SUMMARY SLIDE DECK

Dolutegravir▼ data at a glance

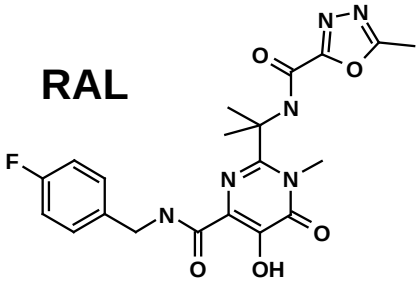
CONTENTS

- What makes dolutegravir different?
- Efficacy of dolutegravir
- Resistance profile of dolutegravir
- Tolerability and safety profile of dolutegravir
- Convenience and drug-drug interactions

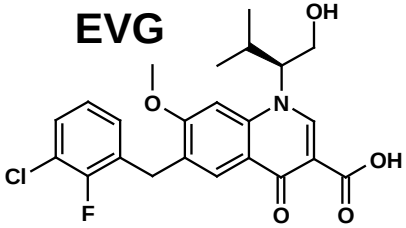
WHAT MAKES DOLUTEGRAVIR DIFFERENT?

STRUCTURE-BASED RATIONALE FOR DISSOCIATION PROFILES OF DTG, RAL AND EVG

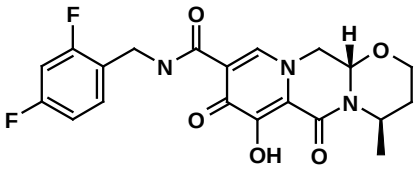
RAL



EVG



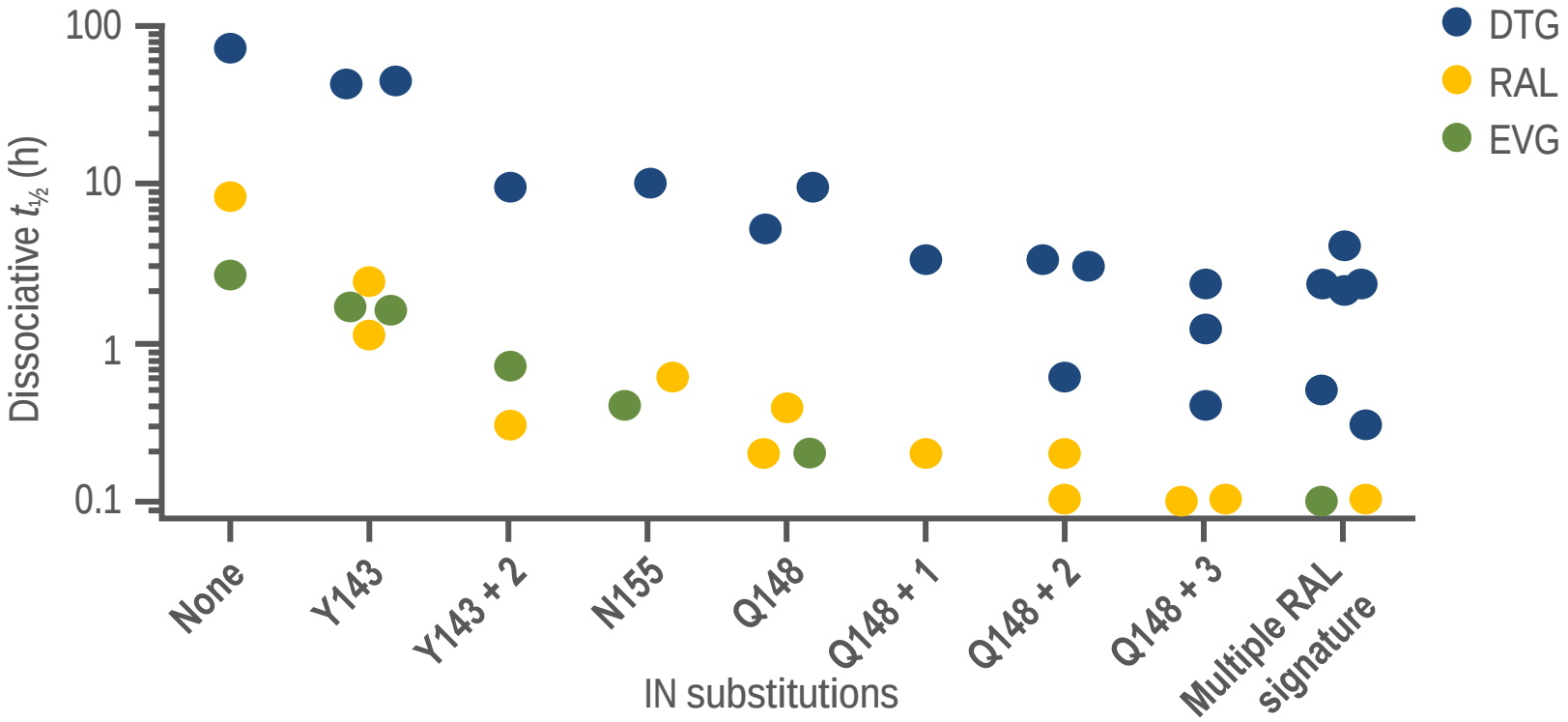
DTG



The structural and electronic characteristics of DTG's metal-binding scaffold may contribute to the slower dissociation kinetics of DTG compared with RAL and EVG

Hightower KE, et al. *Antomicrob Agents Chemother* 2011;5:4552–9

DTG REMAINED BOUND TO HIV INTEGRASE 8 TIMES LONGER THAN RAL AND 26 TIMES LONGER THAN EVG

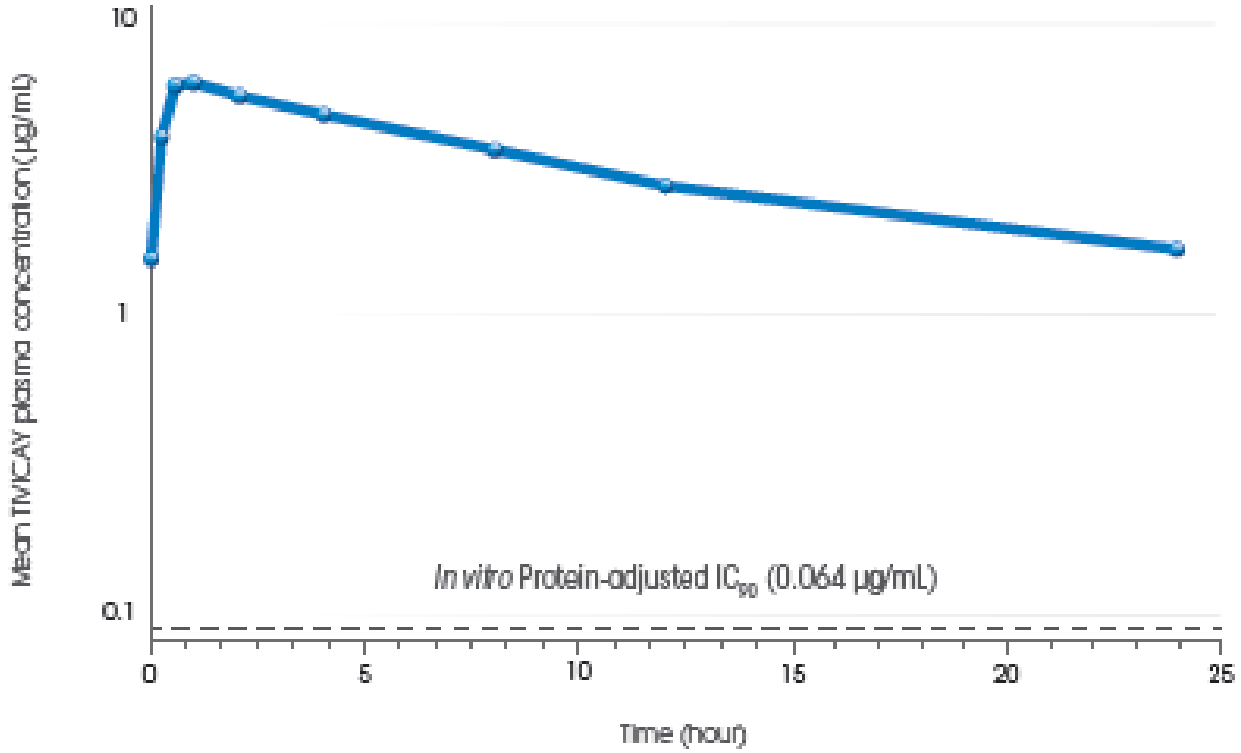


- DTG dissociation from IN-DNA complexes was slower compared with RAL and EVG
- The combination of multiple RAL signature substitutions or the accumulation of RAL secondary substitutions were needed to impact on DTG dissociation

Hightower KE, et al. *Antimicrob Agents Chemother*.2011;55(10):4552-4559

DTG HAD A PREDICTABLE AND CONSISTENT PK PROFILE

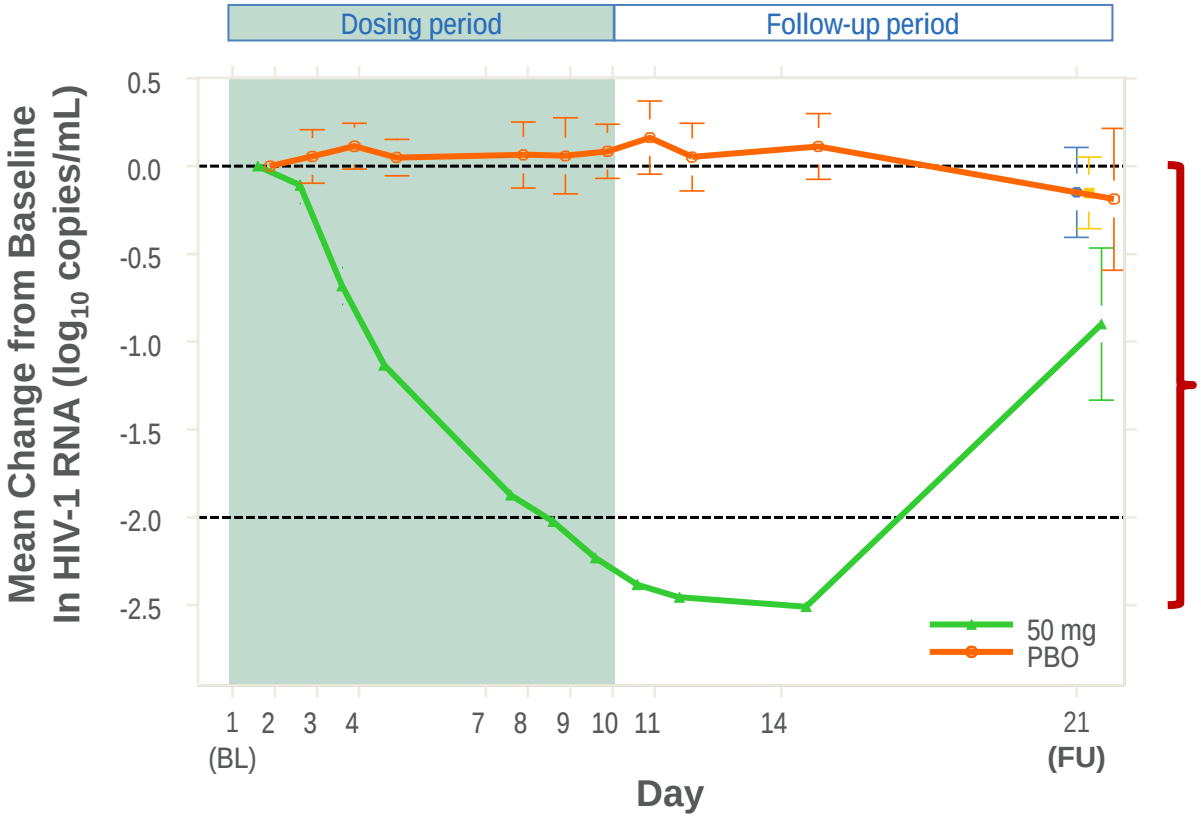
At 24 hours post-DTG administration, plasma concentrations were 19 to 25 fold above IC_{90}



Van Lunzen J et al. *Lancet Infect Dis* 2012 12(2):111-8
Min S et al. *Antimicrob Agents Chemother*. 2010;54:254-258

ANTIVIRAL RESPONSE WITH DTG WAS MAINTAINED 3 TO 4 DAYS AFTER THE LAST DOSE

10 day monotherapy with DTG 50mg QD



- Rapid 2.5 log drop in viral load
- 90% of patients achieved <400 copies/mL
- 70% of patients achieved undetectable viral loads (<50 copies/mL)

Min S. et al. *AIDS* 2011; 25: 1737-1745.

EFFICACY OF DOLUTEGRAVIR

EXTENSIVE DTG CLINICAL PROGRAMME WITH 2,854 TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED, INI-NAÏVE HIV PATIENTS

Treatment-naïve patients

SINGLE[1,2]	N=833	Phase III non-inferiority, randomised, double-blind, double-dummy, multicentre study of: • DTG (50 mg QD) with ABC/3TC FDC plus ATRIPLA® placebo • ATRIPLA® (QD) plus DTG and ABC/3TC FDC placebo
FLAMINGO[3]	N=484	Phase IIIb non-inferiority, randomised, active-controlled, multicentre, open-label study of: • DTG (50 mg QD) + 2 NRTIs • DRV/r (800 mg*/100 mg QD) + 2 NRTIs
SPRING-2[4]	N=822	Phase III non-inferiority, randomised, double-blind, double-dummy, multicentre study of: • DTG (50 mg QD) plus RAL placebo (BID) + 2 NRTIs • RAL (400 mg BID) plus DTG placebo (QD) + 2 NRTIs

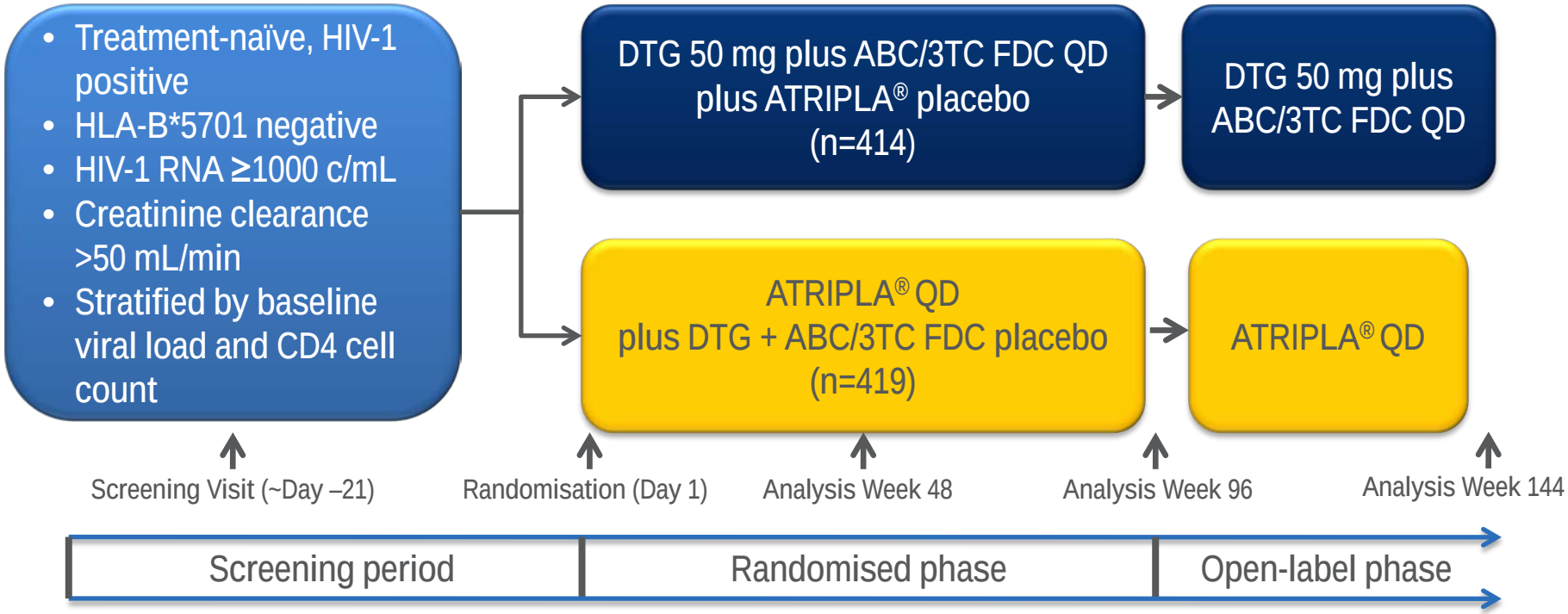
Treatment-experienced, INI-naïve patients

SAILING[5]	N=715	Phase III, randomised, double-blind, active-controlled, parallel group, non-inferiority, multicentre study of: • DTG (50 mg QD) + ART • RAL (400 mg BID) + ART

*Given as 2 x 400 mg tablets
NRTI, nucleoside reverse transcriptase inhibitor
DRV/r, darunavir/ritonavir; QD, once daily; BID, twice daily; FDC, fixed-dose combination

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
3. Clotet B, et al. *Lancet* 2014; 383: 2222-31
4. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
5. Cahn P, et al. *Lancet* 2013;382(9893):700-708

SINGLE STUDY DESIGN



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)

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. Poster presented at: 21st CROI; 2014. Poster 543

BASELINE CHARACTERISTICS

Characteristic	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Median age, years (range)	36 (18-68)	35 (18-35)
Female, n (%)	67 (16)	63 (15)
African American / African Heritage, n (%)	98 (24)	99 (24)
CDC class C, n (%)	18 (4)	17 (4)
Baseline HIV-1 RNA		
Median (log_{10} c/mL)	4.67	4.70
>100,000 c/mL, n (%)	134 (32)	131 (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

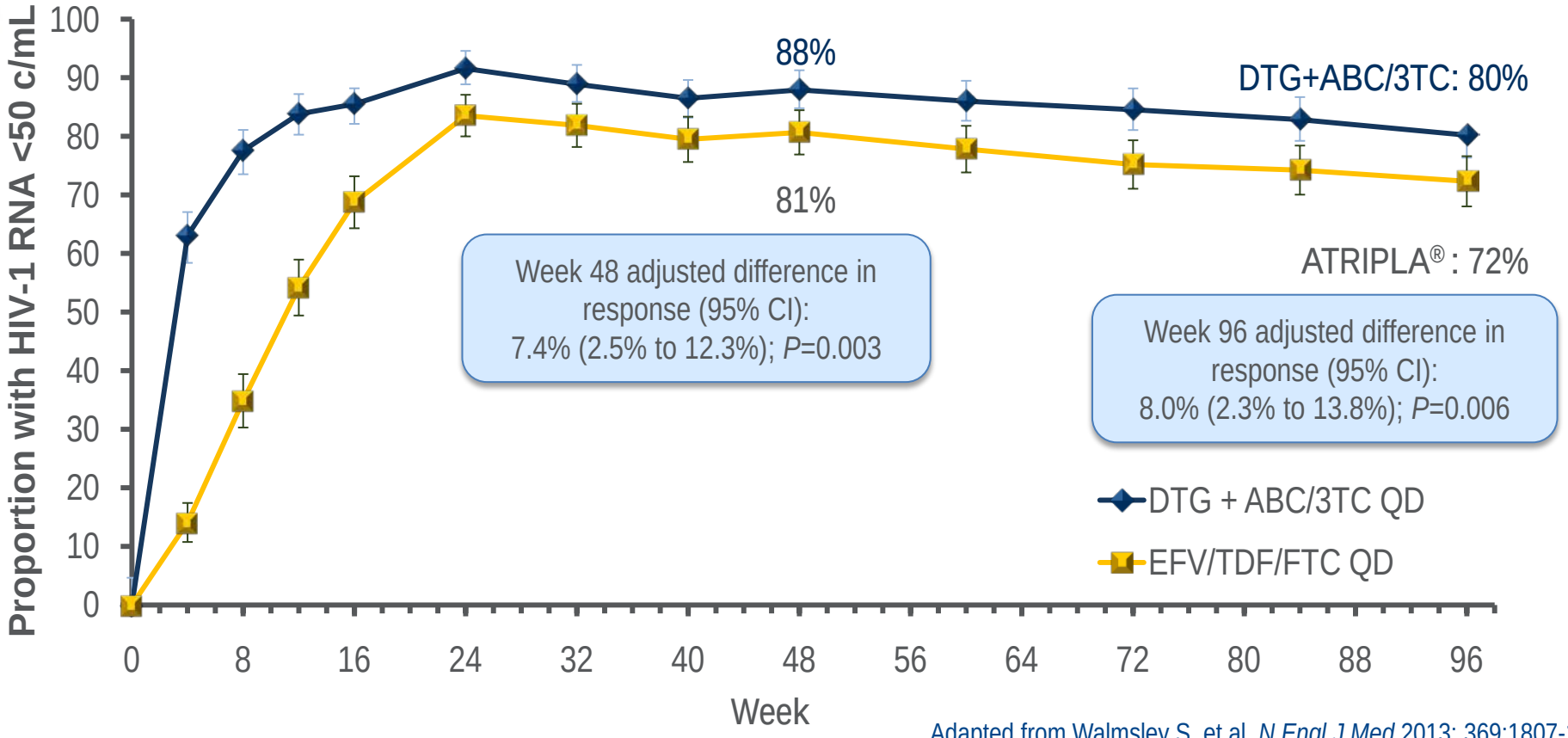
Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18

CDC, Centers for Disease Control

Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18 (appendix)

DTG + ABC/3TC MAINTAINED STATISTICALLY SUPERIOR EFFICACY VS ATRIPLA® THROUGH TO 96 WEEKS

DTG was statistically superior to Atripla® at Week 48 and Week 96
Subjects receiving DTG achieved faster virologic suppression than Atripla®

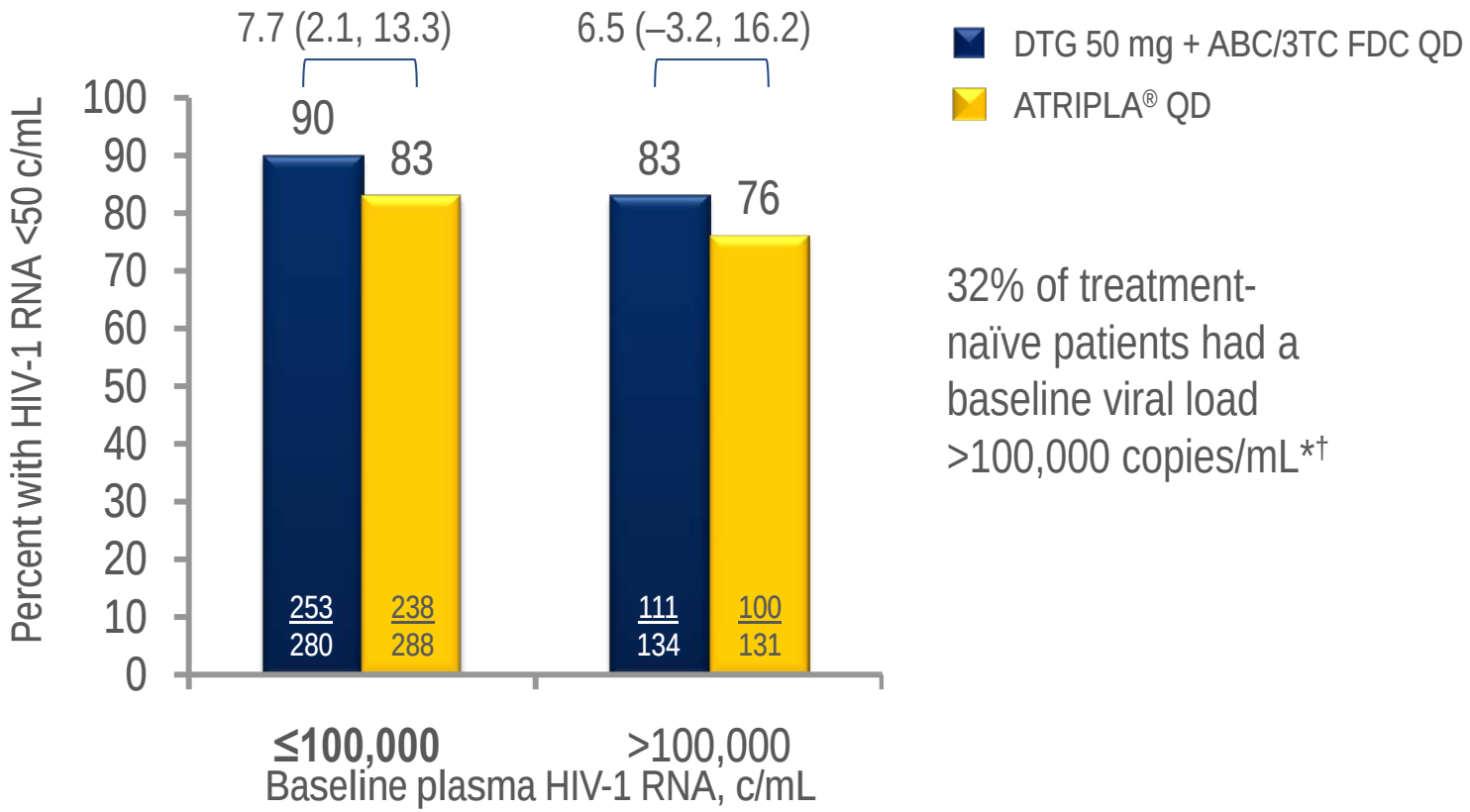


-10% non-inferiority margin with pre-specified tests for superiority

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014
Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

DTG + ABC/3TC WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD

At Week 48, DTG + ABC/3TC was effective regardless of baseline viral load
At 96 weeks, DTG + ABC/3TC was still as effective as Atripla® in patients with high baseline viral loads

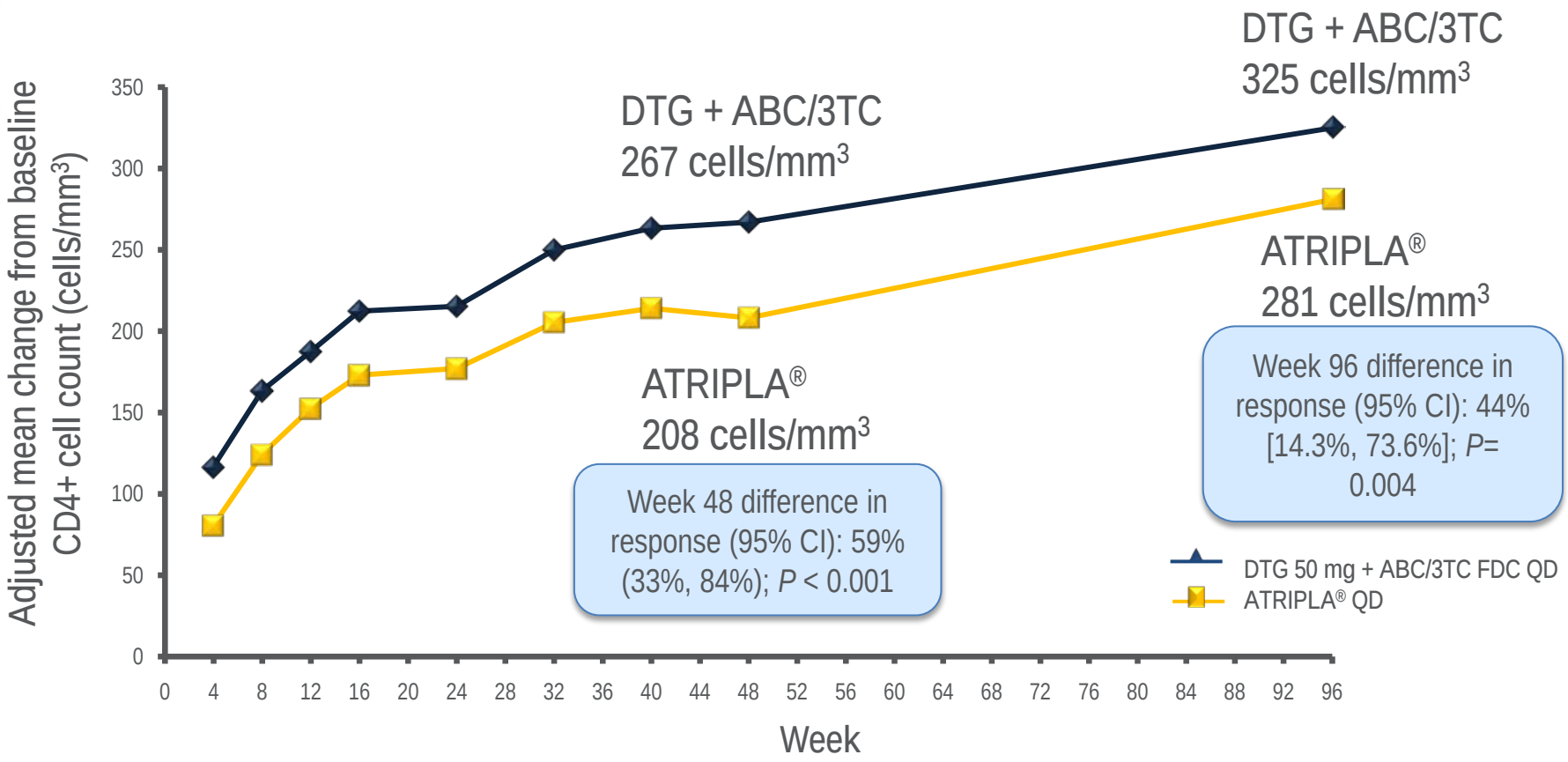


32% of treatment-naïve patients had a baseline viral load >100,000 copies/mL*†

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

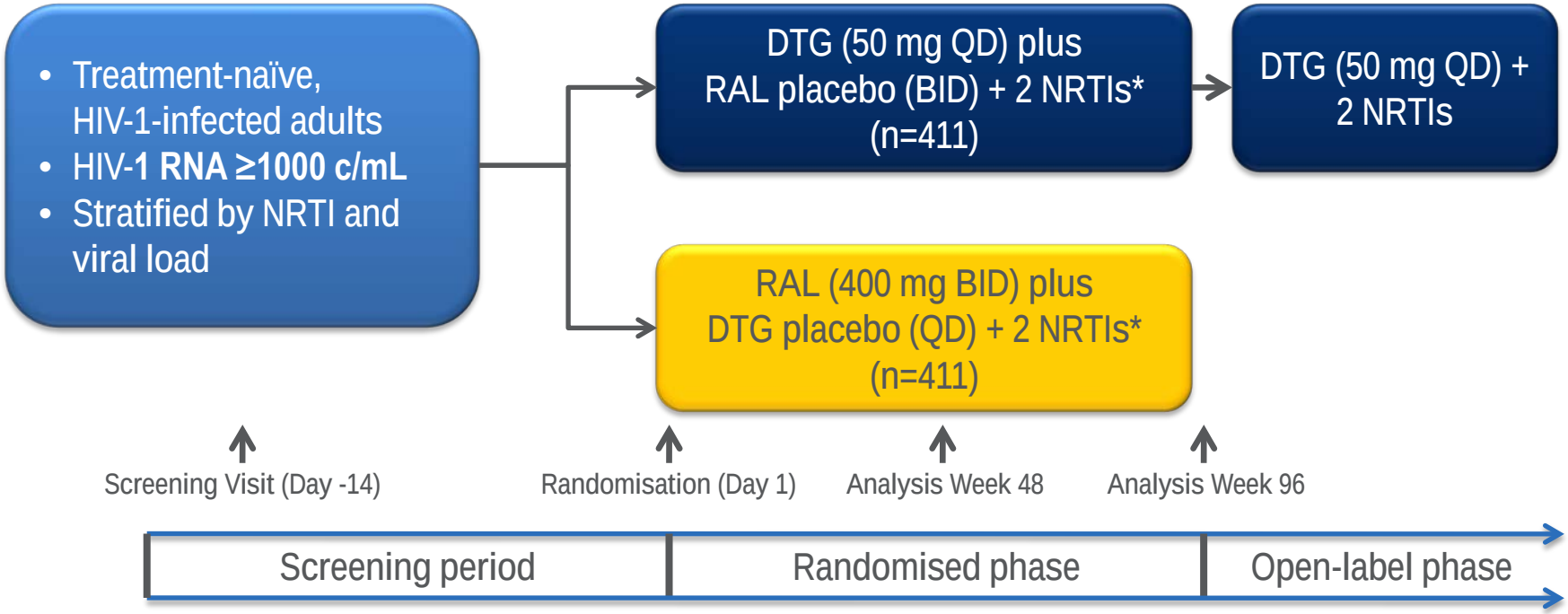
TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014
Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

DTG + ABC/3TC HAD STATISTICALLY SUPERIOR CD4+ T-CELL INCREASES VS ATRIPLA® THROUGH 48 AND 96 WEEKS



Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014
Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

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

*Investigator's selection ABC/3TC or TDF/FTC
FDA, Food and Drug Administration

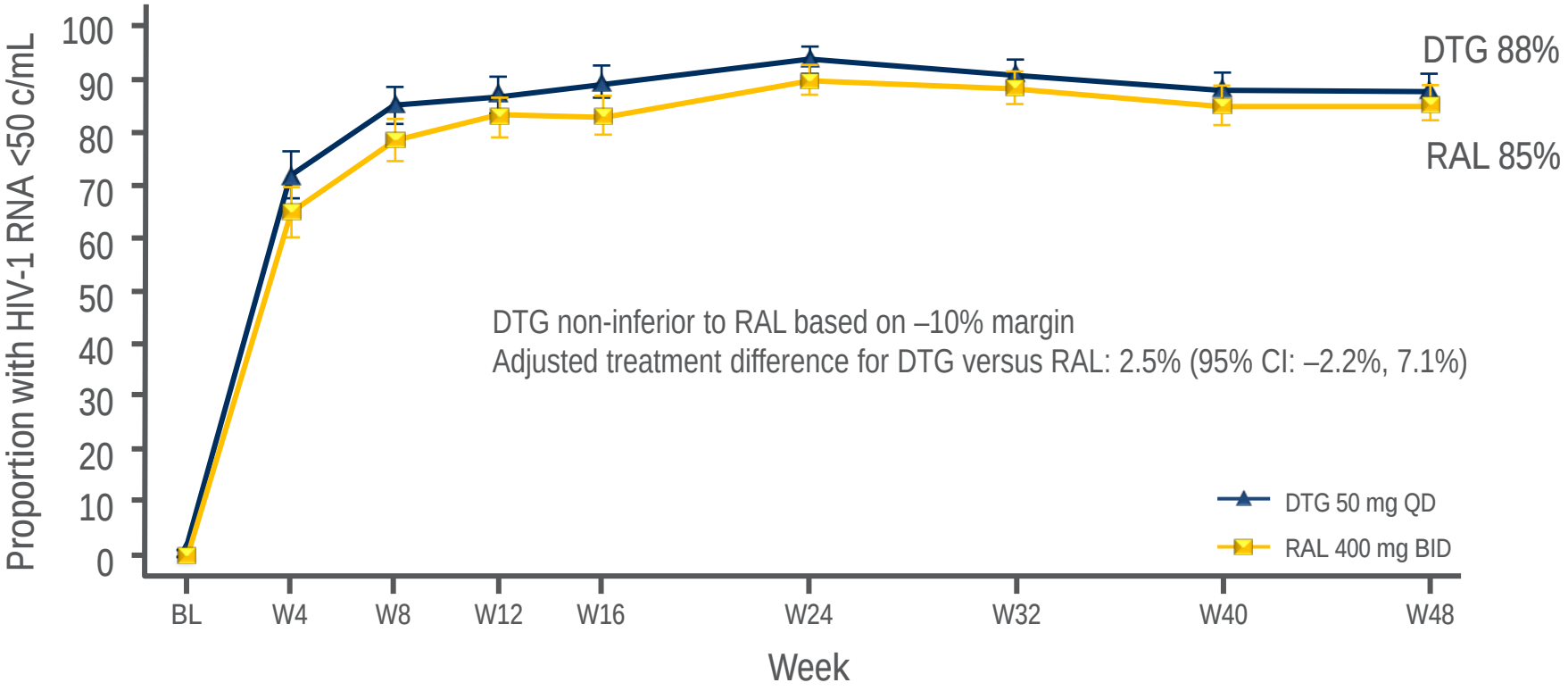
Raffi F et al. *Lancet* 2013;381:735–43

BASELINE CHARACTERISTICS

Characteristic	DTG 50 mg QD (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)	4.52	4.58
>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)

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

IN TREATMENT-NAÏVE PATIENTS, DTG WAS NON-INFERIOR TO RAL AT 48 WEEKS

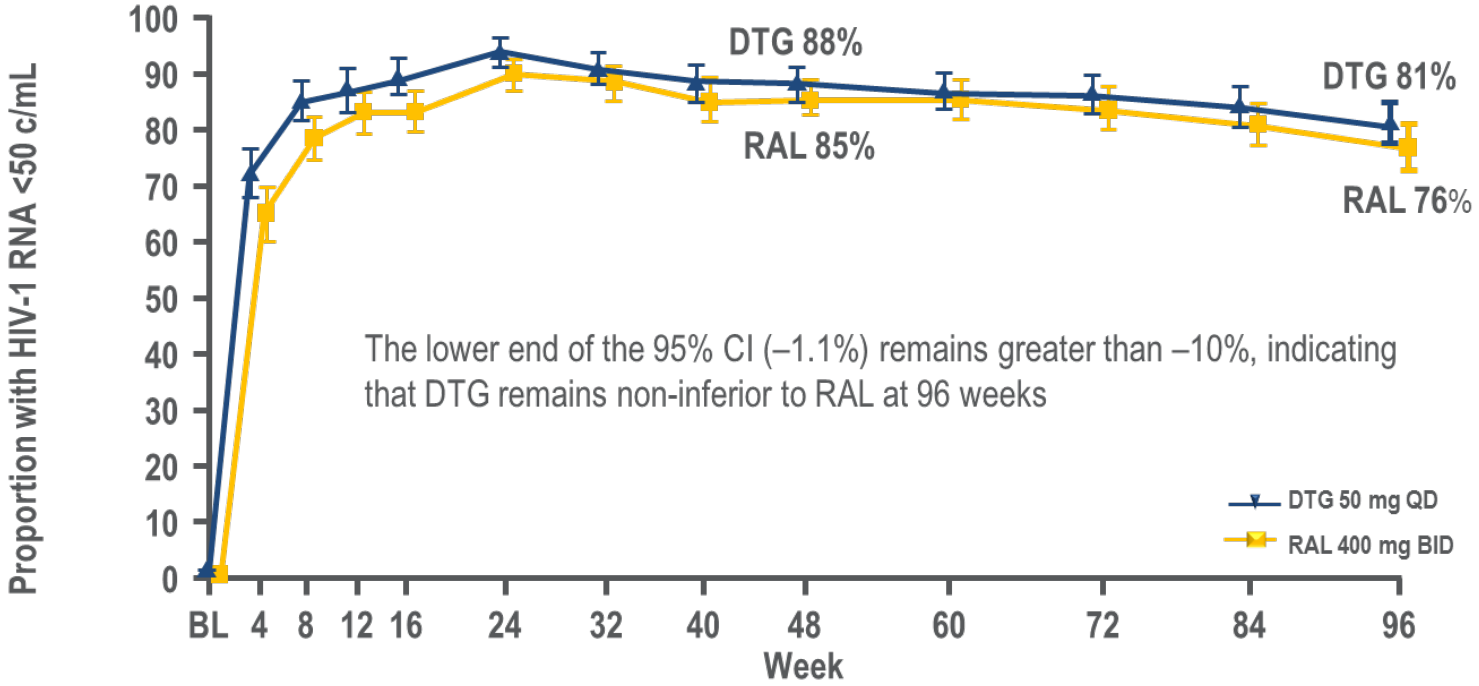


Median (IQR) Change From Baseline $CD4^+$ Cell Count ($cells/mm^3$)

	Week 4		Week 24		Week 48	
DTG 50 mg QD	87	(26, 149)	183	(100, 295)	230	(128, 338)
RAL 400 mg BID	88	(32, 163)	182	(94, 296)	230	(139, 354)

1. Raffi F et al. IAS 2012. Abstract THLBB04
2. Adapted from Raffi F et al. Lancet 2013;381:735–43

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



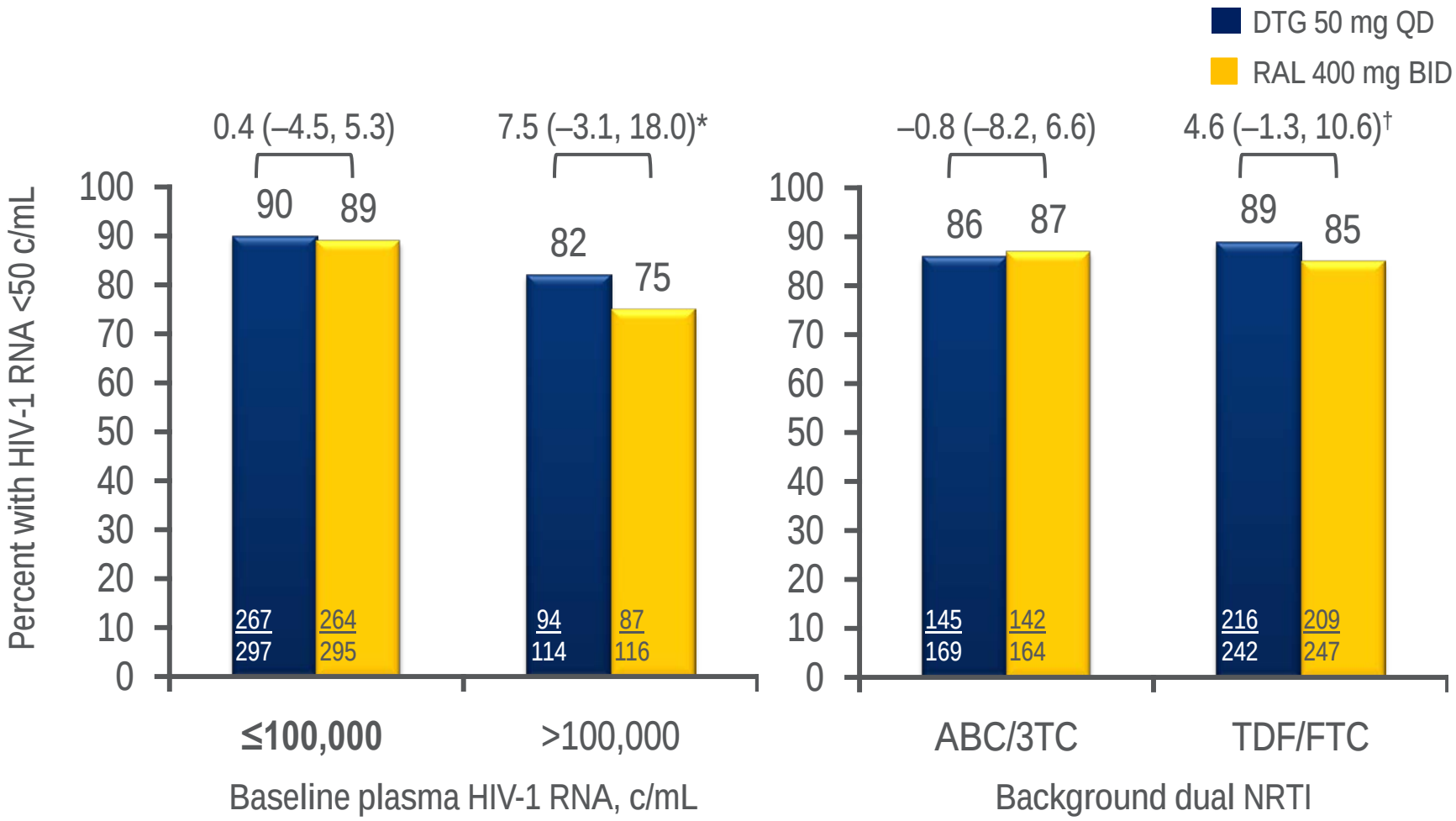
Treatment	Number of responders/ total assessed, n (%)	Difference in proportion (95% CI) (DTG - RAL)	Adjusted difference in proportion (95% CI) (DTG - RAL)
DTG 50 mg QD	332/411 (81)	4.4% (–1.2%, 10.0%)	4.5% (–1.1%, 10.0%)
RAL 400 mg BID	314/411 (76)		

DTG and RAL were associated with similar increases in CD4+ cell count from baseline over time.[1–3]

Error bars indicate 95% CI

1. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
2. Raffi F et al. IAS 2013. Poster TULBPE17
3. Raffi F et al. Lancet 2013;381:735–43

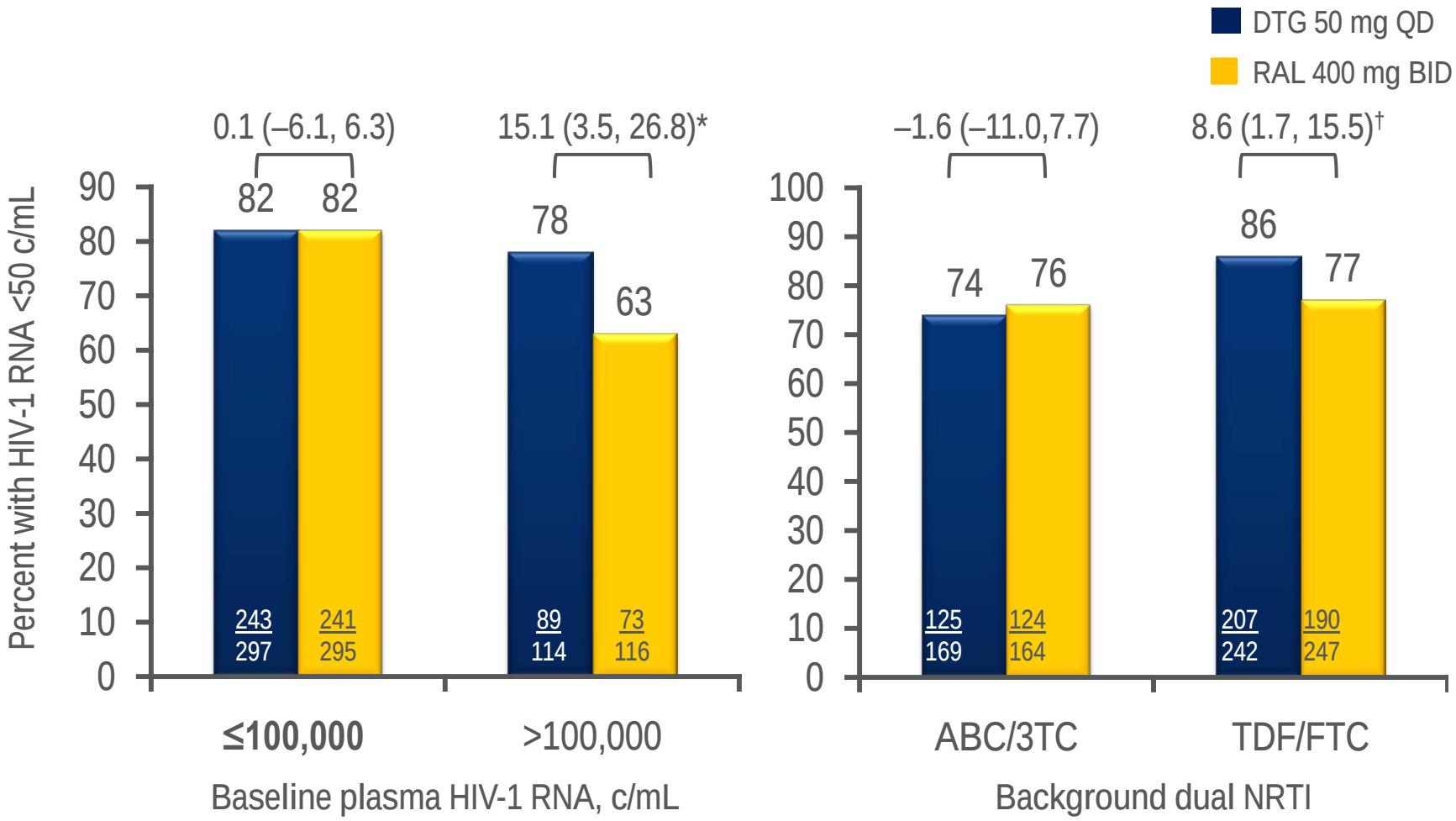
DTG WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD OR BACKGROUND REGIMEN (WEEK 48)



*P=0.236; †P=0.264; p-values evaluated using a test for homogeneity

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

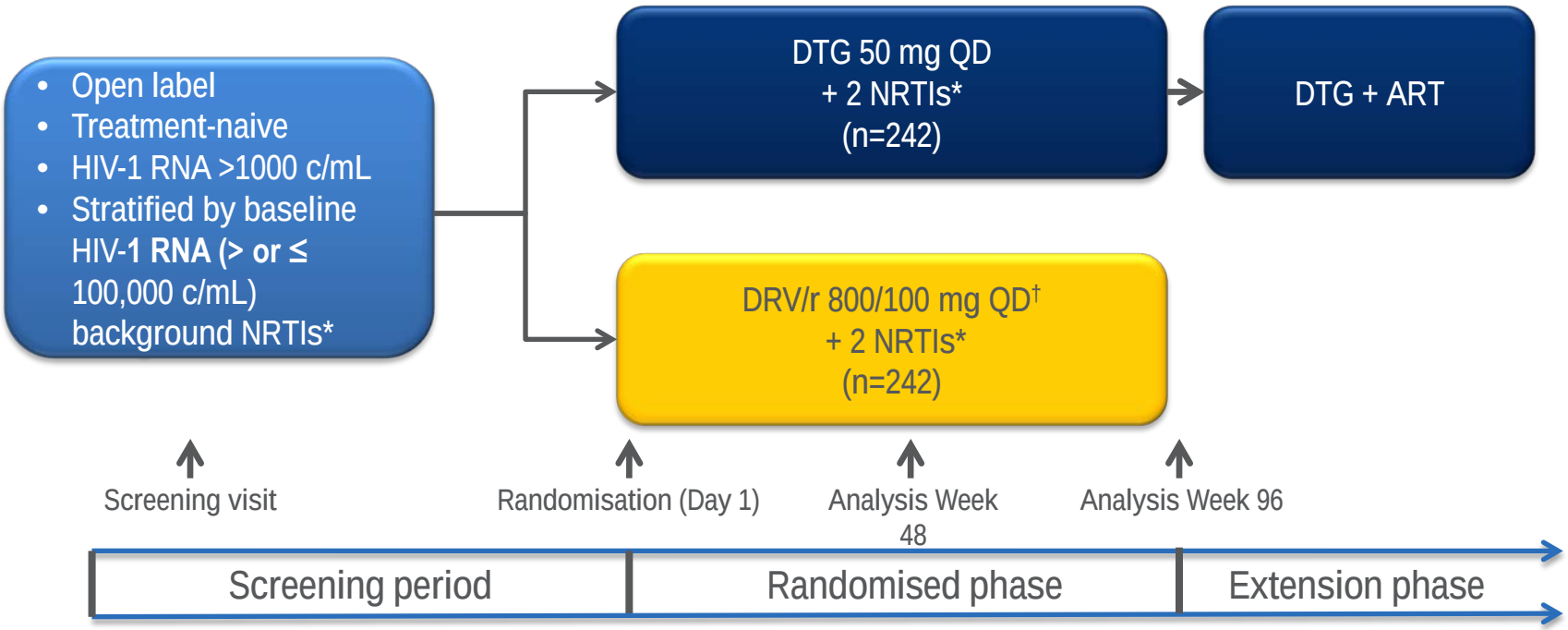
DTG WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD OR BACKGROUND REGIMEN (WEEK 96)



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

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

FLAMINGO STUDY DESIGN



Primary endpoint: Proportion with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot) with non-inferiority margin of -12%

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

† Given as 2 x 400 mg tablets

Adapted from Clotet B, et al. *Lancet* 2014;383:2222-31

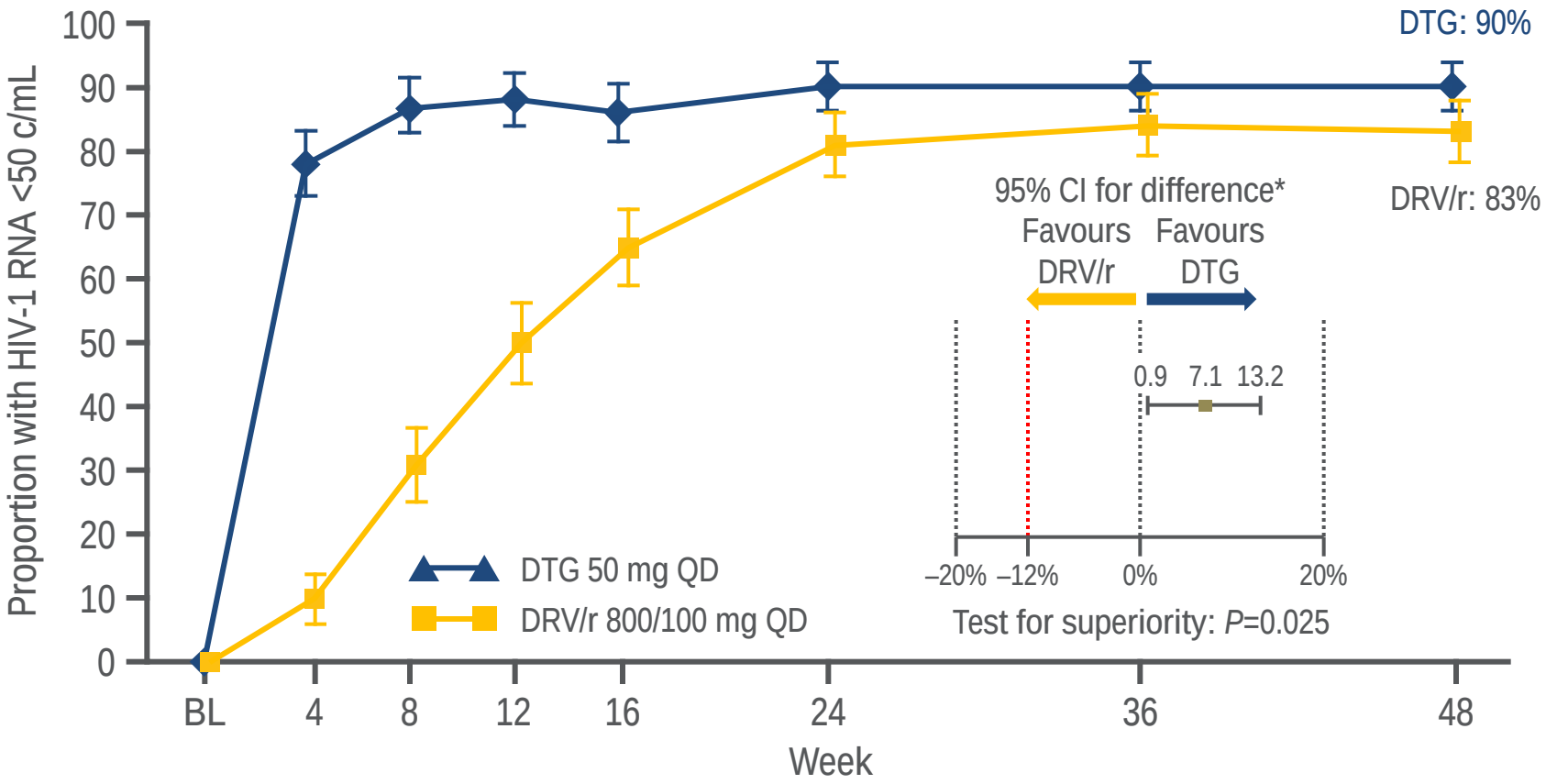
Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)
Age, years		
Median (range)	34 (18-67)	34 (19-67)
Gender, n (%)		
Male	211 (87%)	201 (83%)
Female	31 (13%)	41 (17%)
Race, n (%)		
White	173 (71%)	176 (73%)
African American/African heritage	60 (25%)	53 (22%)
Other	8 (3%)	13 (5%)
Baseline plasma HIV-1 RNA		
Median (log_{10} copies/mL)	4.49	4.48
>100,000 copies/mL, n (%)	61 (25%)	61 (25%)
CD4+ T-cell count, cells/mm3 (median)	390	400
HBV/HCV positive, n (%)	9 (4%)/17 (7%)	4 (2%)/15 (6%)
Investigator selected ABC/3TC, n (%)	79 (33%)	80 (33%)

Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31

IN TREATMENT-NAÏVE SUBJECTS PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS DRV/r AT 48 WEEKS



- Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r

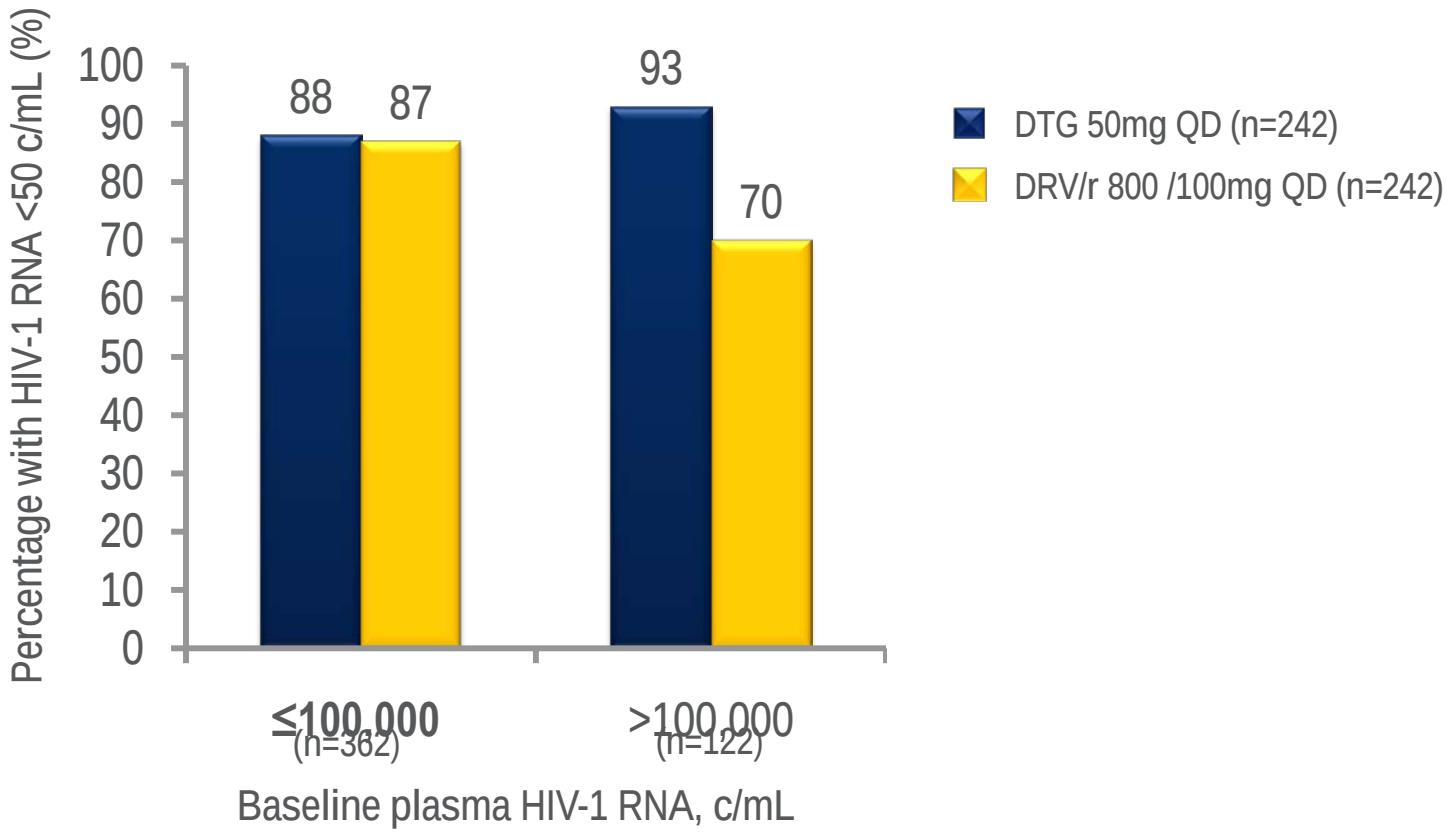
*Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy

Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31

Week 48 snapshot analysis

Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31 (Supplementary Appendix)

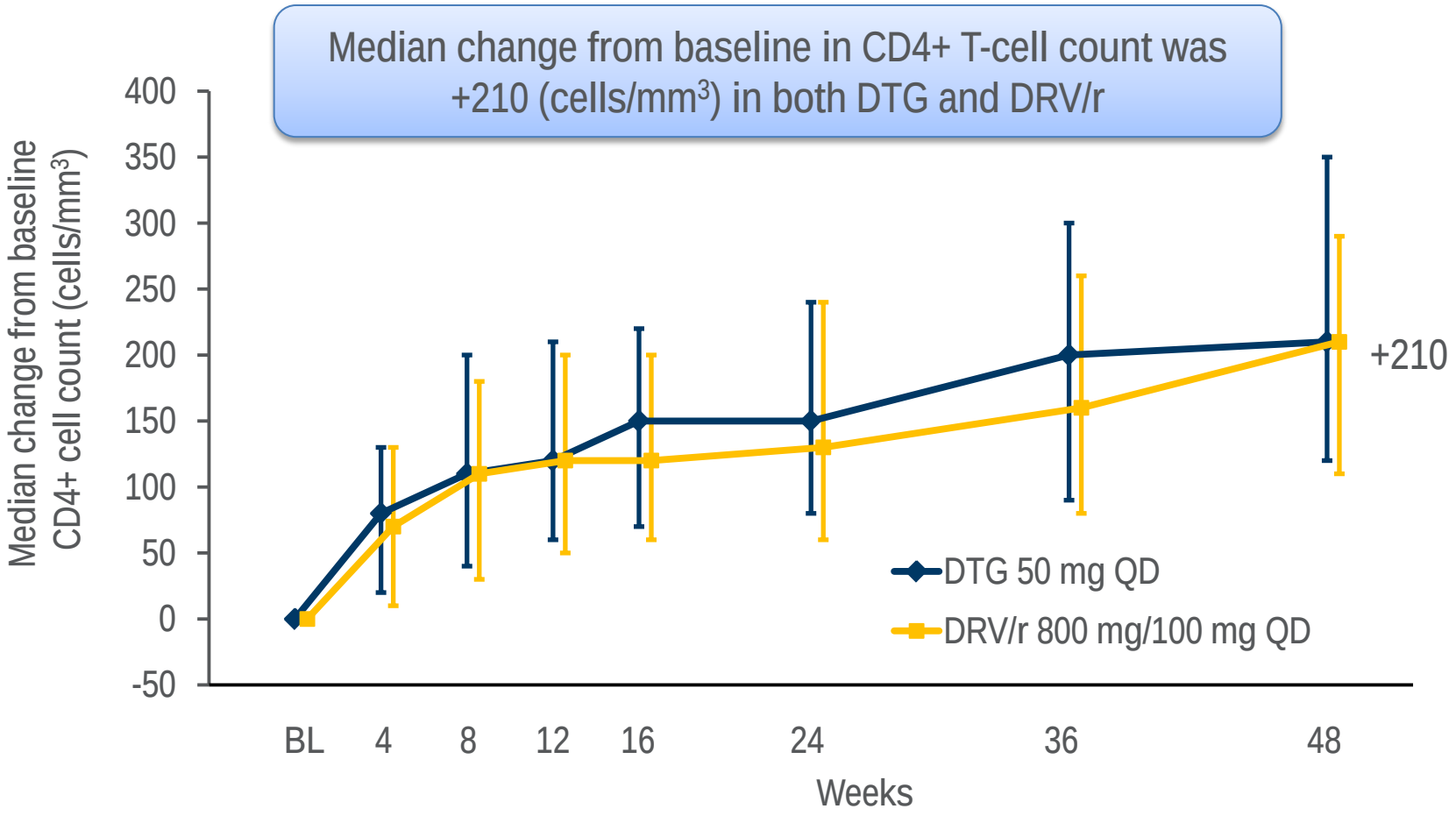
DTG WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD VS DRV/r AT 48 WEEKS



- 25% of treatment-naïve patients had a baseline viral load >100,000 copies/mL[1]

1. Adapted from Clotet B, et al. *Lancet* 2014;383:2222-31
2. Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31 (Appendix)

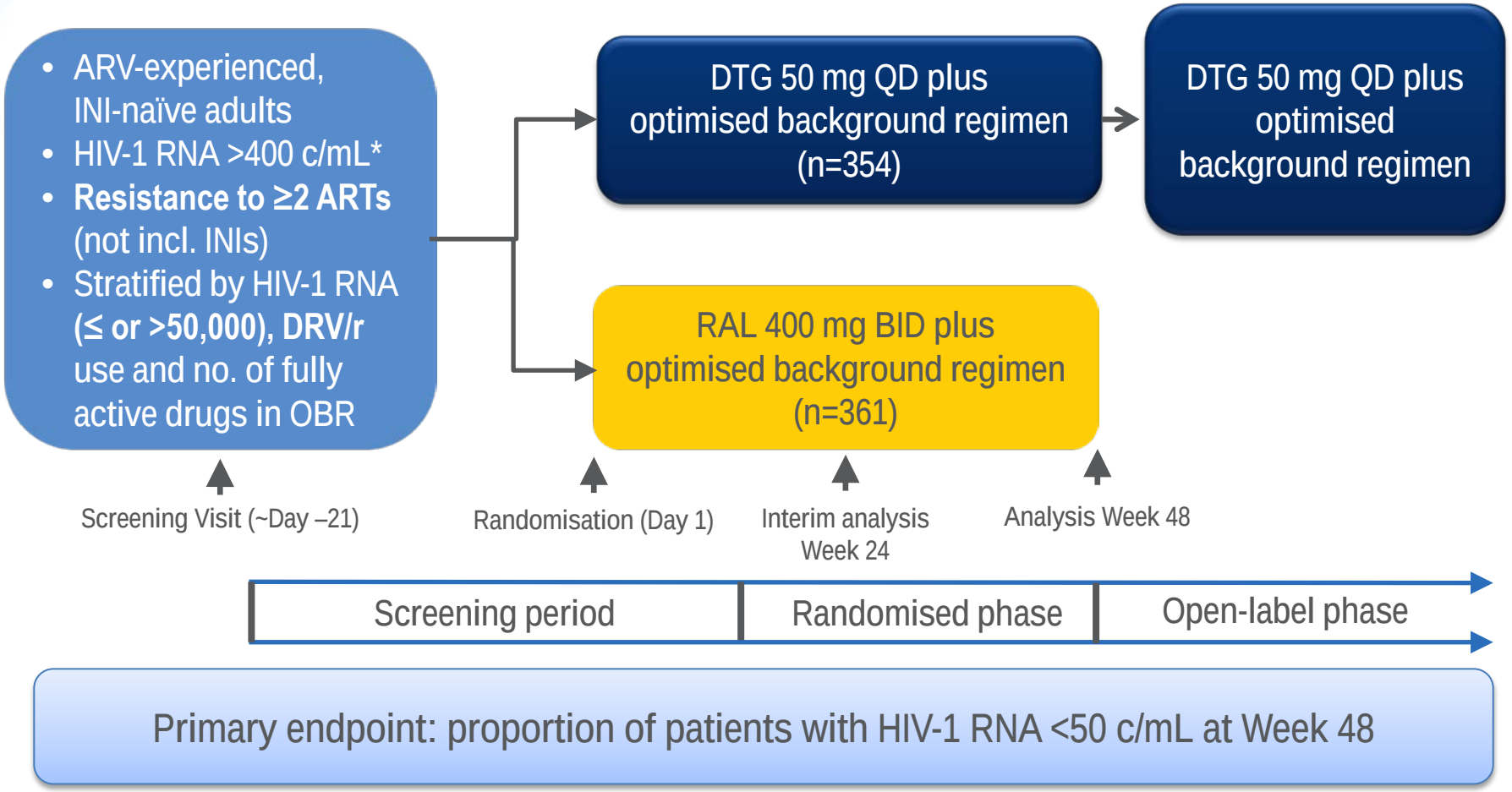
DTG HAD A SIMILAR CD4 CELL COUNT VS DRV/r AT 48 WEEKS



Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

SAILING STUDY DESIGN



*With 2 consecutive HIV-1 RNA ≥400 c/mL, unless screening HIV-1 RNA >1,000 c/mL

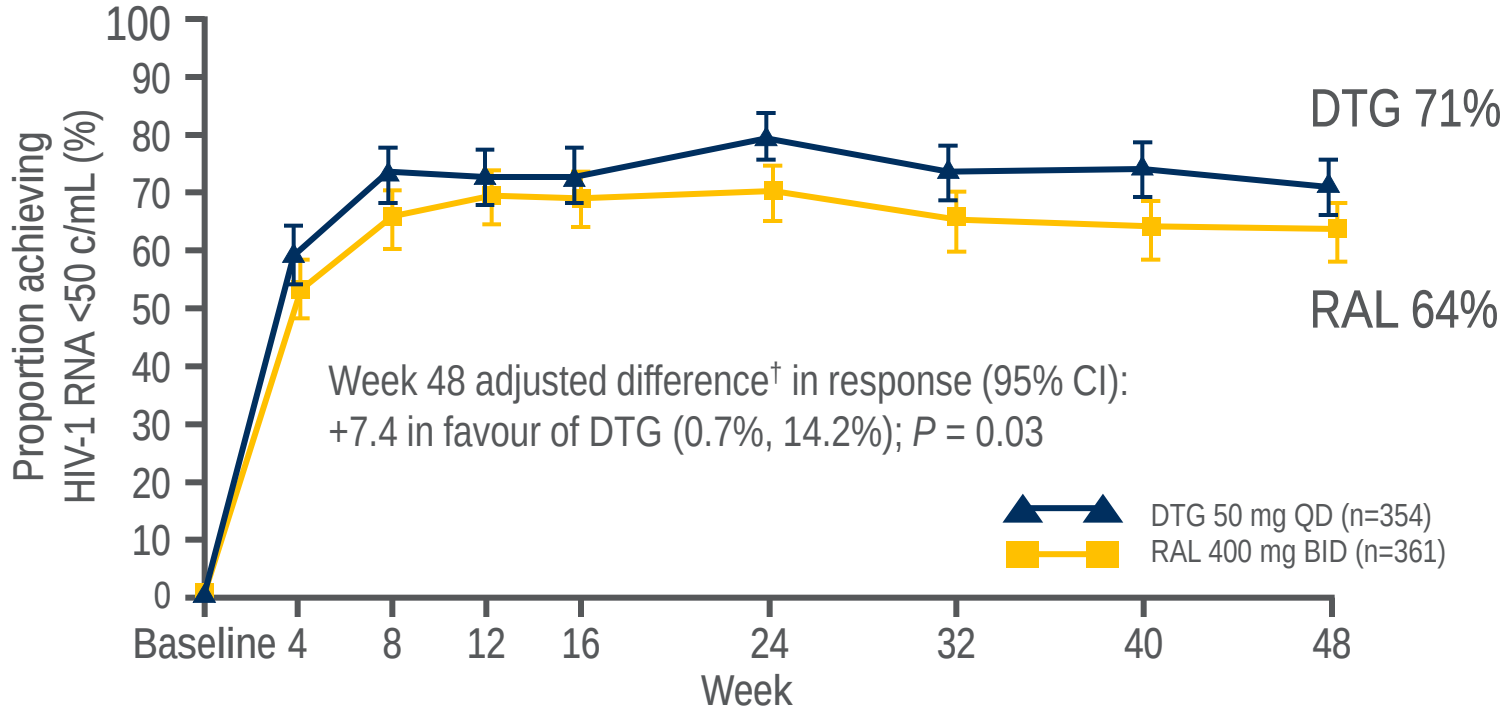
Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708
Pozniak A, et al. CROI 2013. Abstract 179LB

BASELINE CHARACTERISTICS

	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
Median age, years (range)	42 (35-49)	43 (36-49)
Female, n (%)	107 (30)	123 (34)
Race		
White, n (%)	175 (49)	172 (48)
African American or African heritage, n (%)	143 (40)	160 (44)
HIV-1 RNA, median (log_{10} c/mL)	4.17	4.21
>50,000 c/mL, n (%)	105 (30)	107 (30)
CD4+ count, median (cells/mm^3)	204.5	193.0
HBV coinfection (%)	5	4
HCV coinfection (%)	9	13
Duration prior ART, median (months)	80	72
≥3 class resistance, n (%)	168 (47)	183 (51)
Most common background regimens, n (%)		
DRV/r, TDF	62 (18)	73 (20)
LPV/r, TDF	40 (11)	40 (11)
DRV/r, ETR	33 (9)	40 (11)
LPV/r	36 (10)	35 (10)
ATV/r, TDF	37 (10)	33 (9)
DRV/r, MVC	23 (6)	19 (5)

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

IN TREATMENT-EXPERIENCED, INI-NAÏVE PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS RAL AT 48 WEEKS



DTG mg QD was statistically superior to RAL 400 mg BID based on a pre-specified snapshot analysis* (HIV-1 RNA <50 copies / mL) at Week 48 (*P* = 0.03)

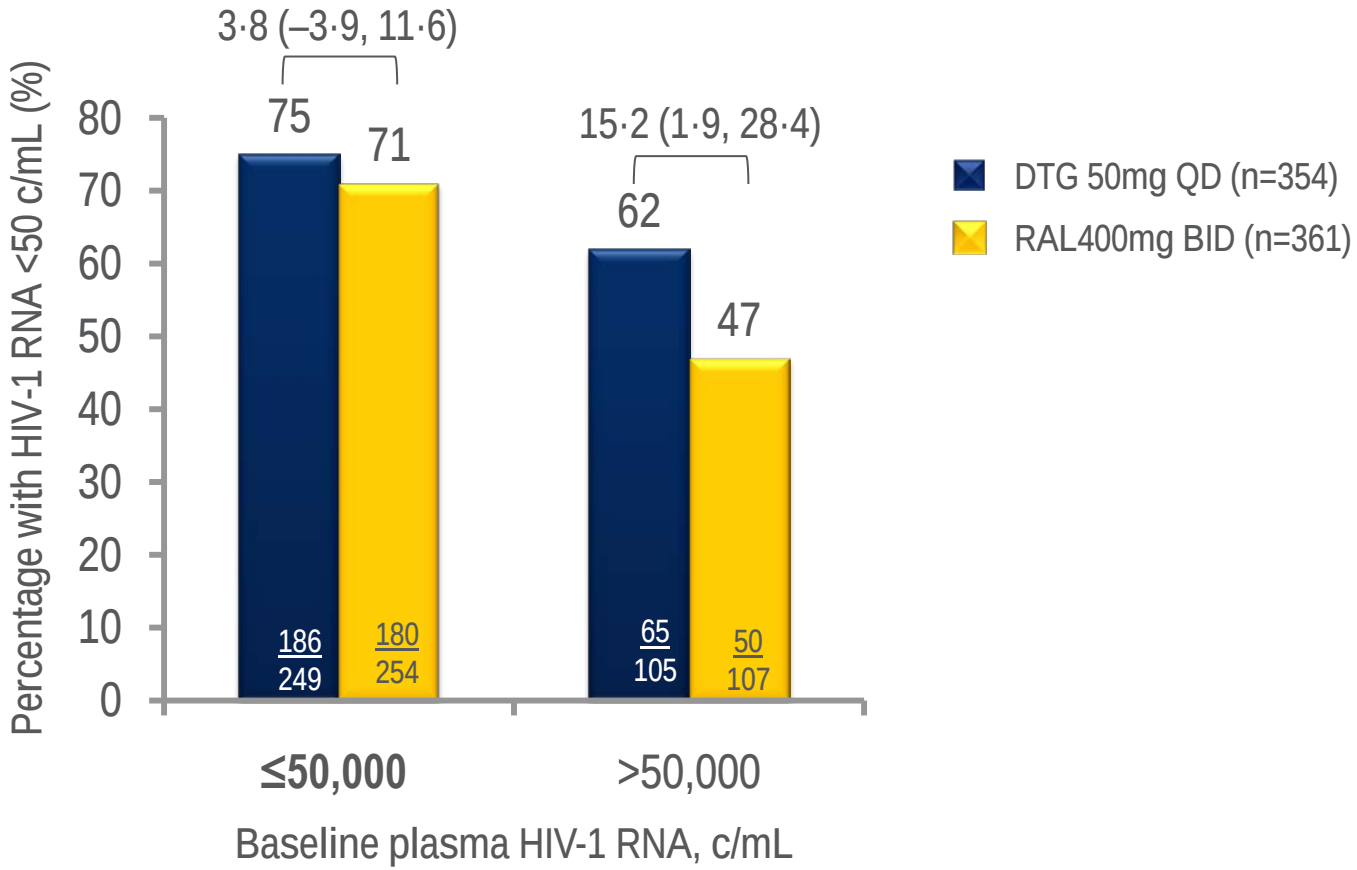
Mean (SD) CD4+ change from baseline to Week 48 was similar between arms: DTG: +162 (151) cells/mm^3; RAL: +153 (144) cells/mm^3

*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; SD, standard deviation

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

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

DTG WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD AT 48 WEEKS



- 30% of patients had baseline viral load >50,000 copies/mL

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

DTG DELIVERS RAPID AND SUSTAINED EFFICACY: EFFICACY SUMMARY

SINGLE

ART-naïve patients (n=833)[1,2]

DTG + ABC/3TC demonstrated **statistically superior efficacy vs Atripla®**

- 88% vs 81% remained undetectable at 48 weeks (*P*=0.003)
- 80% vs 72% remained undetectable at 96 weeks (*P*=0.006)
- DTG + ABC/3TC demonstrated a significantly shorter median time to viral suppression vs Atripla® (28 days vs 84 days respectively; P<0.0001)

SPRING-2

ART-naïve patients (n=822)[3,4]

DTG regimen was **non-inferior vs raltegravir**

- 88% vs 85% remained undetectable at 48 weeks
- 81% vs 76% remained undetectable at 96 weeks

FLAMINGO

ART-naïve patients (n=484)[5]

DTG regimen demonstrated **statistically superior efficacy vs darunavir/r**

- 90% vs 83% remained undetectable at Week 48 (*P*=0.025)

SAILING

Treatment-experienced, INI-naïve (n=715)[6]

DTG regimen demonstrated **statistically superior efficacy vs raltegravir**

- 71% vs 64% remained undetectable at Week 48 (*P*=0.03)

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
5. Clotet B, et al. *Lancet* 2014; 383: 2222-31
6. Cahn P, et al. *Lancet* 2013;382(9893):700-708

RESISTANCE PROFILE OF DOLUTEGRAVIR

DTG SELECTED FEWER SUBSTITUTIONS IN VITRO COMPARED WITH RAL AND EVG

DTG (56 days)
S153F

DTG (84 days)
S153Y, S153F

DTG (112 days)
S153Y, S153F

Raltegravir (84 days)
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
V151I/N155H

Elvitegravir (56 days)
T66I;E92Q;P145S
Q148K;Q148R;T66K
E92V;P145S;Q146L
Q148R;T66I/V72A/A128T
T66I/E92Q; T66I/Q146L

Integrase substitutions observed during passage of wild-type HIV-1 IIIB strain in the presence of DTG, RAL or EVG; list excludes polymorphisms. Mutations in **bold** indicate those seen in clinical trials.

All substitutions observed during DTG passage had low level impact on DTG susceptibility (FC≤4.1)[1]

1. Adapted from Sato A, et al. IAS 2009. Poster WEPEA097
2. Adapted from Kobayashi M, et al. *Antiviral Research* 2008;80;213–22
3. Adapted from Kobayashi M, et al. *Antimicrob Agents Chemother* 2011;55:813–21

NO INI OR NRTI RESISTANCE THROUGH 48 WEEKS WITH DTG IN TREATMENT-NAÏVE PATIENTS

n (%)	SPRING-2[1]		SINGLE[2,3,4]		FLAMINGO[5]	
	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)	DTG 50 mg +ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)	DTG 50 mg (n=242)	DRV/r 800/100 mg QD (n=242)
Subjects with PDVF	20 (5)	28 (7)	18 (4)	17 (4)	2 (<1)	2 (<1)
NRTI-resistant mutations	0	4/19 (21)*	0	1(K65K/R)	0	0
INI-resistant mutations	0	1/18 (6)†	0	N/A	0	N/A
NNRTI-resistant mutations	–	–	N/A	4‡	–	–

*One participant had mutation M184M/I; one had mutation A62A/V; and one had mutation M184M/V.

† One participant had integrase mutations T97T/A, E138E/D, V151V/I, and N155H and NRTI mutations A62A/V, K65K/R, K70K/E, and M184V

‡n=1 with K101E, n=1 with K103K/N, n=1 with G190G/A and n=1 with K103N+G190G/A

BL, baseline; c/mL, copies/mL; INI, integrase inhibitor
PDVF, protocol defined virologic failure

1. Adapted from Raffi F, et al. *Lancet* 2013;381:735–43
2. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
3. Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b
4. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18 (suppl appendix)
5. Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31

NO INI OR NRTI RESISTANCE THROUGH 96 WEEKS WITH DTG IN TREATMENT-NAÏVE PATIENTS

n (%)	SPRING-2[1]		SINGLE[2-5]	
	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)	DTG 50 mg +ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Subjects with PDVF	22 (5)	29 (7)	-	-
NRTI-resistant mutations	0	4*	0	1**
INI-resistant mutations	0	1†	0¶	N/A
NNRTI-resistant mutations	–	–	N/A	6‡

*One participant had mutation M184M/I; one had mutation A62A/V; and one had mutation M184M/V.
† One participant had integrase mutations T97T/A, E138E/D, V151V/I, and N155H and NRTI mutations A62A/V, K65K/R, K70K/E, and M184V

**Treatment emergent NRTI mutations detected: K65R
¶E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility
‡Treatment-emergent NNRTI mutations detected: K101E (n=1); K103N (n=1); K103K/N (n=2) , G190A (n=1) ; K103N+G190A (n=1)

BL, baseline; c/mL, copies/mL; INI, integrase inhibitor
PDVF, protocol defined virologic failure

1. Adapted from Raffi F, et al. Lancet 2013;381:735–43
2. Adapted from Walmsley S, et al. N Engl J Med 2013; 369:1807-18
3. Adapted from Walmsley S, et al. N Engl J Med 2013; 369:1807-18 (suppl appendix)
4. TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014
5. Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

IN TREATMENT-EXPERIENCED AND INI-NAÏVE PATIENTS DTG HAD FEWER RESISTANCE MUTATIONS THAN RAL THROUGH 48 WEEKS

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

	DTG 50 mg QD + OBR (n=354)	RAL 400 mg BID + OBR (n=361)
Protocol-defined virologic failure, n (%)	21 (6)	45 (12)
INI mutations*, n (%)	4(1)†	17 (5) ‡

* Adjusted difference: -3.7% (95% CI:-6.1%,-1.2%); *P*=0.003. As the upper end of the 95% CI for the adjusted treatment difference was greater than 0, this finding demonstrated a statistically significant difference in favour of DTG.

† Treatment-emergent INI mutations detected: R263K, R263R/K, V151V/I; one patient developed a T97A and E138T/A mutation, however this patient was subsequently found to have a Q148 mutation at baseline.

‡One patient in each group had INI resistance at baseline

Substitutions seen at positions R263 and V151 did not confer high levels of resistance to DTG (2<fold change in IC50), or cross resistance to RAL.

Cahn P, et al. *Lancet* 2013;382(9893):700-708

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708(appendix)

DTG HAS A HIGH BARRIER TO RESISTANCE: RESISTANCE SUMMARY

SINGLE

ART-naive patients (n=833)[1,2]

No INI or NRTI resistance through 48 or 96 weeks with DTG

SPRING-2

ART-naive patients (n=822)[3,4]

No INI or NRTI resistance through 48 or 96 weeks with DTG

FLAMINGO

ART-naive patients (n=484)[5]

No emergent INI or NRTI mutations through 48 weeks with DTG

SAILING

Treatment-experienced, INI-naïve (n=715)[6]

Fewer resistance mutations with DTG than raltegravir (1% vs 5%) through 48 weeks

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
5. Clotet B, et al. *Lancet* 2014; 383: 2222-31
6. Cahn P, et al. *Lancet* 2013;382(9893):700-708

OVERALL CONCLUSIONS: RESISTANCE PROFILE OF DTG

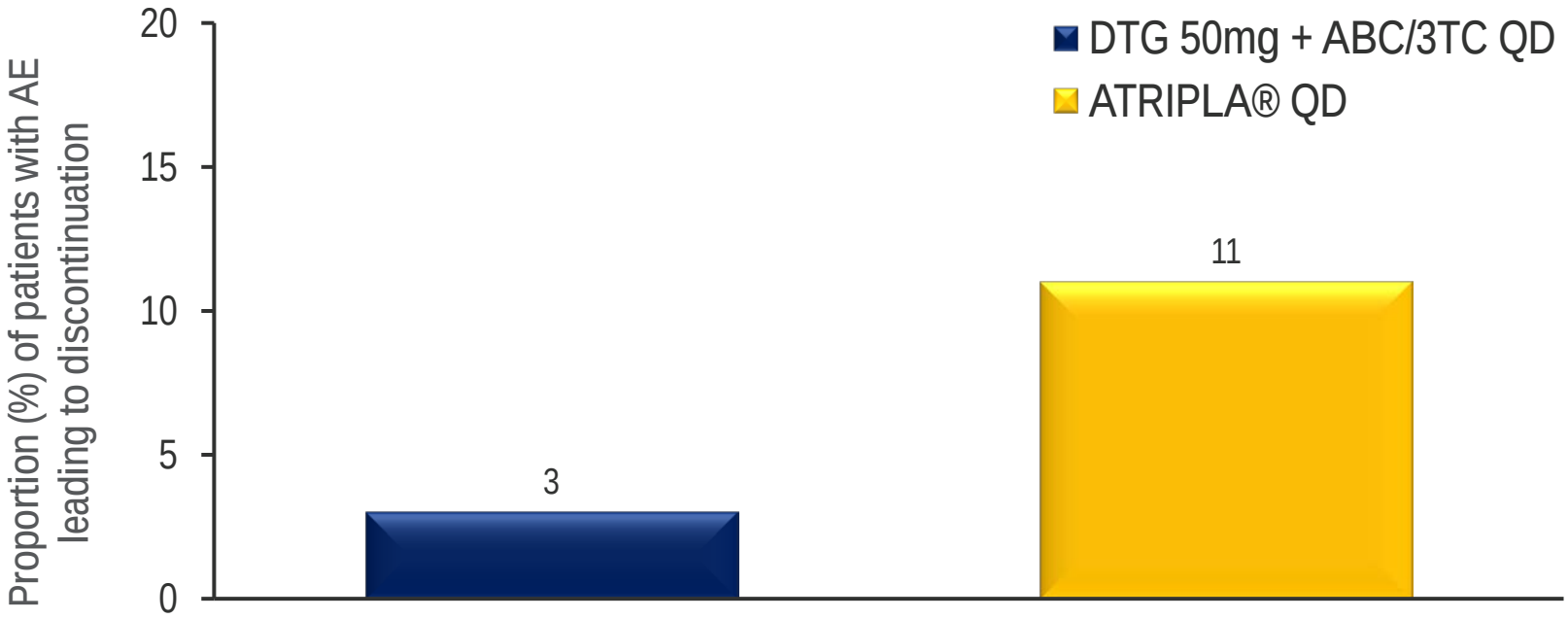
- *In-vitro* studies suggest DTG has a high barrier to resistance[1,2]
- In treatment-naïve subjects, no evidence of treatment-emergent resistance observed with DTG to date[3,4]
- In treatment-experienced, INI-naïve subjects, development of INI resistance was lower with DTG than with RAL, and was associated with low fold change in IC_{50}[5]
- In treatment-experienced, INI-resistant subjects previously treated with RAL or EVG, a number of INI resistance mutations were required to confer reduced susceptibility to DTG[6,7]
- No *in-vivo* evidence of emergence of novel mutations that result in a substantial decrease in DTG susceptibility to date[5–7]
- The slower dissociation of DTG and the need for accumulation of multiple RAL-associated mutations contribute to its distinct resistance profile and potential to have a higher barrier to resistance[8]

1. Sato A, et al. IAS 2009. Abstract WEPEA097; 2. Seki T, et al. CROI 2010. Poster J-122
3. Raffi F, et al. *Lancet* 2013;381:735–43; 4 Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
5. Cahn P, et al. *Lancet* 2013;382(9893):700-708; 6. Eron J, et al. *J Infect Dis* 2013;207:740–8
7 . Castagna et al. *J Infect Dis* 2014; 210(3):354-62
8. Hightower KE, et al. *Antimicrob Agents Chemother* 2011;55:4552–9

TOLERABILITY AND SAFETY PROFILE OF DOLUTEGRAVIR

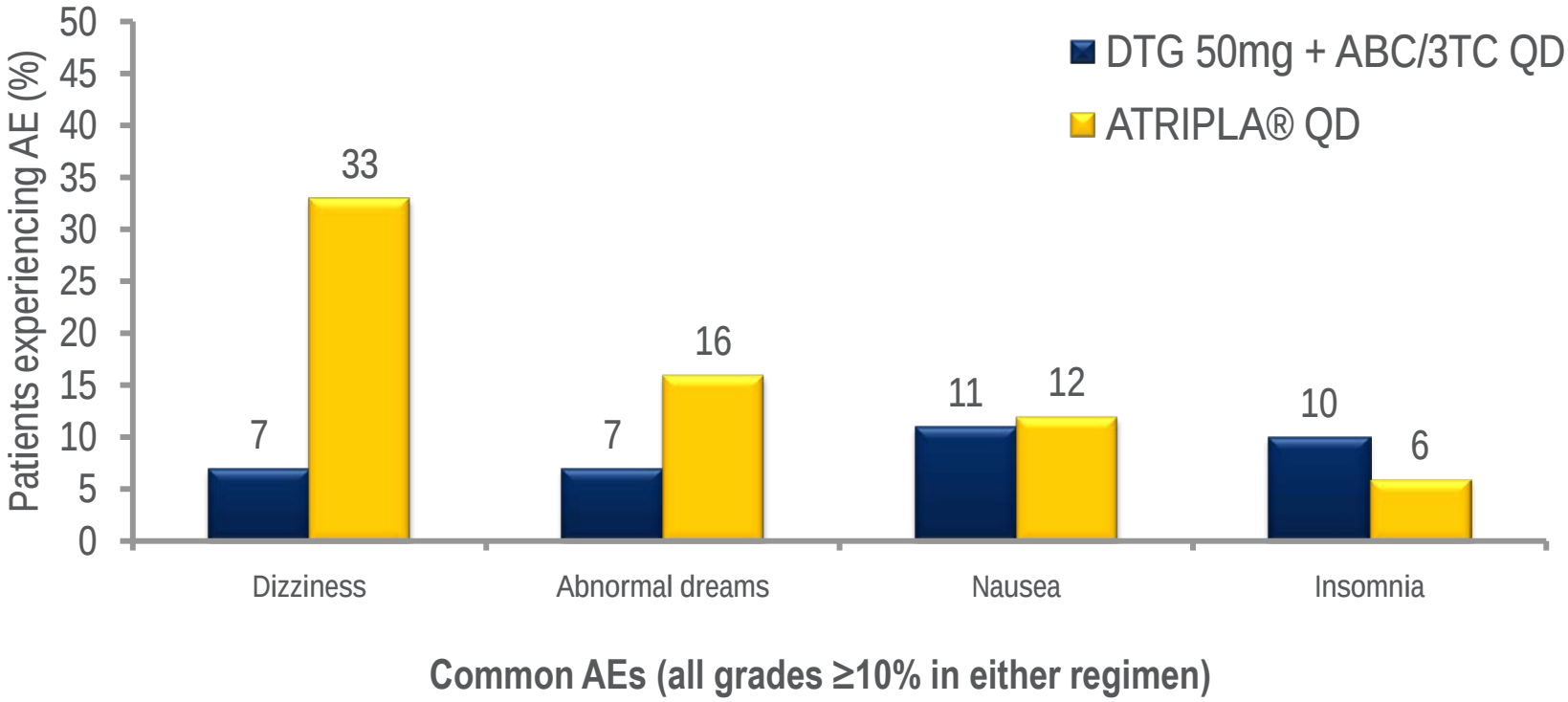
FEWER DISCONTINUATIONS DUE TO ADVERSE EVENTS UP TO 96 WEEKS WITH DTG + ABC/3TC VS ATRIPLA®

Discontinuations due to adverse events were 3% for DTG + ABC/3TC vs 11% for EFV/TDF/FTC at Week 96



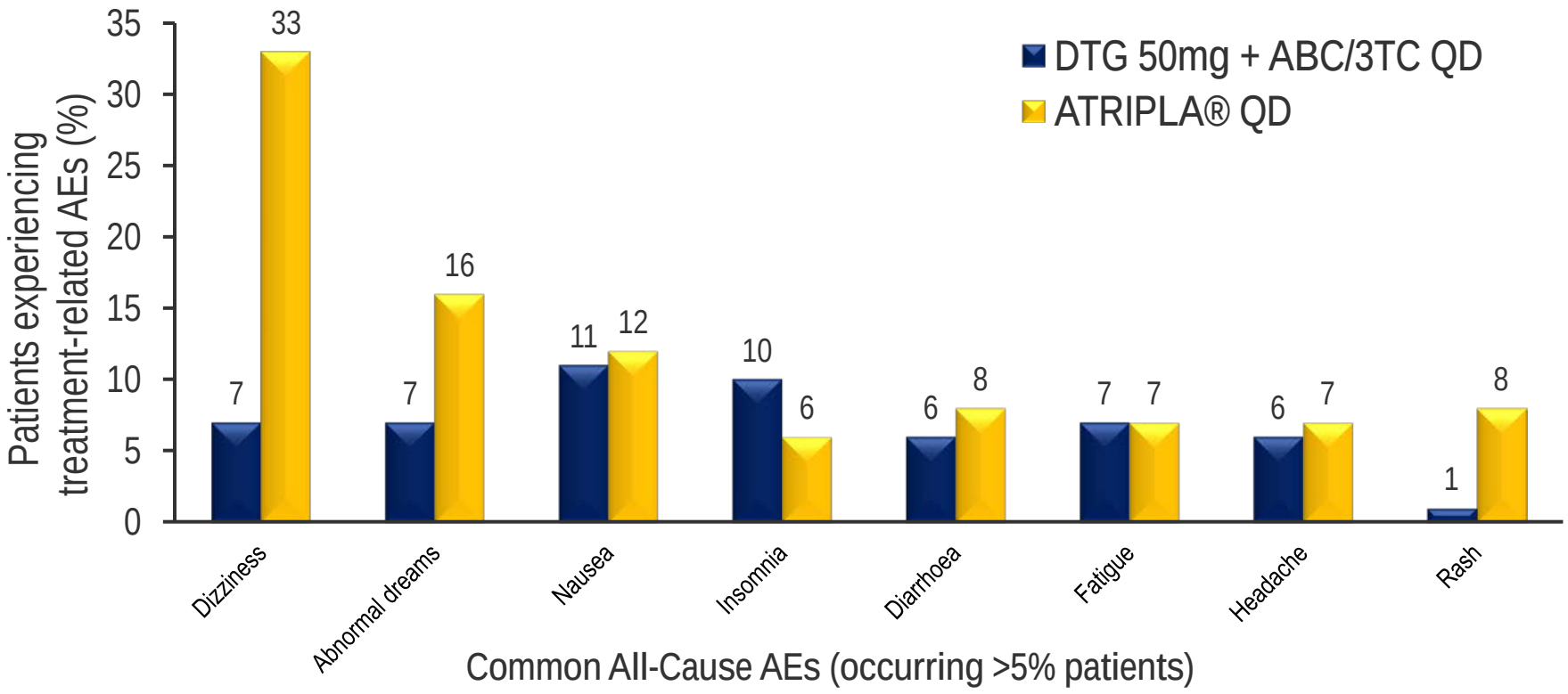
Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

DTG + ABC/3TC WAS GENERALLY BETTER TOLERATED VS ATRIPLA® AT WEEK 96



Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

DTG + ABC/3TC WAS GENERALLY BETTER TOLERATED VS ATRIPLA® AT WEEK 96



Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
Data on file. SINGLE 96 week CSR Table 8.8

DTG WAS GENERALLY WELL TOLERATED WITH FEW DISCONTINUATIONS VS RAL AT WEEK 48

Discontinuations due to AEs were 2% for DTG vs 2% for RAL at week 48[1]

AEs, n (%)	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)
AEs leading to withdrawal[1]	10 (2)	7 (2)
Serious drug related AEs[1,3]	3 (<1) Arrhythmia, hypersensitivity, hepatitis	5 (1)* Convulsion (2), aphasia, hypersensitivity, CPK increased[3], diarrhoea
Fatal AEs[2]	1 (<1)**	1 (<1)†

Drug-related Grade 2 to 4 AEs (any event) were 6% (24/411) for DTG and 7% (27/411) for RAL[1]

* One subject experienced 2 SAEs related to study drug (increased CPK and convulsions)
** Homicide considered not related to DTG
† Suicide considered not related to RAL
AST, aspartate amino transferase

1. Adapted from Raffi F et al. IAS 2012. Abstract THLBB04
2. Raffi F et al. *Lancet* 2013;381:735–43
3. Raffi F et al. Appendix from *Lancet* 2013;381:735–43

DTG DEMONSTRATED SIMILAR TOLERABILITY TO RAL

Discontinuations due to AEs were 2% for DTG vs 2% for RAL at Week 96[3]

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 96[3,4]		
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 THLBB04
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
4. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35 (suppl appendix)

DTG WAS GENERALLY WELL TOLERATED WITH FEW DISCONTINUATIONS VS DRV/r THROUGH 48 WEEKS

DTG was generally well tolerated with lower rates of diarrhoea vs darunavir / r

	DTG 50 mg QD (n=242), n (%)	DRV/r 800/100 mg QD (n=242), n (%)
Any event	206 (85%)	205 (85%)
Diarrhoea	41 (17%)	70 (29%)
Nausea	39 (16%)	43 (18%)
Headache	37 (15%)	24 (10%)
Nasopharyngitis	22 (9%)	19 (8%)
Insomnia	18 (7%)	15 (6%)
Fatigue	15 (6%)	12 (5%)
Vomiting	14 (6%)	15 (6%)
Dizziness	14 (6%)	11 (5%)
Upper respiratory tract infection	13 (5%)	23 (10%)
Cough	13 (5%)	17 (7%)
Pyrexia	13 (5%)	14 (6%)
Depression	11 (5%)	6 (2%)
Rash	9 (4%)	15 (6%)
Back pain	9 (4%)	12 (5%)
Pharyngitis	7 (3%)	12 (5%)
Sinusitis	6 (2%)	12 (5%)
Bronchitis	5 (2%)	13 (5%)
Arthralgia	5 (2%)	11 (5%)

Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31

IN TREATMENT-EXPERIENCED, INI-NAÏVE PATIENTS, DTG WAS GENERALLY WELL TOLERATED WITH FEW DISCONTINUATIONS AT 48 WEEKS

Adverse Events (AE), n (%) at 48 weeks	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
Subjects with AEs leading to discontinuation, n (%)	4 (1)	11 (3)
Serious drug-related AEs	2 (1)	4 (1)
Fatal AEs	0	3 (1)

Low rate of discontinuation due to AEs at 48 weeks (1% for DTG and 3% for RAL)

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

IN TREATMENT-EXPERIENCED, INI-NAÏVE PATIENTS, DTG DEMONSTRATED SIMILAR TOLERABILITY TO RAL AT 48 WEEKS

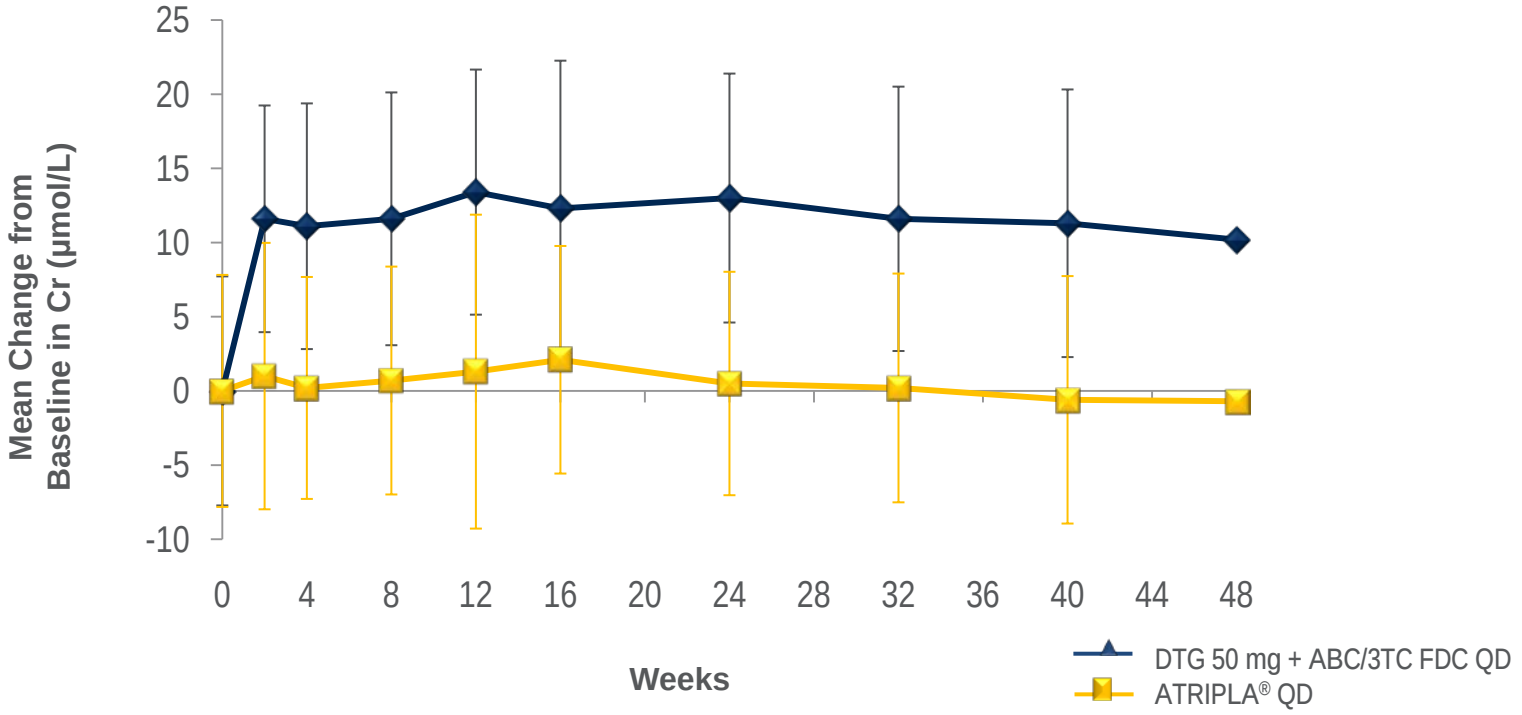
AEs, n (%)	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
AEs (≥5% in either arm)		
Diarrhoea	71 (20)	64 (18)
Upper respiratory tract infection	38 (11)	29 (8)
Headache	33 (9)	31 (9)
Nausea	29 (8)	29 (8)
Cough	33 (9)	24 (7)
Influenza	24 (7)	26 (7)
Nasopharyngitis	23 (6)	22 (6)
Urinary tract infection	26 (7)	18 (5)
Vomiting	20 (6)	20 (6)
Fatigue	15 (4)	24 (7)
Rash	19 (5)	18 (5)
Arthralgia	10 (3)	18 (5)
Upper abdominal pain	17 (5)	5 (1)

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

THE EFFECT OF DTG + ABC/3TC ON SERUM CREATININE UP TO 48 WEEKS IS NOT CLINICALLY RELEVANT

Small increases in serum creatinine occurred in the first week and remained stable through 48 weeks.

These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged.



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

TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014

Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996

THE EFFECT OF DTG + ABC/3TC ON SERUM CREATININE UP TO 96 WEEKS IS NOT CLINICALLY RELEVANT

Small increases in serum creatinine occurred in the first week and remained stable through 96 weeks.

These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged.

	DTG 50 mg+ABC/3TC QD		ATRIPLA® QD	
	Week 48	Week 96	Week 48	Week 96
Urine albumin/creatinine (mg/mmol) Median change (IQR)	0.00 (-0.30, 0.30)	0.00 (-0.30,0.20)	0.05 (-0.20, 0.30)	0.05 (-0.20, 0.30)
Serum creatinine (mg/dL) Median change (IQR)	0.11 (0.05,0.18)	0.14 (0.07,0.20)	-0.01 (-0.06,0.04)	0.02 (-0.04,0.07)

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

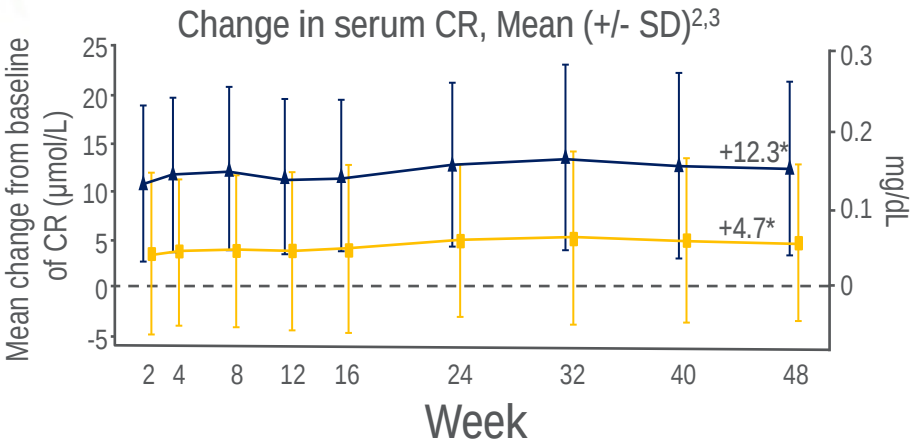
TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014

Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996

Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

THE EFFECT OF DTG ON SERUM CREATININE IS NOT CLINICALLY RELEVANT

These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged[1]



Baseline (µmol/L): DTG: 74.7 versus RAL: 75.2

Creatinine clearance by Cockcroft-Gault, mean (SD)[4]	DTG 50 mg QD + NRTIs*		RAL 400 mg BID + NRTIs*	
	n	mL/min	n	mL/min
Baseline	411	125 (25.8)	411	127.8 (31.2)
Week 24	389	-17.5 (13.4)	384	-6.4 (13.8)
Week 48	369	-16.5 (14.2)	353	-5.4 (13.9)

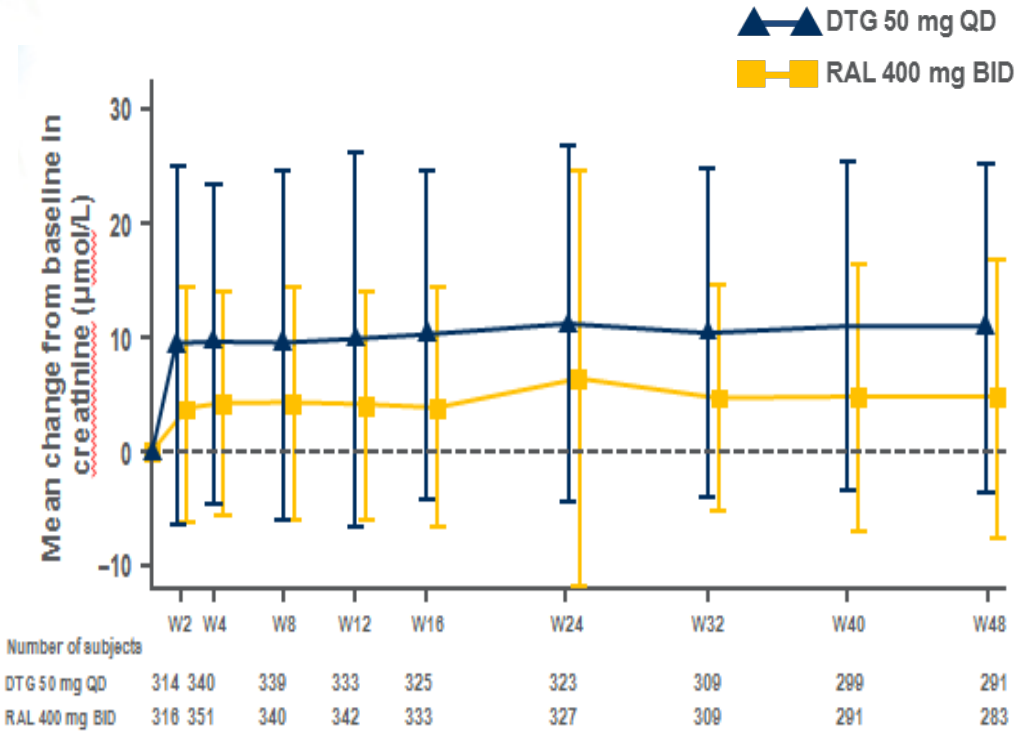
A small initial increase in creatinine was observed with DTG, due to the blockade of creatinine secretion.[2,3] There was no further increase in mean serum CR from Week 48 to Week 96 (Week 0 to 96: DTG +14.6 mmol/L; RAL +8.2 mmol/L)[5]

*Mean change in serum CR (mg/dL): DTG, +0.14mg/dL, RAL, +0.05 mg/dL; based on conversion rate 0.011mg/dL = 1 µmol/L
CR, creatinine

1. Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996
2. Raffi F et al. IAS 2012. Abstract THLBB04
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Adapted from Curtis LD, et al. IAS 2013. Poster TUPE282
5. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35

THE EFFECT OF DTG ON SERUM CREATININE IS NOT CLINICALLY RELEVANT

Small increases in serum creatinine occurred initially and then remained stable through 48 weeks.[1] These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged.[2]



	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
Renal laboratory values[3]		
Change from baseline serum creatinine (µmol/L), mean (SD)	11.1 (15.53)* (n=291)	5.1 (12.23) (n=283)
Change from baseline urine albumin/creatinine ratio (mg/mmol), mean (SD)	-0.33 (27.51) (n= 260)	-0.56 (31.81) (n=253)

*As previously described, small non-progressive increase in serum creatinine due to OCT2 inhibition

ALT, alanine aminotransferase; CPK, creatine phosphokinase

1. Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708
2. Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996
3. Adapted from Cahn P, et al. IAS 2013. Abstract WELBB03

THE EFFECT OF DTG ON SERUM CREATININE IS NOT CLINICALLY RELEVANT AS GFR IS UNCHANGED

- Open-label, randomised, parallel, placebo-controlled study in 34 healthy individuals
- Participants received DTG 50 mg (q12h or q24h) or placebo for 14 days

PD parameter	Ratio of geometric LS means (90% CI) Day 14/Day –1		Interpretation
	DTG q24 h vs placebo	DTG q12h vs placebo	
Iohexol clearance* ($mL/min/1.73m^2$)	0.993 (0.915–1.08)	1.045 (0.963–1.135)	DTG does not affect GFR
PAH clearance* ($mL/min/1.73m^2$)	1.029 (0.921–1.150)	0.969 (0.866–1.08)	DTG does not affect renal plasma flow
Creatinine clearance* ($mL/min/1.73m^2$)	0.900 (0.808–1.00)	0.861 (0.772–0.960)	DTG leads to a modest (10–14%) decrease in creatinine clearance

*BSA-adjusted

BSA, body surface area; GFR, glomerular filtration rate; LS, least square; PAH, para-aminohippurate; q12h, every 12 hours; q24h, every 24 hours

Koteff J et al. *Br J Clin Pharmacol*. 2013;75(4):990-996]

RENAL SAFETY OF DTG: SUMMARY

The effect of DTG on serum creatinine is not clinically relevant

- DTG inhibits OCT2,[1] but without affecting glomerular filtration[2]
  - this is similar to other drugs such as trimethoprim or cimetidine
  - these drugs decrease tubular secretion of creatinine and therefore increase concentrations of serum creatinine without affecting glomerular filtration
- In Phase III trials, a small initial increase in creatinine was observed with DTG, due to this blockade of creatinine secretion[3–5]
  - no patients discontinued treatment in Phase III trials because of a renal AE
- No dosage adjustment is required in patients with mild, moderate or severe (CrCl <30 mL/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population.[6]

1. Koteff J, et al. ICAAC 2011. Abstract A1–1728
2. Koteff J et al. *Br J Clin Pharmacol*. 2013;75(4):990-996
3. Raffi F, et al. *Lancet* 2013;381:735–43]
4. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
5. Clotet B, et al. *Lancet* 2014; 383: 2222-31
6. TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014

DTG IS GENERALLY WELL TOLERATED: TOLERABILITY SUMMARY

SINGLE

ART-naïve patients (n=833)[1,2]

DTG + ABC/3TC was better tolerated vs Atripla® with fewer discontinuations

- 2% vs 10% discontinued due to AEs at 48 weeks
- 3% vs 11% discontinued due to AEs at 96 weeks

SPRING-2

ART-naïve patients (n=822)[3,4]

DTG demonstrated similar tolerability to RAL

- 2% vs 2% discontinued due to AEs at 48 weeks
- 2% vs 2% discontinued due to AEs at 96 weeks

FLAMINGO

ART-naïve patients (n=484)[5]

DTG was generally well tolerated with lower rates of diarrhoea vs darunavir/r

- 2% vs 4% discontinued due to AEs at 48 weeks

SAILING

Treatment-experienced, INI-naïve (n=715)[6]

DTG demonstrated similar tolerability to RAL at 48 weeks

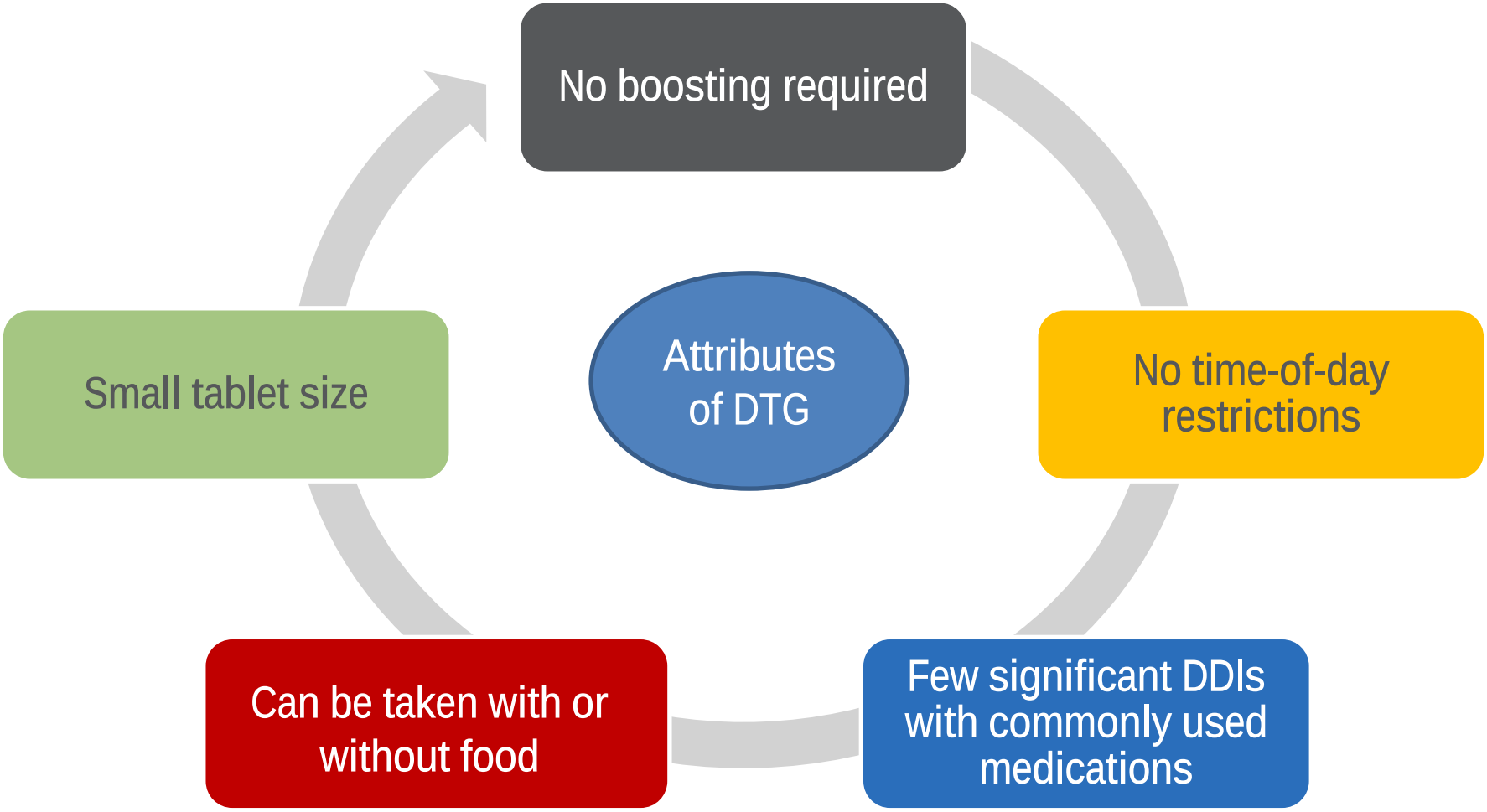
- 1% vs 3% discontinued due to AEs

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
5. Clotet B, et al. *Lancet* 2014; 383: 2222-31
6. Cahn P, et al. *Lancet* 2013;382(9893):700-708

CONVENIENCE

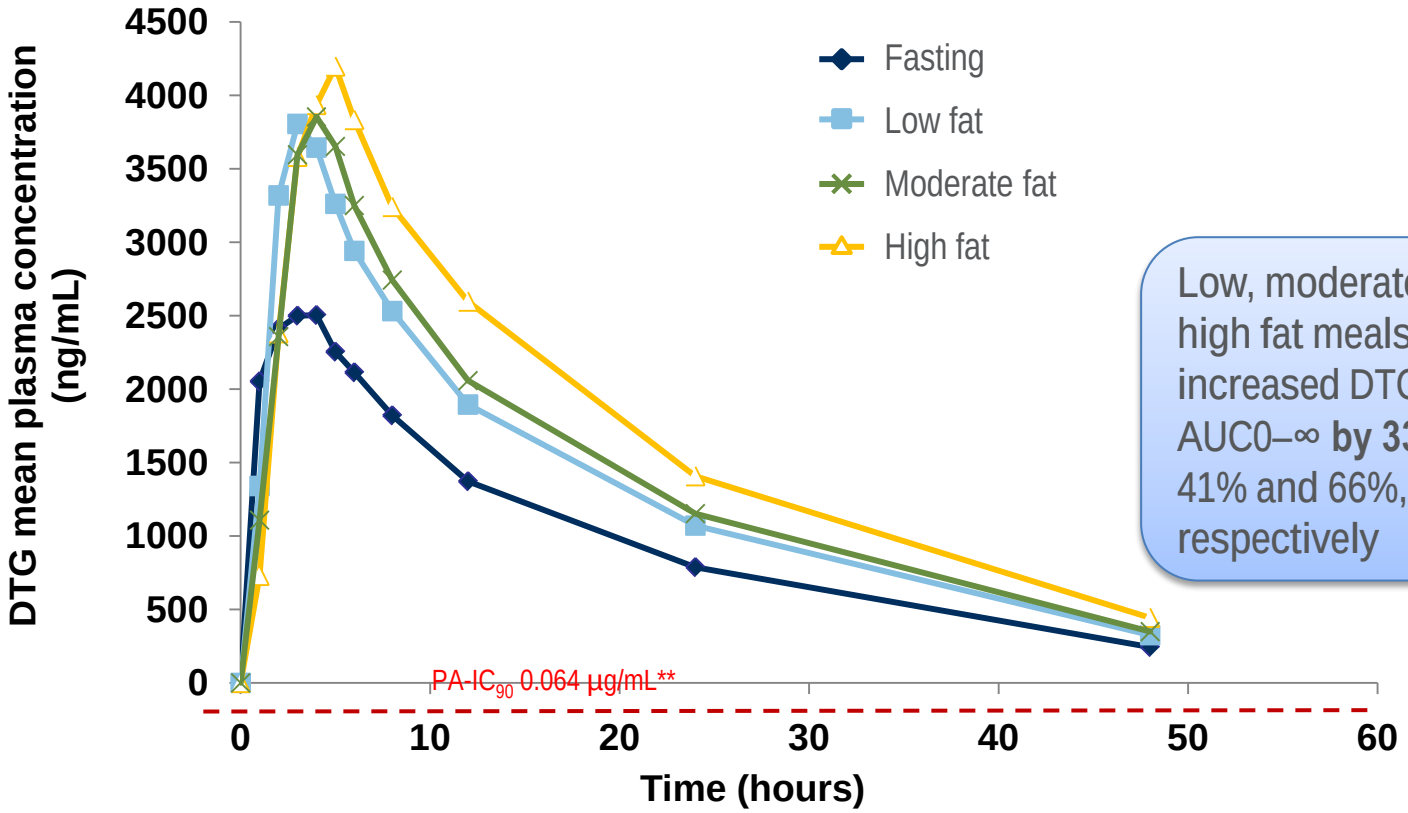
Including drug-drug interactions

CONVENIENCE BEYOND ONCE-DAILY DOSING



TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014

DTG CAN BE TAKEN WITH OR WITHOUT FOOD*



Low, moderate and high fat meals increased DTG † AUC0–∞ **by 33%,** 41% and 66%, respectively

Administration with food increased DTG exposure, but this was not clinically significant and therefore DTG can be taken without regard to meals*

*In the presence of INI-class resistance, DTG should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations)

**PA-IC_{90} is the protein-adjusted 90% inhibitory concentration;

†Phase III (50 mg) formulation

TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014

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

DTG HAS FEW SIGNIFICANT INTERACTIONS WITH COMMONLY USED MEDICATIONS[1,2,3]

Commonly used medications	Dose adjustment required
Oral contraceptives	No
Proton pump inhibitors	No
H_2 antagonists (including cimetidine, famotidine, nizatidine, ranitidine)	No
Methadone	No
Hepatitis B transcriptase inhibitor (adefovir)	No*
Hepatitis C protease inhibitors (telaprevir, boceprevir)	No
Antidepressants	No*
Statins	No*
Rifampicin	Dose DTG 50 mg BID Avoid in INI-class resistance
Magnesium/aluminium-containing antacids Calcium and iron supplements Multivitamins	Dose DTG 2 hours before or 6 hours after these medicines
EFV, NVP, and TPV/r	Dose DTG 50 mg BID Avoid in INI-class resistance
ETV	Must only be used in combination with ATV/r, DRV/r or LPV/r

- DTG and dofetilide co-administration contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration
- DTG is not primarily metabolised via the CYP450 pathway†
- List is not complete, and for further information the TIVICAY SmPC should be consulted

* Based on results from other drug interaction trials, DTG is not expected to affect the pharmacokinetics of these drugs

† DTG is metabolised by the UGT1A1 pathway

1. TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014
2. Fantauzzi A et al. *HIV/AIDS (Auckl)* 2013;5:29-40
3. Teixeira R et al. *Braz J Infect Dis* 2013;17(2):194-204)

DOSING RECOMMENDATIONS FOR DTG (PATIENTS AGED ≥12 YEARS AND ≥40KG)

As part of combination therapy in patients without documented or clinically suspected resistance to the integrase class the usual dose is	One tablet daily with or without food

DTG should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin).

TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014

IN PATIENTS WITH INI-CLASS RESISTANCE

- The recommended dose of DTG is one 50 mg tablet twice-daily
- DTG should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations)
- Co-administration of DTG with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin)

TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014

PK/PD PROFILE OF DTG VERSUS ELVITEGRAVIR AND RALTEGRAVIR

	DTG[1–3]	RAL[4]	EVG[5,6]
Clinical dose	50 mg QD (INI-naïve), 50 mg BID (INI-resistant)	400 mg BID	150 mg QD boosted (quad pill)
$t_{1/2}$	~14 hours	~9 hours	~12.9 hours (boosted)
PK variability	Low to moderate	High	Low (with boosting)
Food effect	Can be taken with or without food	No food restriction, but fat content affects absorption and increases PK variability	Taken with food
Protein binding	High: 99.5–99.7%	Moderate: 83%	High: 98–99%
Metabolism and excretion	UGT1A1 (major), CYP3A (minor), renal elimination <1%	UGT1A1, renal elimination ~9%	CYP3A (major), UGT1A1/3 (minor), renal elimination 6.7%
PK/PD relationship	Yes, C_{trough}-driven efficacy	No	Yes, C_{trough}-driven efficacy

DTG has a favourable PK/PD profile compared with other INIs, including EVG and RAL

1. TIVICAY (dolutegravir) Summary of Product Characteristics, June 2014
2. Min S, et al. *Antimicrob Agents Chemother* 2010;54:254–8
3. Min S, et al. *AIDS* 2011;25:1737–45; 4. ISENTRESS (raltegravir) Summary of Product Characteristics, August 2013
5. STRIBILD Summary of Product Characteristics, March 2014; 6. Ramanathan S, et al. *Clin Pharmacokinet* 2011;50:229–44

Tivicay®▼ (dolutegravir) Prescribing Information
(Refer to SPC before prescribing)

Presentation: 50mg film-coated tablets of dolutegravir. **Indications:** Treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age, in combination with other anti-retroviral medicinal products. **Dosage and administration:** For use by physicians experienced in management of HIV infection. *Adults infected with HIV-1 without documented or clinically suspected resistance to the integrase class:* 50mg once daily with or without food. *Adults with resistance to the integrase class (documented or clinically suspected):* 50mg twice daily, preferably with food to enhance exposure (particularly in patients with Q148 mutations). Dolutegravir use should be informed by integrase resistance pattern. The recommended dose of Tivicay is 50mg twice daily when co-administered with efavirenz, nevirapine, tipranavir/ritonavir or rifampicin. *Adolescents aged 12 years and above (weighing at least 40kg) without integrase resistance*: 50mg once daily with or without food. *Children less than 12 years or weighing <40kg*: insufficient data to recommend a dose. *Elderly:* Limited data in patients over 65 years of age. *Renal impairment*: No dosage adjustment required in mild, moderate or severe (CrCl<30ml/min, not on dialysis) renal impairment. *Hepatic impairment*: No dosage adjustment required in mild or moderate hepatic impairment. No data in severe hepatic impairment. **Contraindications:** Hypersensitivity to dolutegravir or to any of the excipients. Co-administration with dofetilide. **Warnings and precautions:** Hypersensitivity reactions have been reported characterised by rash, constitutional findings, and organ dysfunction, including severe liver reactions. Discontinue dolutegravir and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop. Delay in stopping treatment may result in a life-threatening reaction. Monitor clinical status including liver aminotransferases and bilirubin. Institution of combination antiretroviral therapy may result in an inflammatory reaction to asymptomatic or residual opportunistic pathogens and cause serious clinical conditions, or aggravation of symptoms.Liver biochemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver biochemistries in hepatitis B and/or C co-infection is recommended. Initiate or maintain effective hepatitis B therapy when starting dolutegravir in hepatitis B co-infection. Osteonecrosis has been reported, particularly with acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure. Avoid factors that decrease dolutegravir exposure in the presence of integrase class resistance, including co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/aluminium-containing antacids, iron and calcium supplements, multivitamins and inducing agents, tipranavir/ritonavir, rifampicin and certain anti-epileptic drugs). Careful monitoring required with concomitant metformin. **Interactions:** Dolutegravir is metabolised mainly by UGT1A1. Co-administration with medicinal products inhibiting UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase plasma concentration. Dolutegravir is a substrate for UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; medicinal products inducing those enzymes may decrease dolutegravir plasma concentration and reduce its therapeutic effect. Dolutegravir may increase plasma concentrations of OCT2 dependent drugs (e.g. dofetilide, metformin). Avoid co-administration with enzyme inducers including anticonvulsants and St John's Wort. Administer dolutegravir 2 hours before or 6 hours after magnesium/aluminium-containing antacids, calcium, iron or multivitamin supplements. Dose with 50mg twice daily when co-administered with efavirenz, nevirapine, tipranavir/ritonavir or rifampicin. Consider alternative agents to these and fosamprenavir/ritonavir where possible in integrase resistant patients. Co-administration with etravirine is not recommended unless concomitant atazanavir + ritonavir, lopinavir + ritonavir or darunavir+ritonavir are given. **Pregnancy and lactation:** Not recommended in pregnant women. Avoid breast-feeding. **Side effects:** See SPC for full details. Very common (≥1/10): headache, diarrhoea, nausea. Common (≥1/100 to <1/10): insomnia, abnormal dreams, dizziness, vomiting, flatulence, abdominal pain or discomfort, rash, pruritus, fatigue, elevations of ALT, AST and CPK. Uncommon (≥1/1,000 to <1/100): hypersensitivity, Immune Reconstitution Syndrome, hepatitis. Serum creatinine increases within the first week of treatment and remains stable through 48 weeks (mean change from baseline 9.96 µmol/L). Creatinine increases were comparable by background regimen. These changes do not reflect alteration in glomerular filtration rate. **Basic NHS costs:** £498.75 for 30 tablets (Licence number: EU/1/13/892/001). Marketing authorisation holder: ViiV Healthcare UK Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS. Further information is available from Customer Contact Centre, GlaxoSmithKline UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

POM

Date of approval: January 2014
Zinc code: UK/DLG/0055/13(2)

Adverse events should be reported. For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard. For Ireland, adverse events should be reported directly to the IMB, Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Tel: +353 1 6764971. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441 in the UK or 1800 244 255 in Ireland.