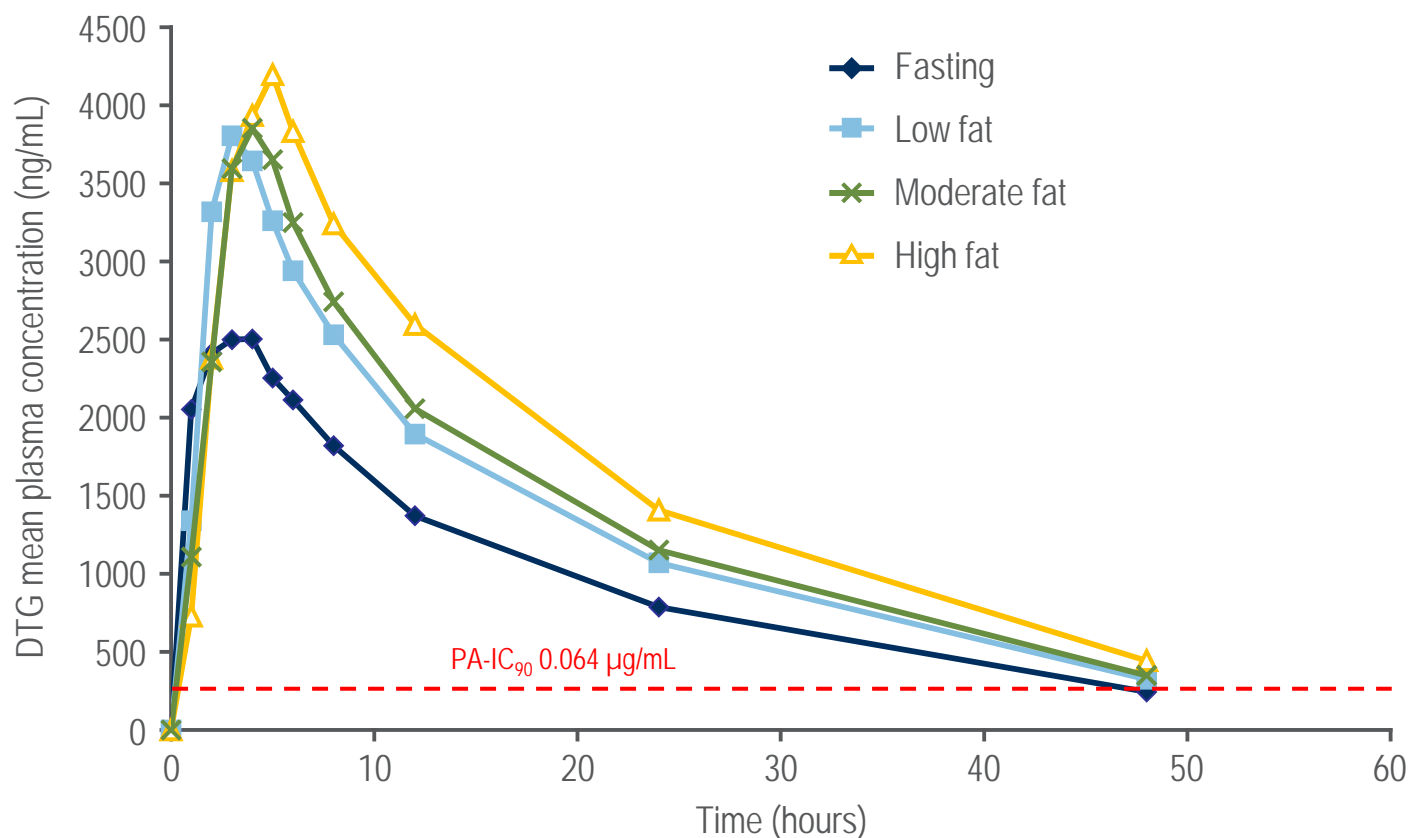
ORIGINAL RESEARCH ARTICLE

Comparative Changes of Lipid Levels in Treatment-Naive, HIV-1-Infected Adults Treated with Dolutegravir vs. Efavirenz, Raltegravir, and Ritonavir-Boosted Darunavir-Based Regimens Over 48 Weeks

Romina Quercia • Jeremy Roberts •
Louise Martin-Carpenter • Carlos Zala

A broadly neutral lipid effect, as shown in this analysis, adds to the strength of dolutegravir as an initial therapy for the treatment of HIV.

NO FOOD REQUIREMENT IN INI-NAÏVE PATIENTS ALLOWS EASIER CONVENIENCE



Low, moderate and high fat meals increased DTG* AUC_{0-∞} by 33%, 41% and 66%, respectively in INI-naïve patients, dose with or without food. In INI-resistant patients, preferably dose with food

EFFECTIVE AND RAPID DISTRIBUTION TO CSF

- Plasma protein binding: $\geq 98.9\%$ ¹
- Blood:plasma ratio: 0.44–0.54 → minimal association with blood cellular components¹
- A Phase IIIb study assessed the distribution of DTG in CSF²
 - DTG concentrations in CSF at Weeks 2 and 16 averaged 13–16 ng/ml (comparable to unbound concentration)
 - Exceeded the in vitro IC_{50} against wild-type viruses (0.2 ng/mL)² for all subjects, suggesting that DTG was able to achieve therapeutic concentrations in the CSF

DTG in Plasma vs CSF (N = 12)²

	Week 2 Mean (SD)	Week 16 Mean (SD)
Plasma total ($\mu\text{g/mL}$)	3.42 (0.83)	3.03 (1.35)
Plasma unbound (ng/mL)	16.8 (4.10)	23.0 (8.24)
Unbound fraction (%)	0.495 (0.082)	0.995 (1.05)
CSF total (ng/mL)	16.2 (5.84)*	12.6 (3.64)
CSF:plasma total (%)	0.467 (0.178)*	0.546 (0.480)

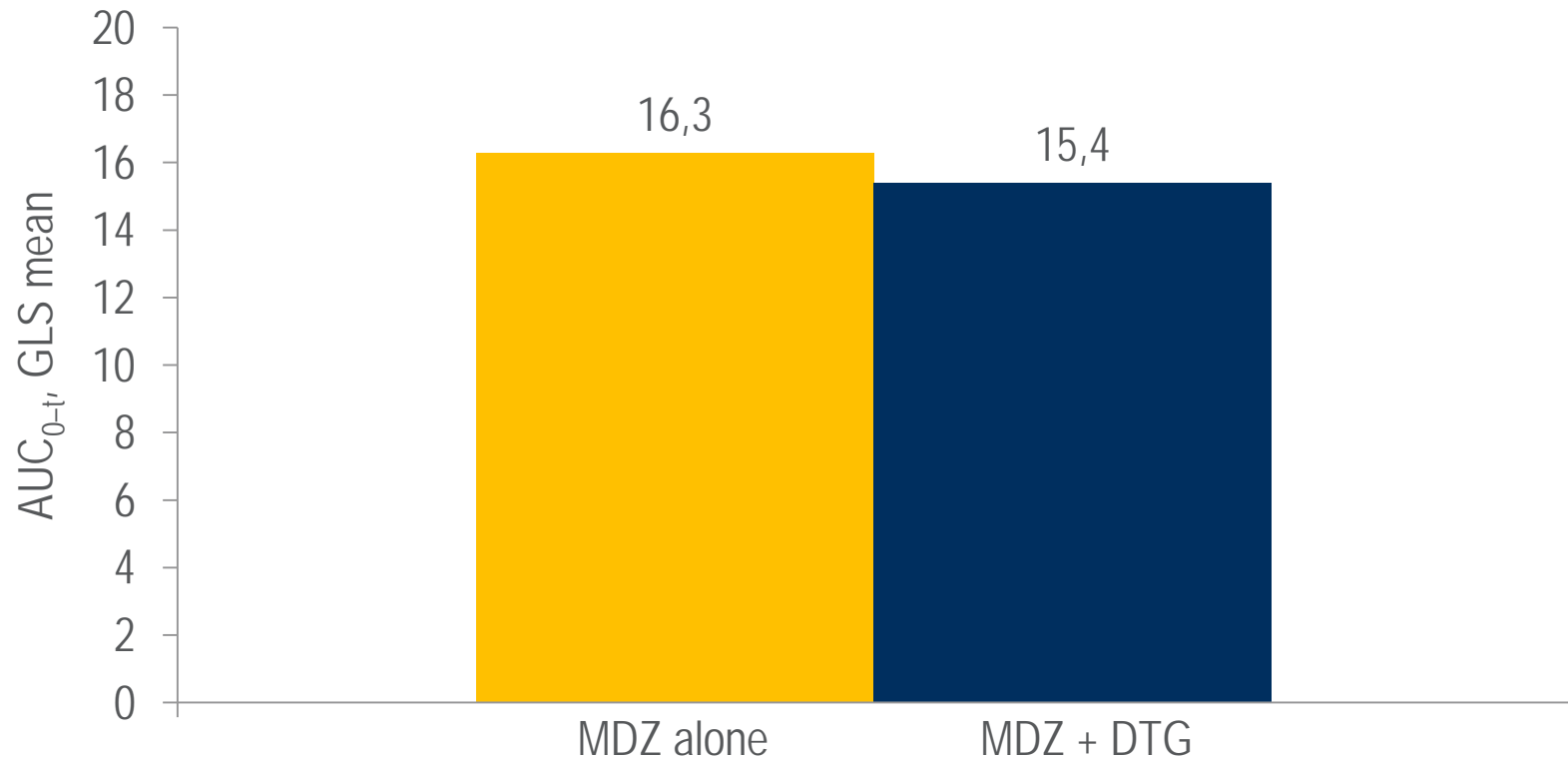
*N = 11



NO IMPACT OF DTG ON CYP3A

Midazolam (MDZ) being used as a CYP3A metabolic probe

GLS mean ratio (MDZ+DTG/MDZ alone): 0.945 (90% CI: 0.82–1.10)



Plasma MDZ AUC_{0-t} was similar with MDZ + DTG 25 mg versus MDZ alone

CI, confidence interval; DTG, dolutegravir;

GLS, geometric least squares

Adapted from Min S, et al. Antimicrob Agents Chemother 2010;54:254–258

COMPARISON OF CLINICAL PK PROFILES FOR CURRENT INTEGRASE INHIBITORS

	DTG ¹	RALTEGRAVIR ²	ELVITEGRAVIR ^{3,4}
Clinical dose	50 mg QD (INI-naïve), 50 mg BD (INI-resistant)	400 mg BID	150 mg QD boosted with cobicistat
t _{1/2}	~14 hours	~9 hours	Elvitegravir ~13 hours (boosted) Cobicistat ~3.5 hours
PK variability	Low to moderate	High	Moderate (with boosting) ⁴
Food requirement	In INI-naïve patients, take with or without food. In INI-resistant patients, preferably with food	No food restriction, but fat content affects absorption and increases PK variability	Take with food
Protein binding	≥98.9%	83%	98–99%
Metabolism and excretion	UGT1A1 (major), CYP3A (minor), renal elimination <1%	UGT1A1, renal elimination ~9%	Elvitegravir- CYP3A (major), UGT1A1/3 (minor), renal elimination 6.7% Cobicistat – CYP3A and/or CYP2D6-mediated oxidation

IMPACT OF ARVs ON DOLUTEGRAVIR EXPOSURE

Co-administered drug	DTG C _τ or C ₂₄ Geometric mean change	Recommendation
Protease inhibitors		
DRV/r 600/100 mg BID*	↓38%	No DTG dose adjustment required
ATV 400 mg OD*‡	↑180%	No DTG dose adjustment required
ATV/r 300/100 mg OD*	↑121%	No DTG dose adjustment required
NNRTIs		
RPV 25 mg OD	↑22%	No DTG dose adjustment required
EFV 600 mg OD	↓75%	DTG 50 mg BID should be given [‡]
ETR 200 mg BD	↓88%	DTG should not be given with ETR without co-administration of ATV/r, DRV/r or LPV/r
NRTIs		
TDF 300 mg OD	↓8%	No DTG dose adjustment required

C_τ: Trough concentration

*DTG 30 mg OD studied; ‡ Unboosted ATV is not licensed in the EU; †INI-naive patients; alternative combinations should be considered where possible for INI-experienced patients with certain INI-associated resistance substitutions or clinically suspected INI resistance

IMPACT OF DRUGS USED TO TREAT TB AND HCV ON DOLUTEGRAVIR EXPOSURE

Co-administered drug	DTG C_{τ} or C_{24} <i>Geometric mean change</i>	Recommendation ¹
Anti-TB drug		
Rifampicin 600 mg OD*	↓72%	DTG 50 mg BID should be given [‡]
Rifabutin 300 mg OD	↓30%	No DTG dose adjustment required
Anti-HCV drug		
TVR 750 mg every 8 hours	↑37%	No DTG dose adjustment required
BCV 800 mg every 8 hours	↑8%	No DTG dose adjustment required

C_{τ} : Trough concentration

*DTG 50 mg BID studied

[‡]INI-naïve patients; alternative combinations should be considered where possible for INI-experienced patients with certain INI-associated resistance substitutions or clinically suspected INI resistance

IMPACT OF ACID-REDUCING AGENTS AND MULTIVITAMINS ON DTG EXPOSURE

Co-administered drug	DTG C_{τ} or C_{24} <i>Geometric mean change</i>	Recommendation
Antacids and supplements[‡]		
Magnesium / aluminium-containing antacid	AUC* ↓74%	Take antacids and supplements a minimum of 2 hours after or 6 hours before DTG ¹
Calcium supplements	↓39%	
Iron supplements	↓56%	
Multivitamins	↓32%	
Acid-lowering agents		
Omeprazole	↓5%	No significant effect observed ²

C_{τ} : Trough concentration

* C_{τ} not available in UK SmPC

[‡] Complex binding to polyvalent ions

1. Tivicay EU SmPC, May 2015

2. Patel P et al. J Antimicrob Chemother 2011; 66: 1567–1572

IMPACT OF OTHER DRUGS ON DTG EXPOSURE

Co-administered drug	DTG C_{τ} or C_{24} Geometric mean change	Recommendation ¹
Oral contraceptives		
Ethinyl estradiol 0.035 mg*	AUC** ↑3%	No DTG dose adjustment required
Norgestromin 0.25 mg*	AUC** ↓2%	No DTG dose adjustment required
Opioids		
Methadone (individualised dose)	↓1%	No DTG dose adjustment required
Steroids		
Prednisone 60 mg OD	↑17%	No DTG dose adjustment required

C_{τ} : Trough concentration

*DTG 50 mg BID studied; †DTG levels not assessed

** C_{τ} not available in UK SmPC. Values from US Prescribing Information:²
↑2% and ↓7% respectively

1. Tivicay EU SmPC, May 2015
2. Tivicay US Prescribing Information, August 2013

IMPACT OF OCT2 INHIBITION BY DTG ON DOFETILIDE AND METFORMIN

Co-administered drug	Potential effect on concentration of co-administered drug	Recommendation
Dofetilide*	Increase	DTG and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration
Metformin	Increase	Close monitoring of metformin efficacy and safety is recommended when starting or stopping DTG in patients receiving metformin. A dose adjustment of metformin may be necessary

*Dofetilide is an anti-arrhythmic drug which is not licensed in Europe

CONCLUSION

- Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age.
- Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class. The recommended dose of dolutegravir is 50 mg (one tablet) orally once daily.
- Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected). The recommended dose of dolutegravir is 50 mg (one tablet) twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern.
- No dosage adjustment is required in patients with mild, moderate or severe ($\text{CrCl} < 30 \text{ mL/min}$, not on dialysis) renal impairment.
- No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B).

LATEST ARTICLES

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 - [Drug Interactions - Elvitegravir/cobicistat and methadone.](#)
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INTERACTIONS ON MOBILE DEVICES

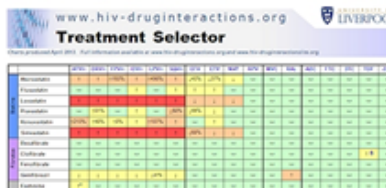
HIV iCharts - we want your opinions

Recent changes to the Apple operating system have caused issues with the update feature of the HIV iCharts app. We are taking this opportunity to investigate alternative options for accessing our drug interaction information on mobile devices and would be grateful if you could take a few minutes to answer a few short questions and to give us any comments.

[Click here to take the survey](#)

TREATMENT SELECTOR TABLES

Treatment Selector Tables - now with dolutegravir



We have produced a series of printable tables showing interactions between key antiretrovirals and drugs used to treat a range of common comorbidities. The tables can be accessed from the Printable Chart & Treatment Selector sub menu on the Interaction Charts menu.



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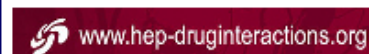
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SHORT SMPC

Tivicay 50 mg plėvele dengtos tabletės. Vienoje tabletėje yra dolutegravio natrio druskos kiekis atitinkantis 50 mg dolutegravio. **Receptinis** vaistinis preparatas. **Indikacijos.** Vartoti kartu su kitais antiretrovirusiniais vaistiniais preparatais gydant žmogaus imunodeficitu virusais (ŽIV) užsikrėtusius suaugusiuosius ir vyresnius kaip 12 metų paauglius. **Dozavimas.** 50 mg (viena tabletė) per burną vieną kartą per parą. Vartoti du kartus per parą, jeigu vartojamas kartu su kai kuriais vaistiniais preparatais (pvz.: efavirenzu, nevirapinu, tipranaviru / ritonaviru arba rifampicinu). Kai yra atsparumas integrazių klasei (įrodytas arba kliniškai įtariamasis) rekomenduojama dolutegravio dozė yra po 50 mg du kartus per parą. Atsargiai vartoti pacientams, kuriems yra sunkus kepenų funkcijos sutrikimas. Galima vartoti valgant arba be maisto. **Kontraindikacijos.** Padidėjęs jautrumas veikliajai arba bet kuriai pagalbinei medžiagai. Vartojimas kartu su dofetilidu. **Specialūs įspėjimai ir atsargumo priemonės.** Nors įrodytas antiretrovirusinio gydymo virusų slopinimo veiksmingumas reikšmingai sumažinant kitų asmenų užkrėtimo virusais lytiniu keliu riziką, liekamosios rizikos paneigti negalima. Kad būtų išvengta kitų asmenų užkrėtimo virusais, reikia laikytis atsargumo priemonių pagal nacionalines rekomendacijas. Gali pasireikšti padidėjusio jautrumo reakcijos, kurios apibūdintos išbėrimu, konstituciniais pokyčiais ir kartais organų funkcijos sutrikimais, įskaitant sunkias kepenų reakcijas. Jeigu atsiranda padidėjusio jautrumo reakcijų požymių, reikia nedelsiant nutraukti dolutegravio vartojimą. Pradėjus kombinuotą antiretrovirusinį gydymą (KARG), gali išsivystyti uždegiminė reakcija į besimptomius arba likusius sąlyginai patogeninius mikroorganizmus. Buvo pranešta apie autoimuninius sutrikimus (pvz., Greivso [Graves] liga), vis dėlto tokių sutrikimų atsiradimo laikas labai skiriasi ir jie gali pasireikšti praėjus daug mėnesių nuo gydymo pradžios. Reikia stebėti pacientų, kurie kartu yra užsikrėtę hepatito B ir (arba) C infekcija, biocheminius kepenų funkcijos rodmenis. Nors manoma, kad etiologija susijusi su daugeliu veiksnių, buvo pranešta apie osteonekrozės atvejus pacientams, sergantiems progresavusia ŽIV liga ir (arba) patyrusiems ilgalaikę KARG ekspoziciją. Pacientams reikia patarti, kad kreiptųsi medicininės pagalbos, jeigu pasireiškia sąnarių diegliai ir skausmai, sąnarių sąstingis arba darosi sunku judėti. **Sąveika su kitais vaistiniais preparatais ir kitokia sąveika.** Dolutegraviras eliminuojamas daugiausia metabolizmo veikiant UGT1A1 būdu. Tivicay negalima vartoti kartu su etravirinu, nevartojant kartu atazanaviro / ritonaviro, darunaviro / ritonaviro arba lopinaviro / ritonaviro. Vartojant kartu su efavirenzu, nevirapinu, tipranaviru / ritonaviru, rifampicinu dozė yra po 50 mg du kartus per parą. Esant atsparumui integrazių klasei apgalvotai skirti deriniai su efavirenzu, nevirapinu, tipranaviru / ritonaviru, fosamprenaviru / ritonaviru, rifampicinu. Tivicay vartoti kartu su dofetilidu negalima dėl galimo gyvybei pavojingo toksinio poveikio. Vengti vartoti kartu su okskarmazepinu, fenitoinu, fenobarbitaliu, karbamazepinu, jonažolių preparatais. Antacidinius preparatus, kurių sudėtyje yra magnio / aliuminio, kalcio papildus, geležies papildus ir multivitaminus reikia išgerti kitu laiku nei vartojamas dolutegraviras (praėjus ne mažiau kaip 2 valandoms arba likus ne mažiau kaip 6 valandoms). Pradėjus vartoti dolutegravirą arba nutraukus dolutegravio vartojimą pacientams, kurie vartoja metforminą, rekomenduojama atidžiai stebėti metformino veiksmingumą ir saugumą. Gali prireikti keisti metformino dozę. Kartu su Tivicay vartojamų geriamųjų kontraceptikų dozės keisti nebūtina. **Nepageidaujamas poveikis.** Labai dažnas: galvos skausmas, pykinimas, viduriavimas. Dažnas: nemiga, nenormalūs sapnai, depresija, svaigulys, vėmimas, pilvo pūtimas, viršutinės pilvo dalies skausmas, pilvo skausmas, diskomfortas pilve, išbėrimas, niežėjimas, nuovargis, alaninaminotransferazių (ALT) ir (arba) aspartataminotransferazių (AST) suaktyvėjimas, kreatinfosfokinazės (KFK) suaktyvėjimas. Nedažnas: padidėjusio jautrumo reakcija, imuniteto atsistatymo sindromas, mintys apie savižudybę arba bandymas nusižudyti (ypač pacientams, kuriems jau buvo pasireiškusi depresija arba psichinė liga), hepatitas. **Pakuotė:** buteliukai, uždaryti užsukamu polipropileno uždoriu su karštu būdu sandariai užlydytu polietileno sluoksniu, kuriuose yra 30 arba 90 plėvele dengtų tablečių. **Rinkodaros teisės turėtojas.** ViiV Healthcare UK Limited. 980 Great West Road. Brentford, Middlesex TW8 9GS, Jungtinė Karalystė. Daugiau informacijos teikia UAB „GlaxoSmithKline Lietuva“, Ukmergės g. 120, LT-08105 Vilnius, (8-5) 264 9000, info.lt@gsk.com. Įtarus nepageidaujamą reakciją į vaistą, praneškite Valstybinei vaistų kontrolės tarnybai: nemokamu faksu 8-800-201-31, el. paštu nepageidaujamar@vkt.lt arba paštu: VVKT, Žirmūnų g. 139A, LT-09120, Vilnius, ir UAB „GlaxoSmithKline Lietuva“ aukščiau nurodytais adresais ar telefonu. Čia pateikta sutrumpinta informacija apie vaistą. Visą informaciją rasite preparato charakteristikų santraukoje žr. <http://extranet.vkt.lt/paieska/>. Informacija parengta: 2015 04 28

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▼ Vykdoma papildoma šio vaistinio preparato stebėseną. Tai padės greitai nustatyti naują saugumo informaciją.

Svarbu pranešti apie įtariamas nepageidaujamas reakcijas, pastebėtas po vaistinio preparato pateikimo į rinką, nes tai leidžia nuolat stebėti vaistinio preparato naudos ir rizikos santykį. Sveikatos priežiūros specialistai turi pranešti apie bet kokias įtariamas nepageidaujamas reakcijas, užpildę interneto svetainėje <http://www.vvkt.lt/> esančią formą, ir atsiųsti ją paštu Valstybinei vaistų kontrolės tarnybai prie Lietuvos Respublikos sveikatos apsaugos ministerijos, Žirmūnų g. 139A, LT-09120 Vilnius, faksu 8 800 20131 arba el. paštu NepageidaujamaR@vvkt.lt.

Taip pat prašome pranešti apie įtariamas nepageidaujamas reakcijas ir UAB „GlaxoSmithKline Lietuva“, Ukmergės g. 120, LT-08105 Vilnius, (8-5) 264 9000, info.lt@gsk.com.