Tivicay (dolutegravir) 50 mg tablets

WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

SUMMARY SLIDE DECK

Dolutegravir data at a glance

IL/DLG/0043/14 June 2014
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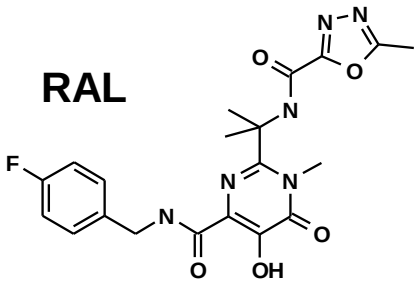
- What makes dolutegravir different?
- Efficacy of dolutegravir
- Resistance profile of dolutegravir
- Tolerability and safety profile of dolutegravir
- Convenience and drug-drug interactions

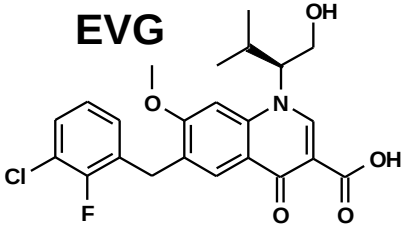
WHAT MAKES DOLUTEGRAVIR DIFFERENT

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

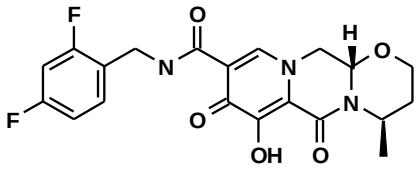
RAL



EVG



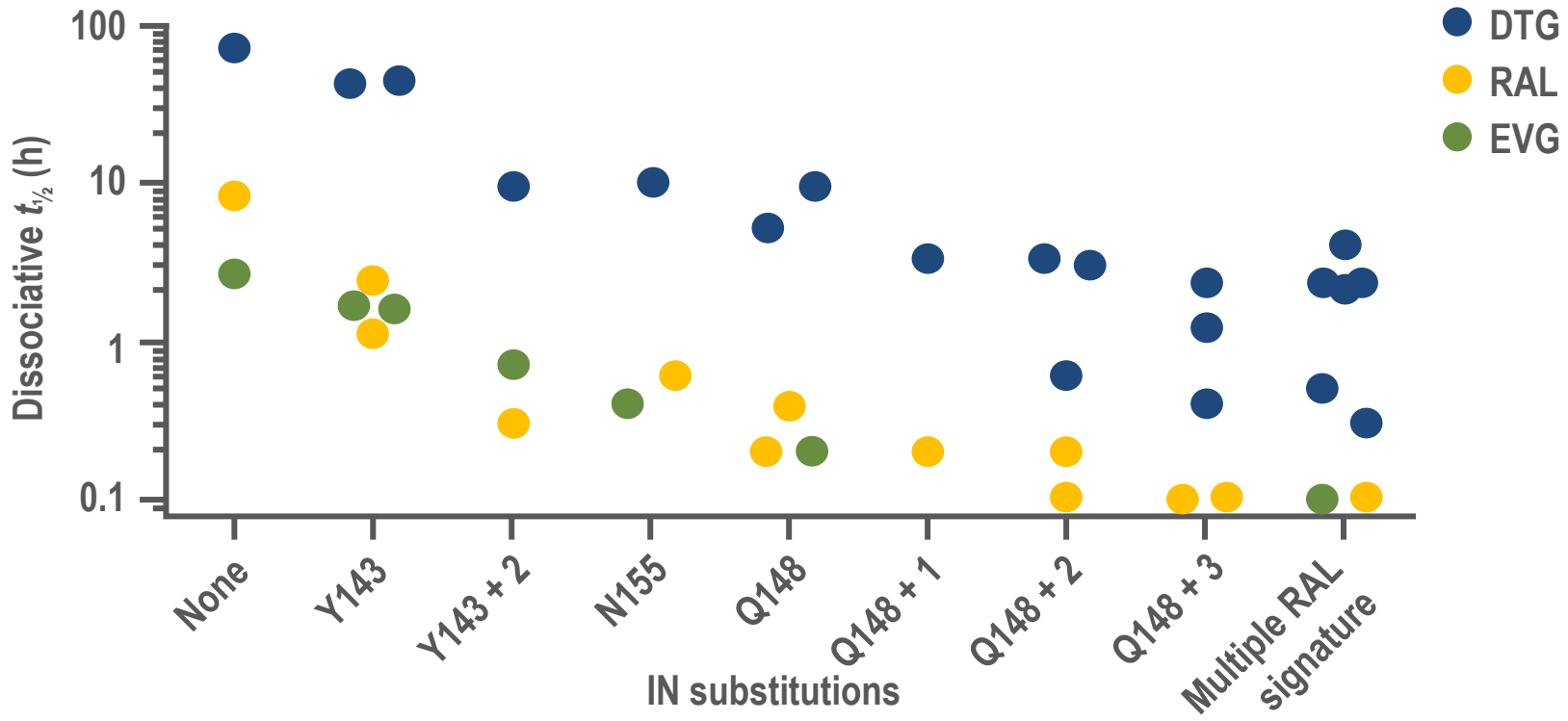
DTG



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

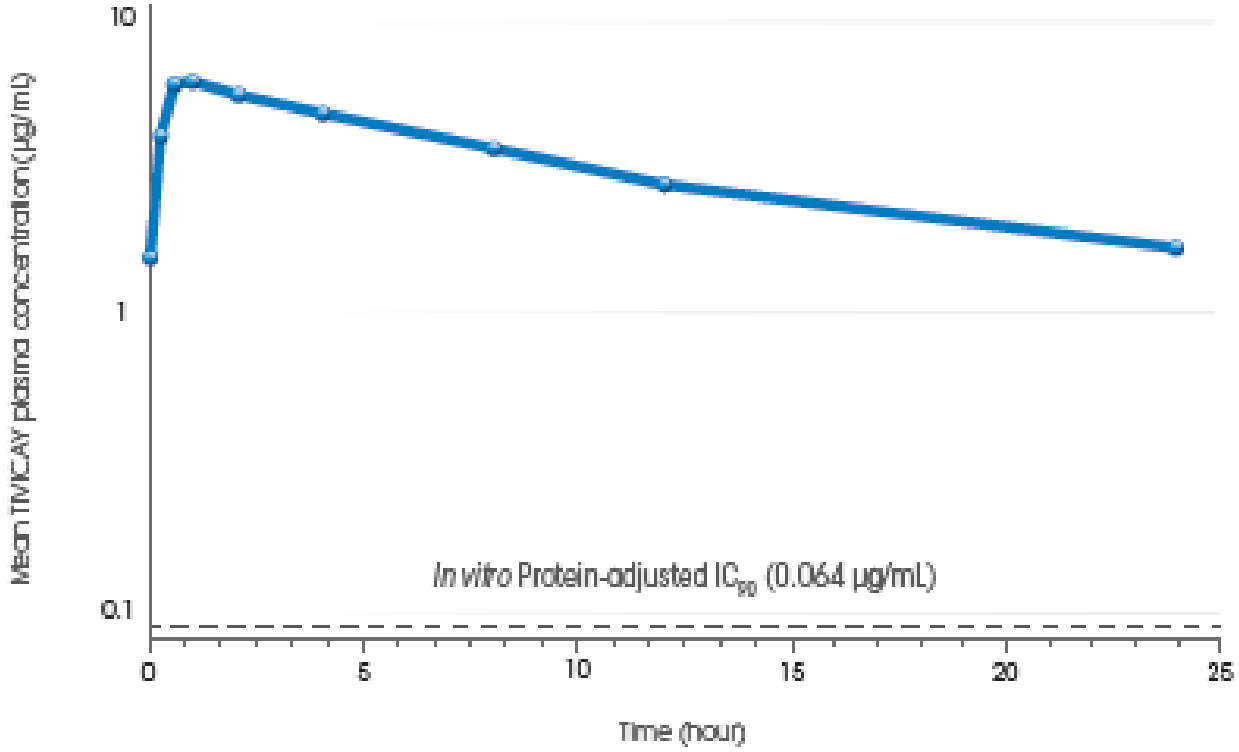


- DTG dissociation from IN-DNA complexes was slower compared with RAL and EVG
- The combination of multiple RAL signature substitutions or the accumulation of RAL secondary substitutions were needed to impact on DTG dissociation

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

DTG HAD A PREDICTABLE AND CONSISTENT PK PROFILE

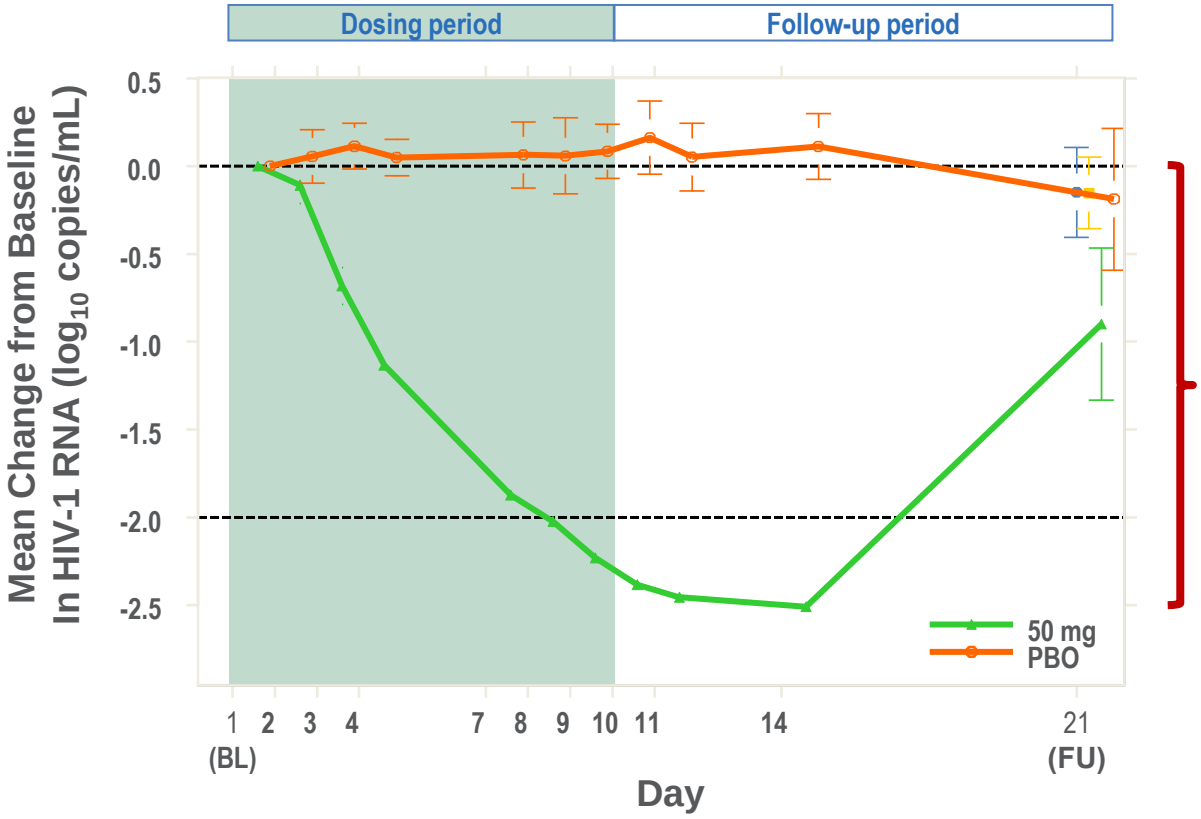
At 24 hours post-DTG administration, plasma concentrations were 19 to 25 fold above IC_{90}



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 CLINICAL PROGRAM WITH 2,854 PATIENTS ACROSS DTG TRIALS IN TREATMENT-NAÏVE AND INI-NAIVE ADULT SUBJECTS WITH HIV

Treatment- naïve patients

INI - naïve patients

SINGLE[1]	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[2]	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[3]	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
SAILING[4]	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

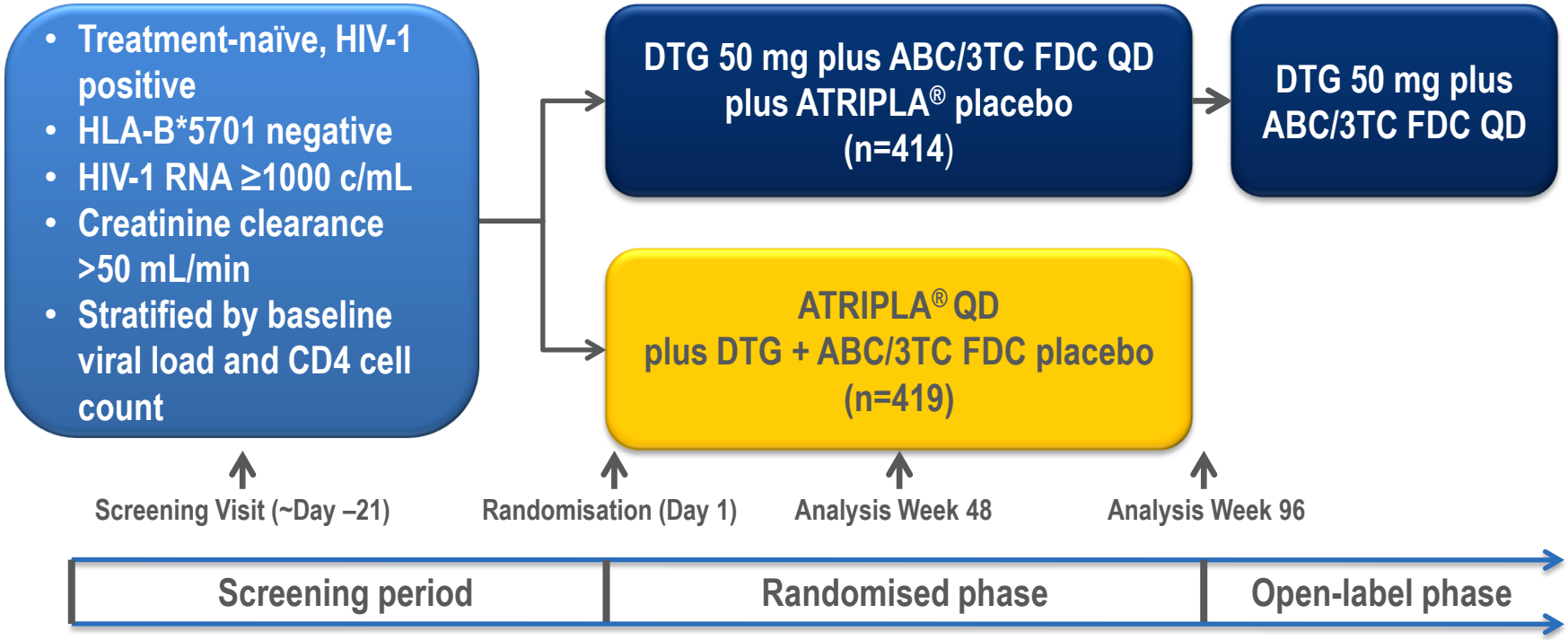
*Given as 2 x 400 mg tablets

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. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
3. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
4. 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. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

BASELINE CHARACTERISTICS

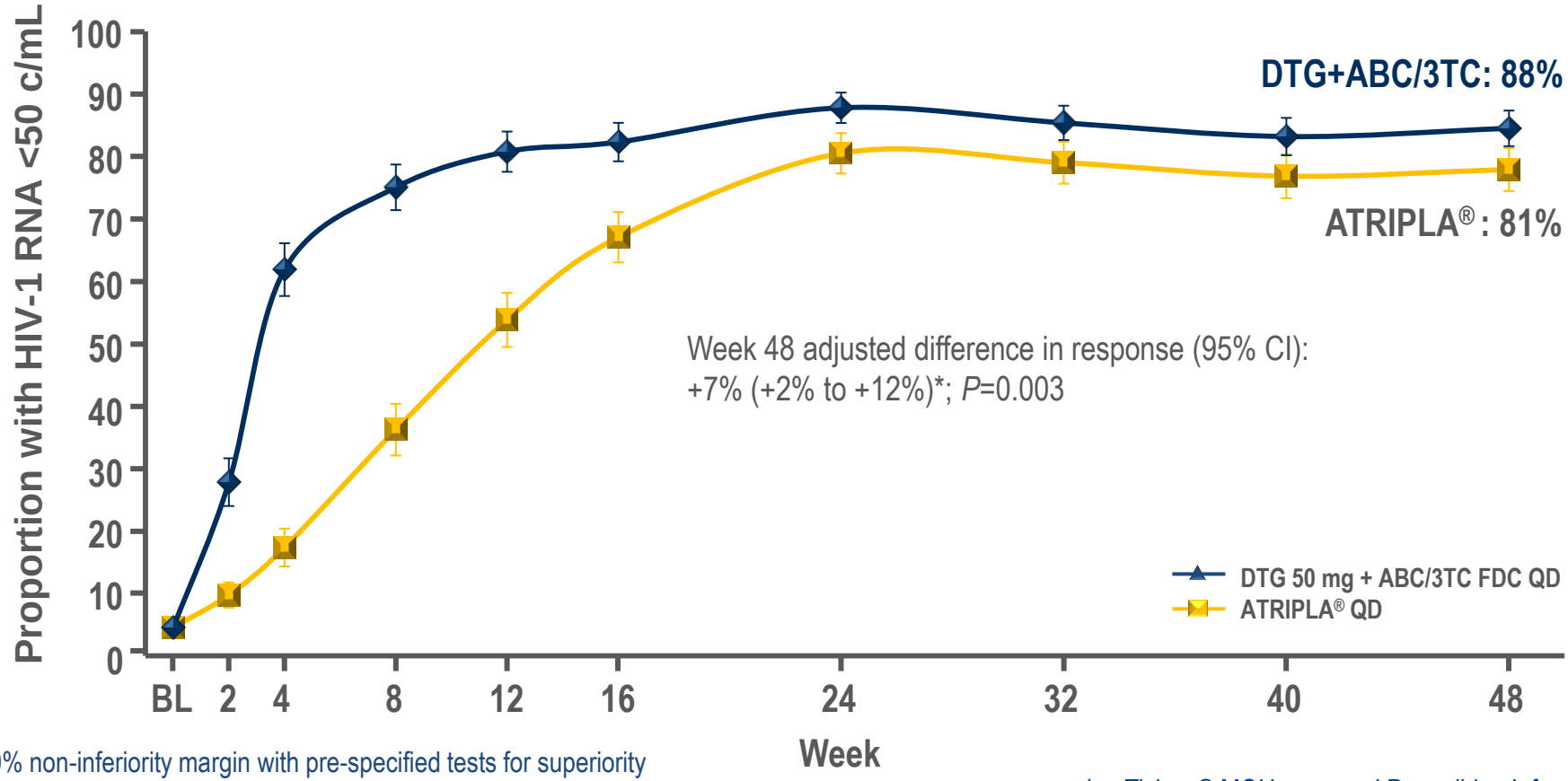
Characteristic	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Median age, years	36	35
Female, %	16	15
African American / African Heritage, %	24	24
CDC class C, %	4	4
Baseline HIV-1 RNA		
Median (log_{10} c/mL)	4.7	4.7
>100,000 c/mL, %	32	31
Median CD4 cell count, cells/mm^3	335	339
<200, %	14	14
200 to <350, %	39	38
350 to <500, %	32	31
≥500, %	15	17

CDC, Centers for Disease Control

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

IN TREATMENT-NAÏVE PATIENTS, DTG + ABC/3TC HAD STATISTICALLY SUPERIOR EFFICACY VS ATRIPLA®

DTG was statistically superior to Atripla® at Week 48
Subjects receiving DTG achieved faster virologic suppression than Atripla® (*P*<0.0001)*[1]

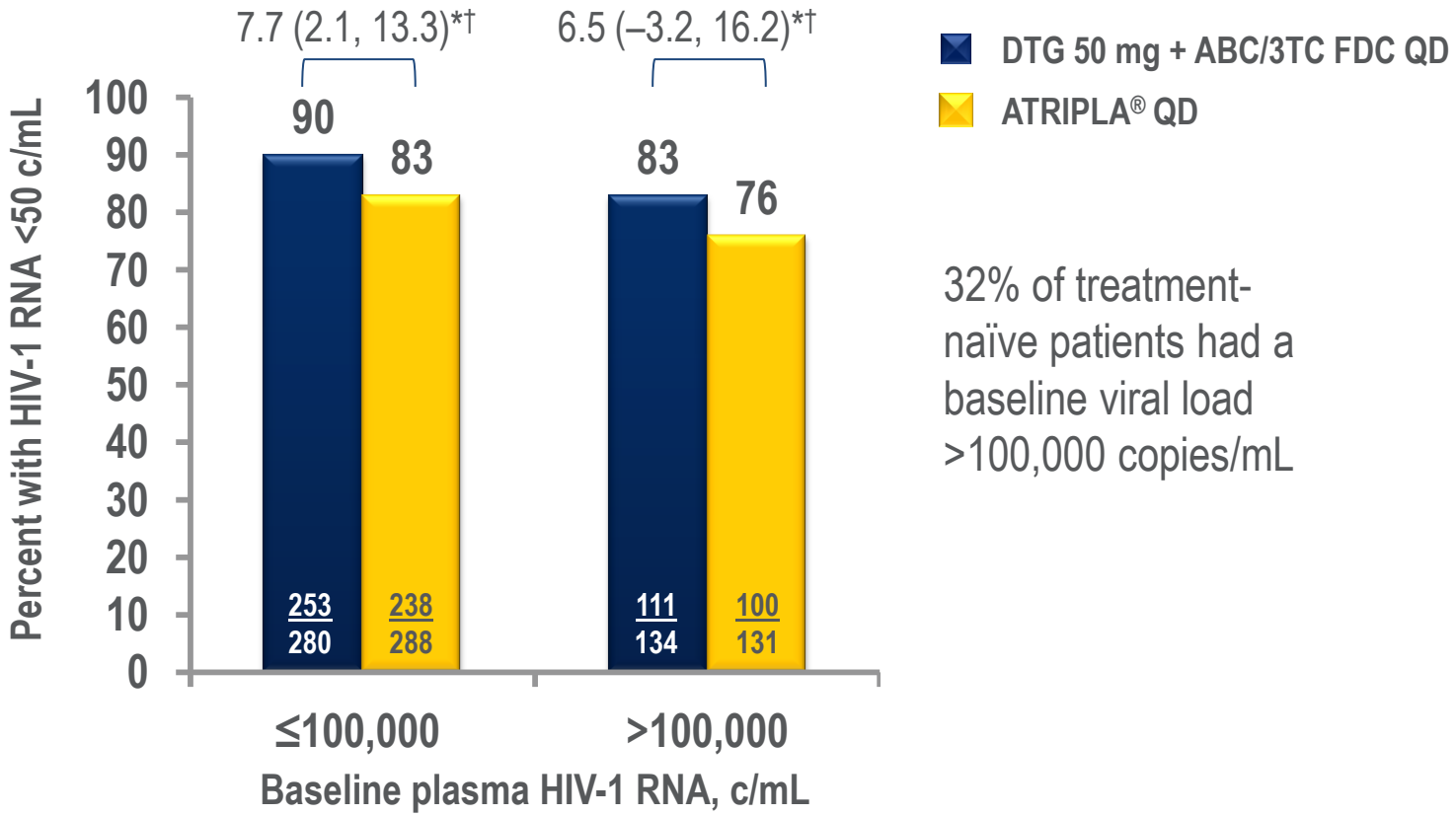


*-10% non-inferiority margin with pre-specified tests for superiority

1. Tivicay® MOH approved Prescribing Information.
2. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18

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

At Week 48, the number of patients achieving virologic response was numerically higher in the DTG + ABC/3TC group vs the Atripla® group, regardless of baseline viral load

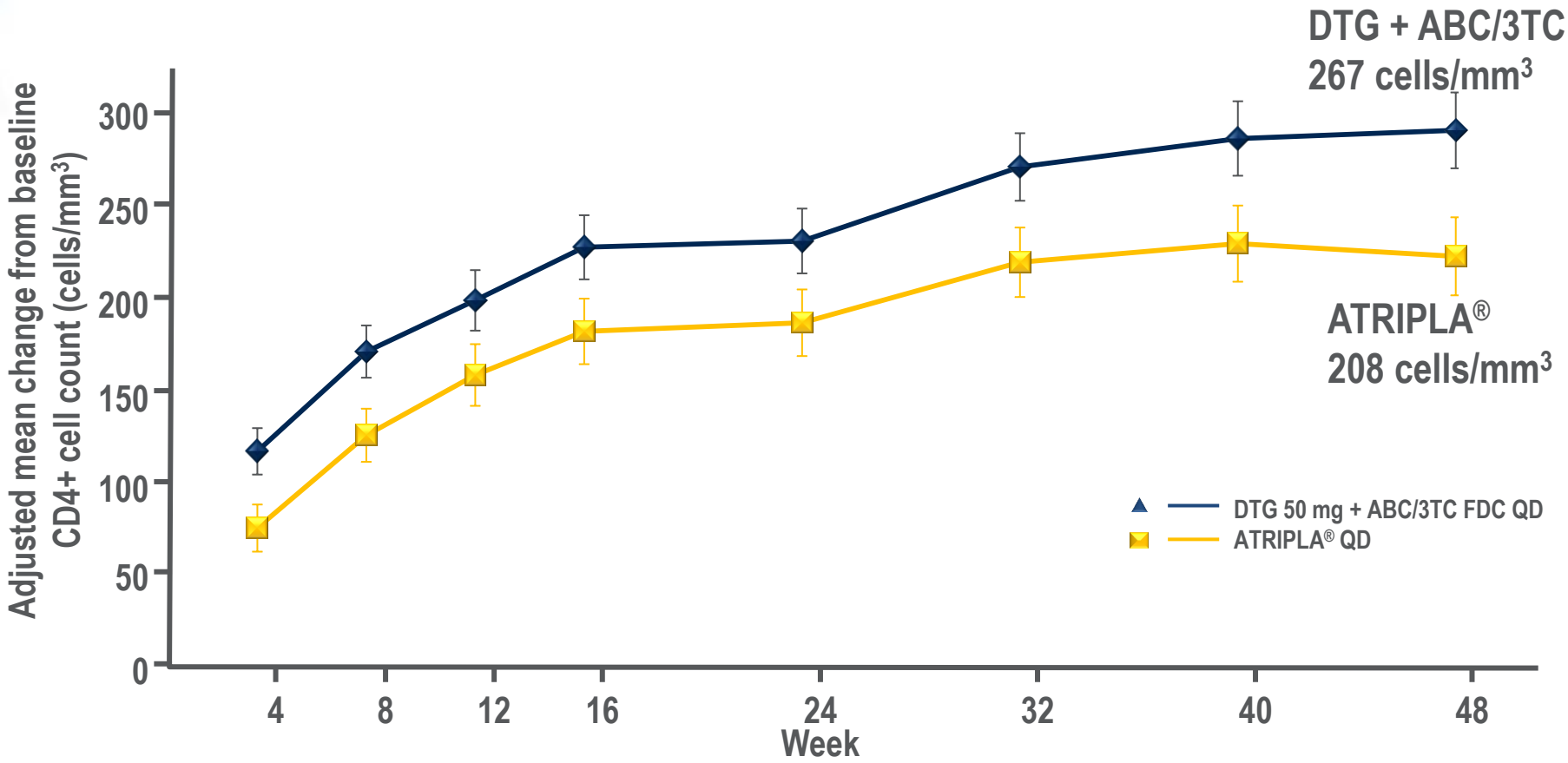


32% of treatment-naïve patients had a baseline viral load >100,000 copies/mL

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

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® AT WEEK 48

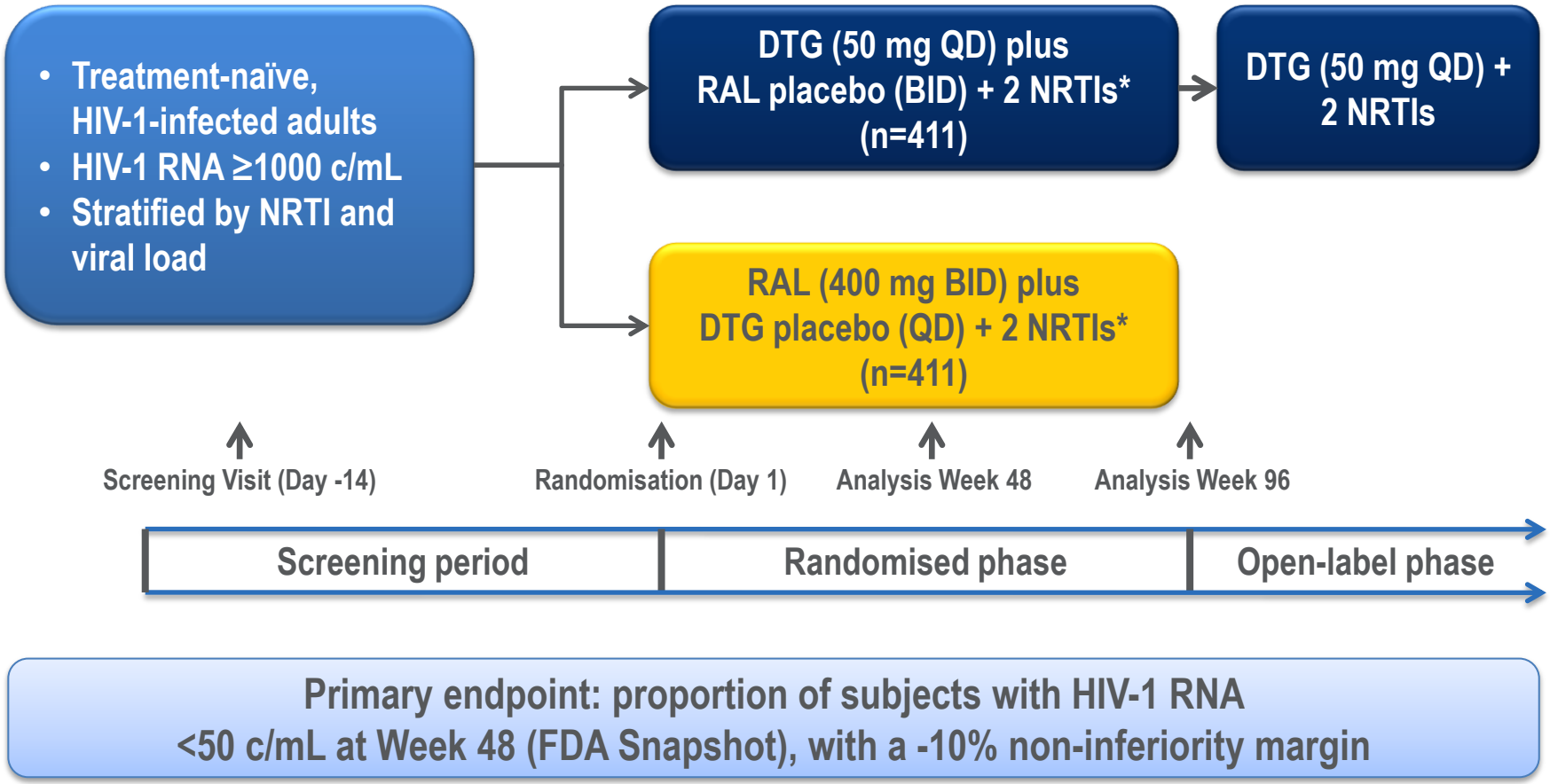


Week 48 difference in response (95% CI): 59 (33 to 84); $P<0.001$[2]

Significant at pre-specified level of 4%[2]

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

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

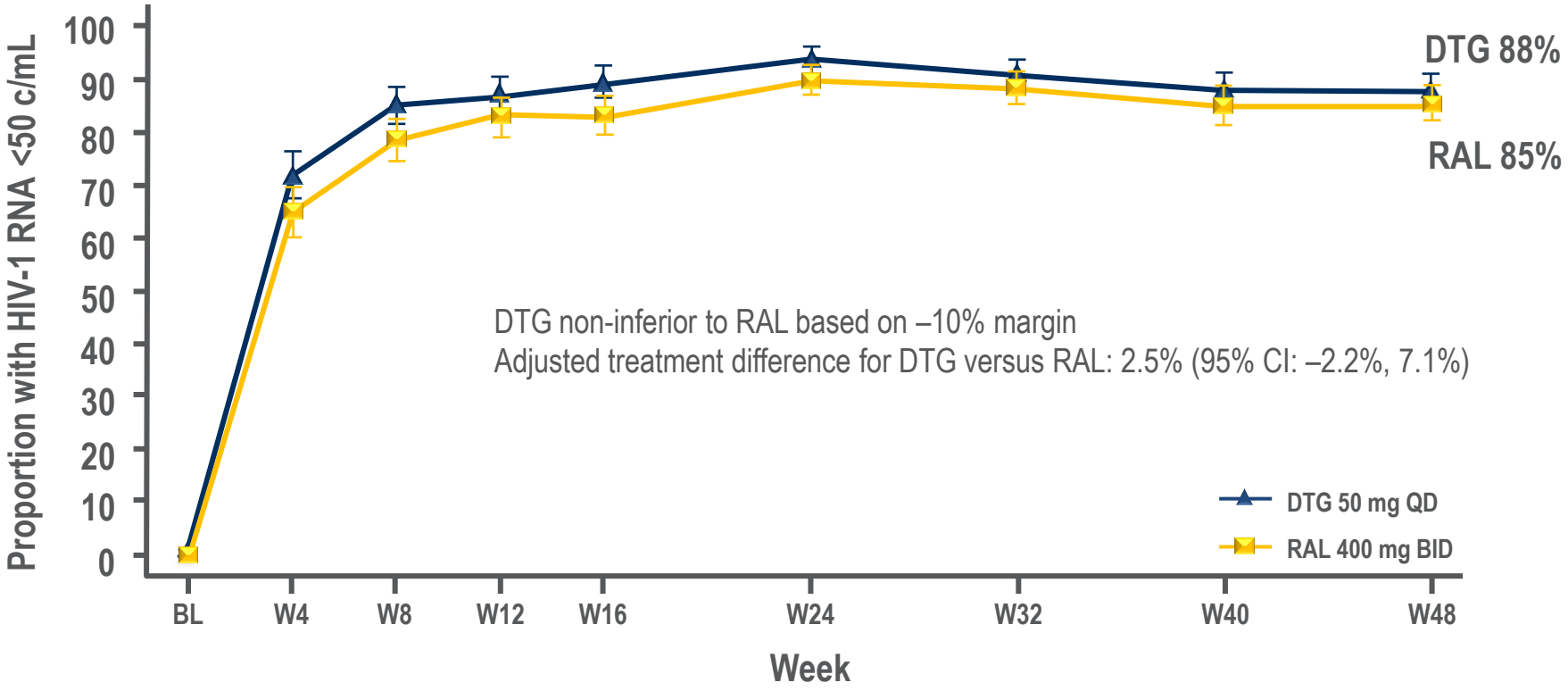
Raffi F et al. *Lancet* 2013;381:735–43

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)	4.5	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)

Adapted from Table 1 in Raffi F et al. *Lancet* 2013;381:735–43

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

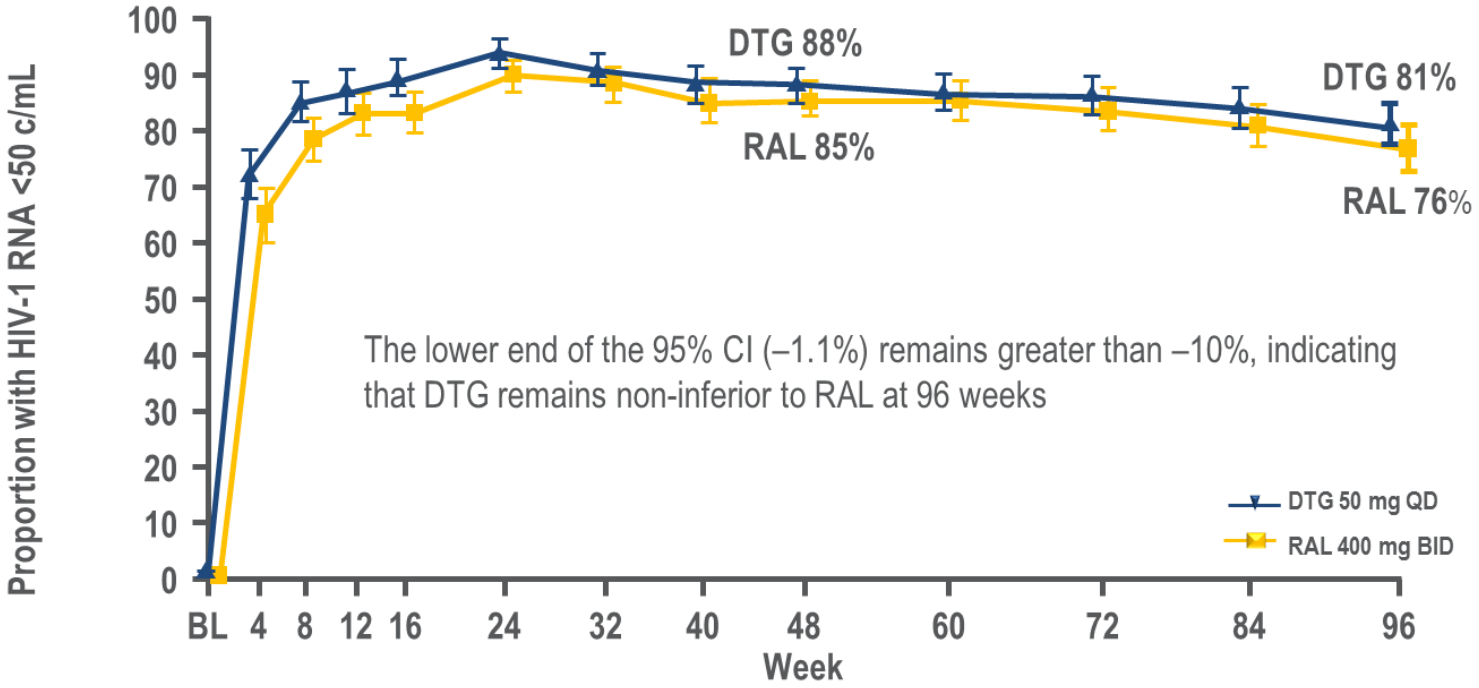


Median (IQR) Change From Baseline CD4+ Cell Count (cells/mm^3)

	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



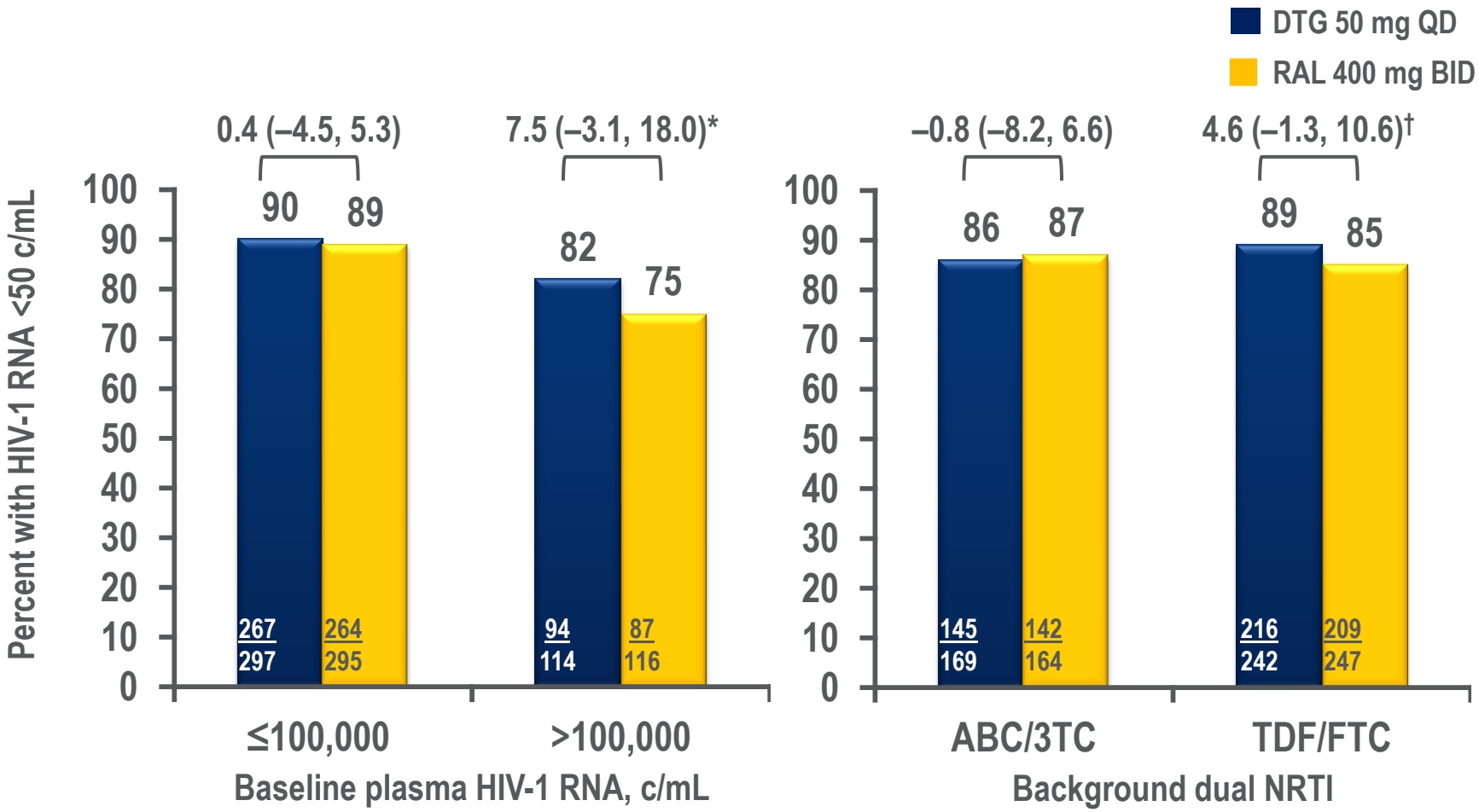
Treatment	Number of responders/ total assessed, n (%)	Difference in proportion (95% CI) (DTG - RAL)	Adjusted difference in proportion (95% CI) (DTG - RAL)
DTG 50 mg QD	332/411 (81)	4.4% (–1.2%, 10.0%)	4.5% (–1.1%, 10.0%)
RAL 400 mg BID	314/411 (76)		

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

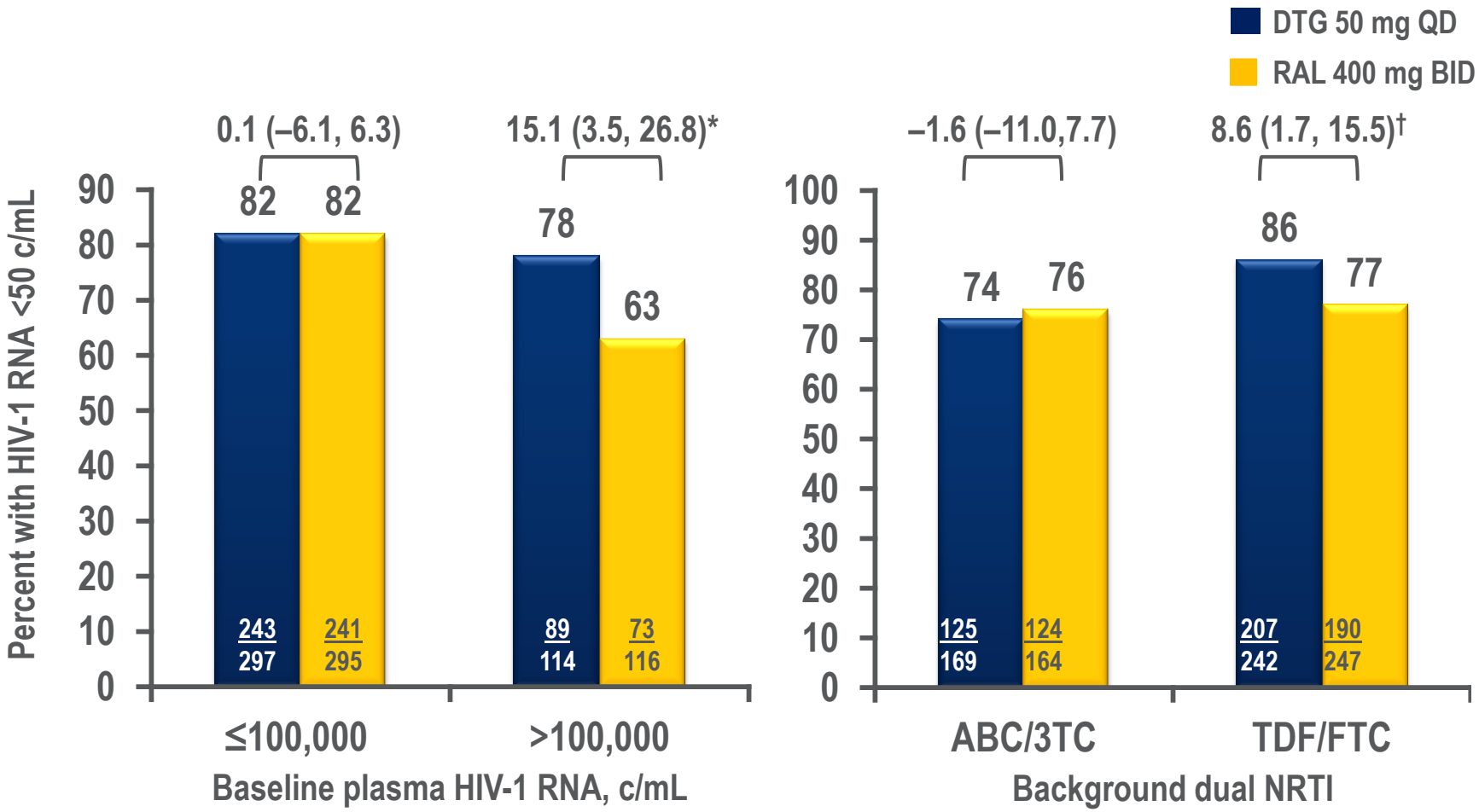
DTG EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD OR BACKGROUND REGIMEN (WEEK 48)



*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

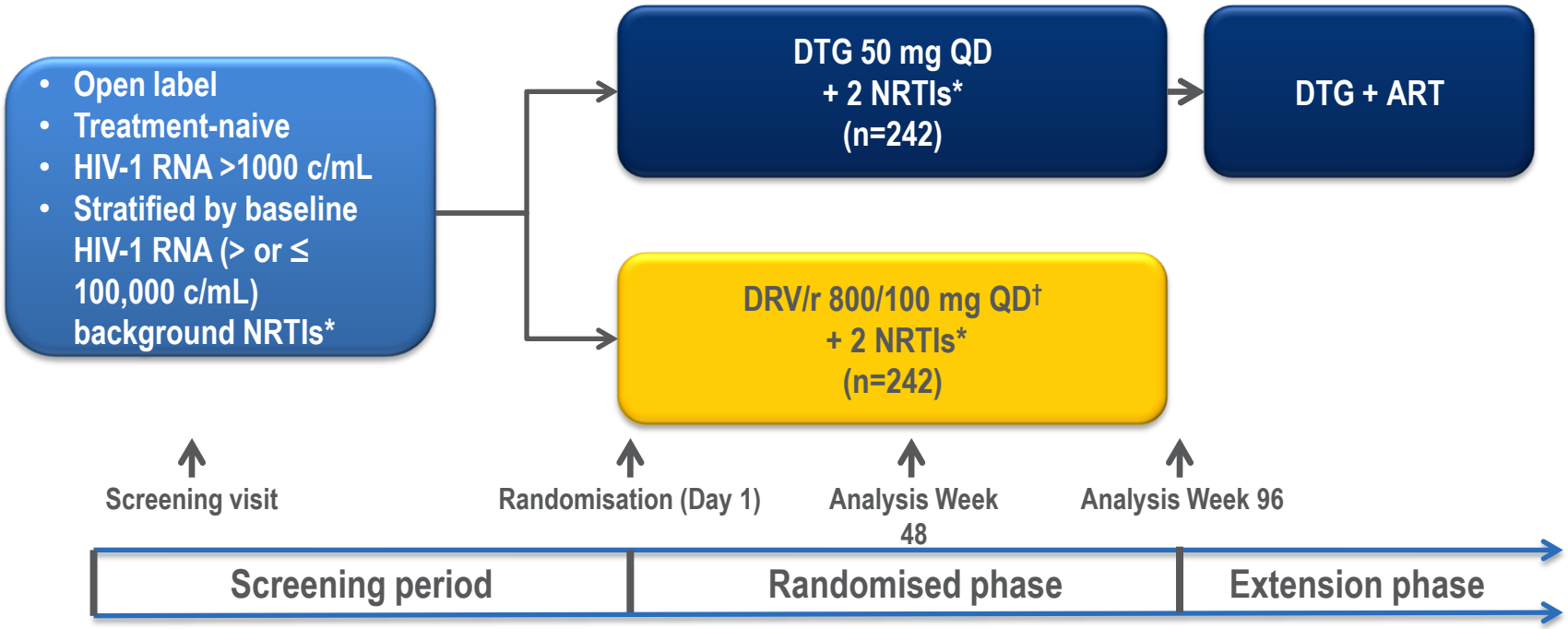
DTG EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD OR BACKGROUND REGIMEN (WEEK 96)



*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: ONGOING PHASE III TRIAL IN TREATMENT-NAÏVE SUBJECTS WITH HIV



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

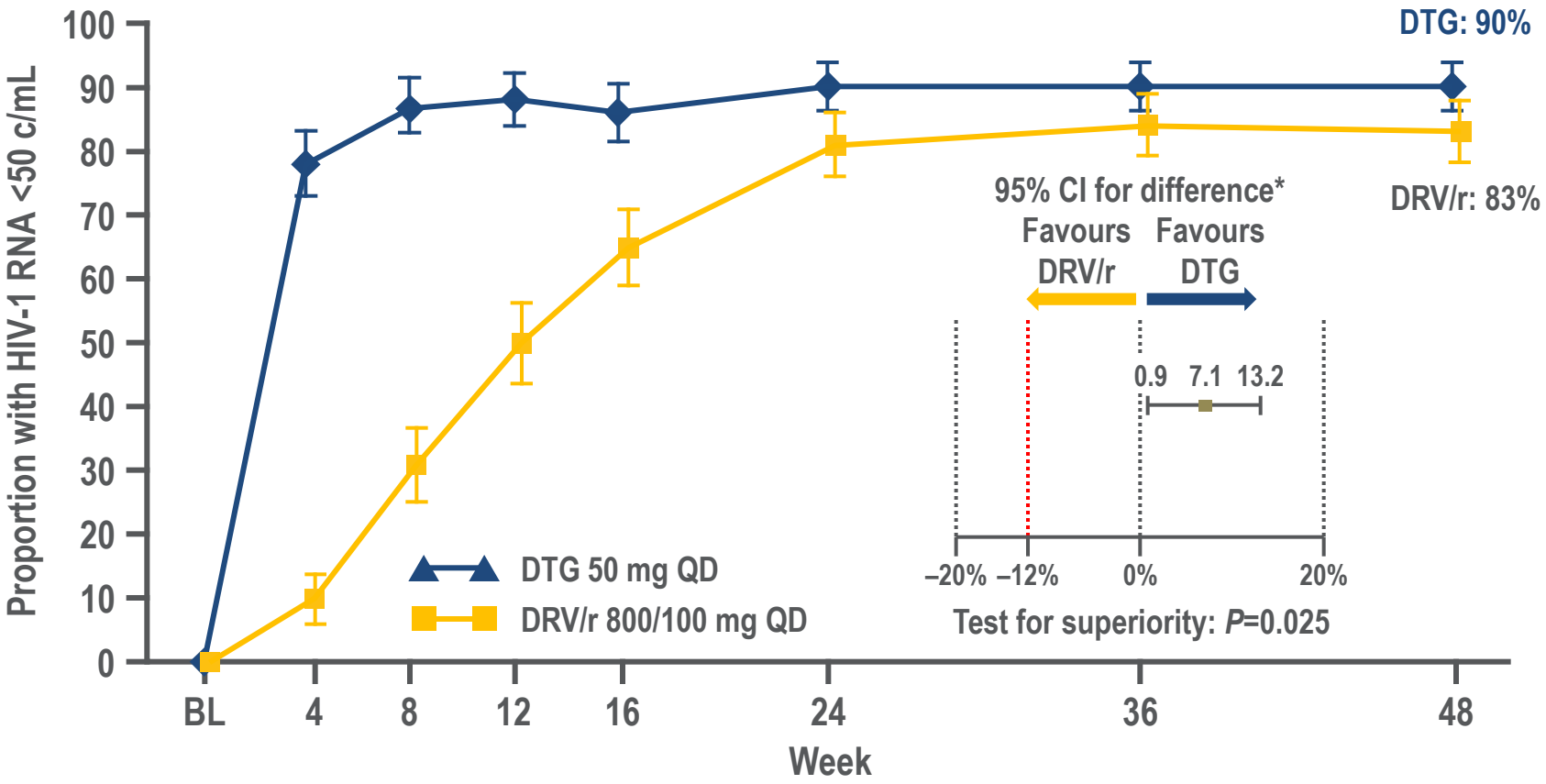
Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

BASELINE CHARACTERISTICS

	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)	Total (N=484)
Age (years), median	34	34	34
Female, %	13	17	15
African American/African heritage, %	25	22	23
HBV/HCV positive, %	4/7	2/7	3/7
CDC class C, %	4	2	3
HIV-1 RNA (log_{10} c/mL), median	4.49	4.48	4.49
>100,000 c/mL, %	25	25	25
CD4+ (cells/mm^3), median	390	400	395
<50, %	2	2	2
50 to <200, %	8	8	8
200 to <350, %	30	21	26
350 to <500, %	33	38	36
≥500, %	27	31	29
Investigator-selected ABC/3TC, %	33	33	33

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

IN TREATMENT-NAIVE SUBJECTS PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS DRV/r



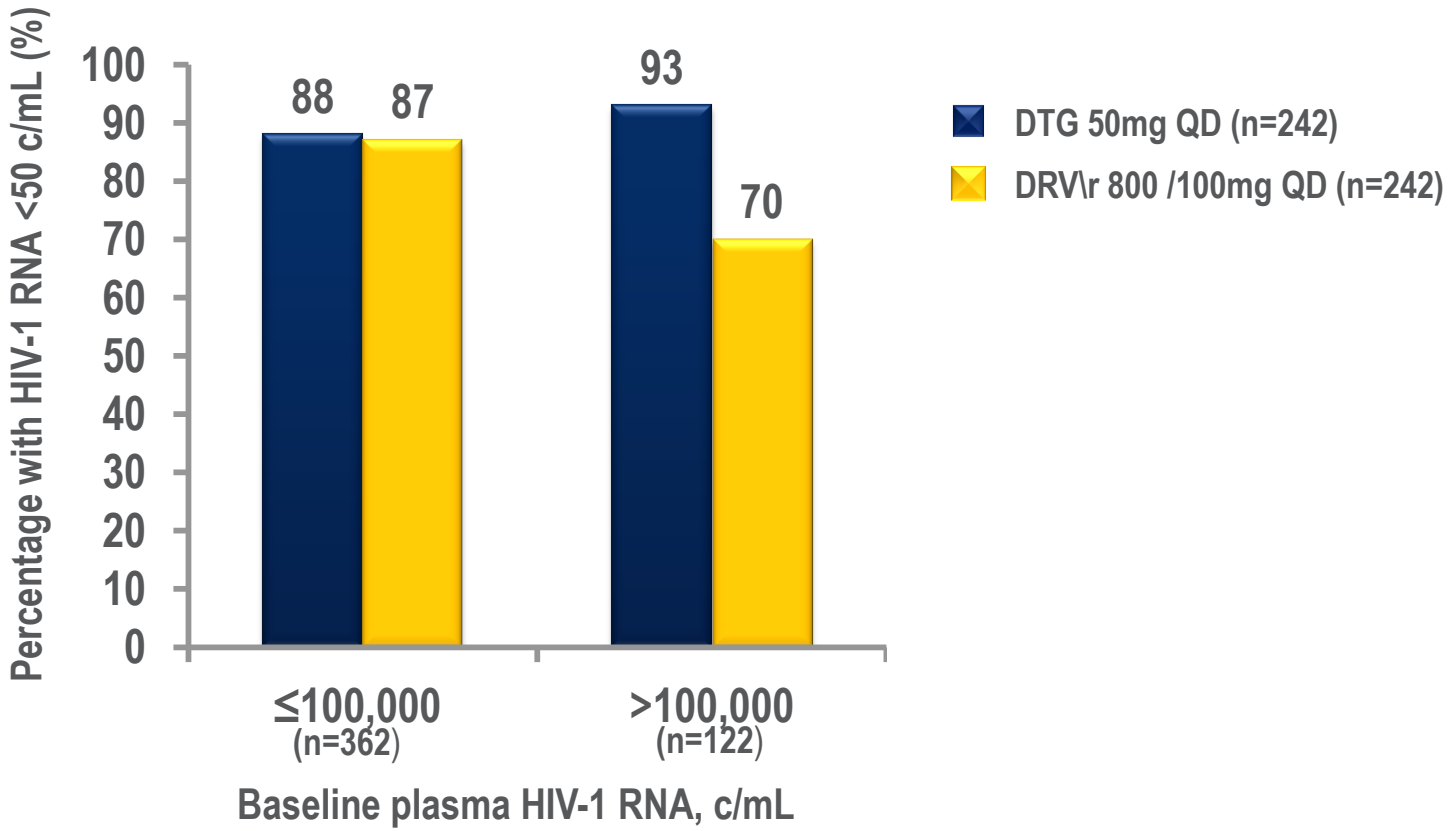
- Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r

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

Week 48 snapshot analysis

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

DTG WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD

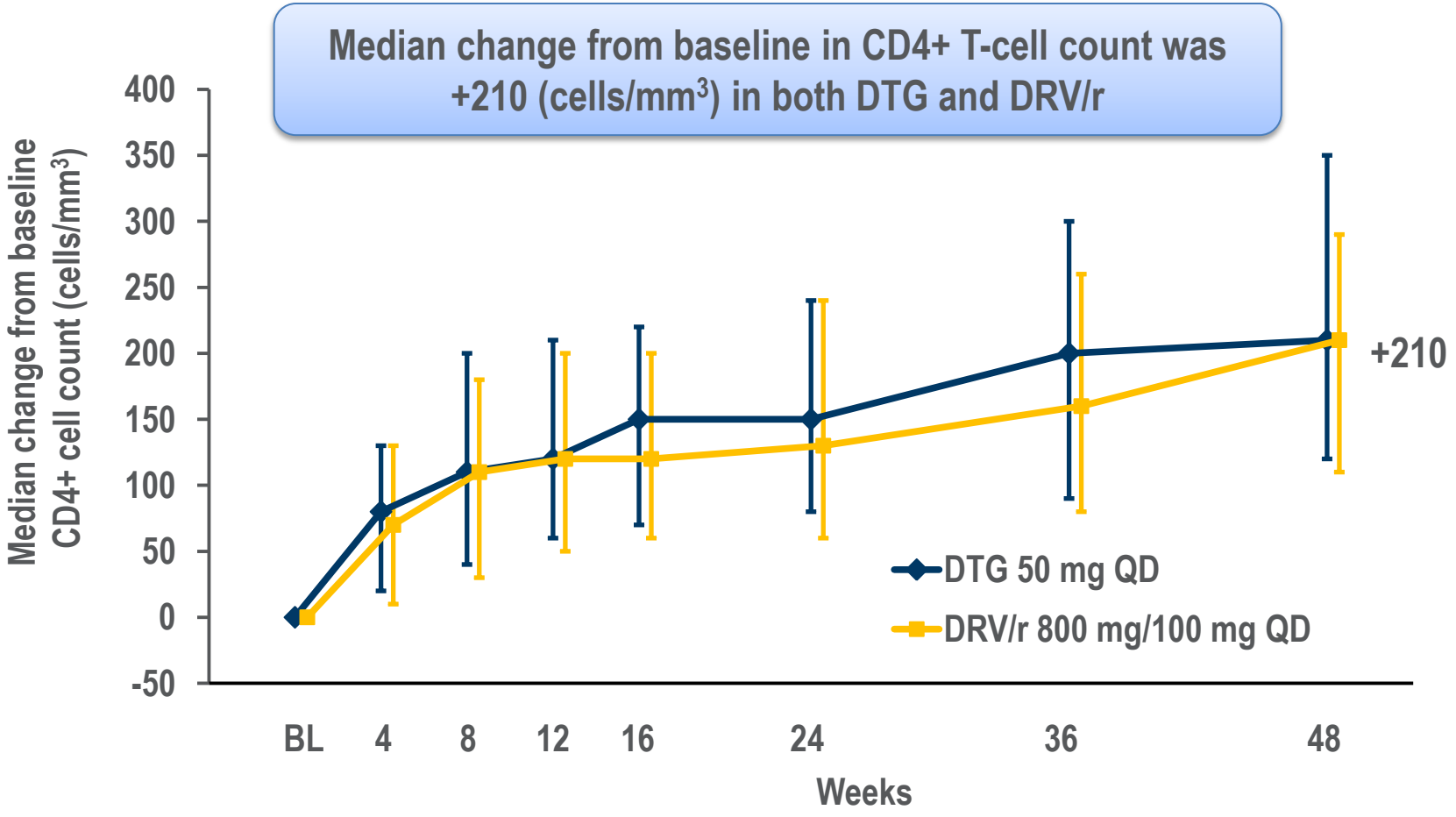


- 25% of treatment-naïve patients had a baseline viral load >100,000 copies/mL

Week 48 snapshot analysis

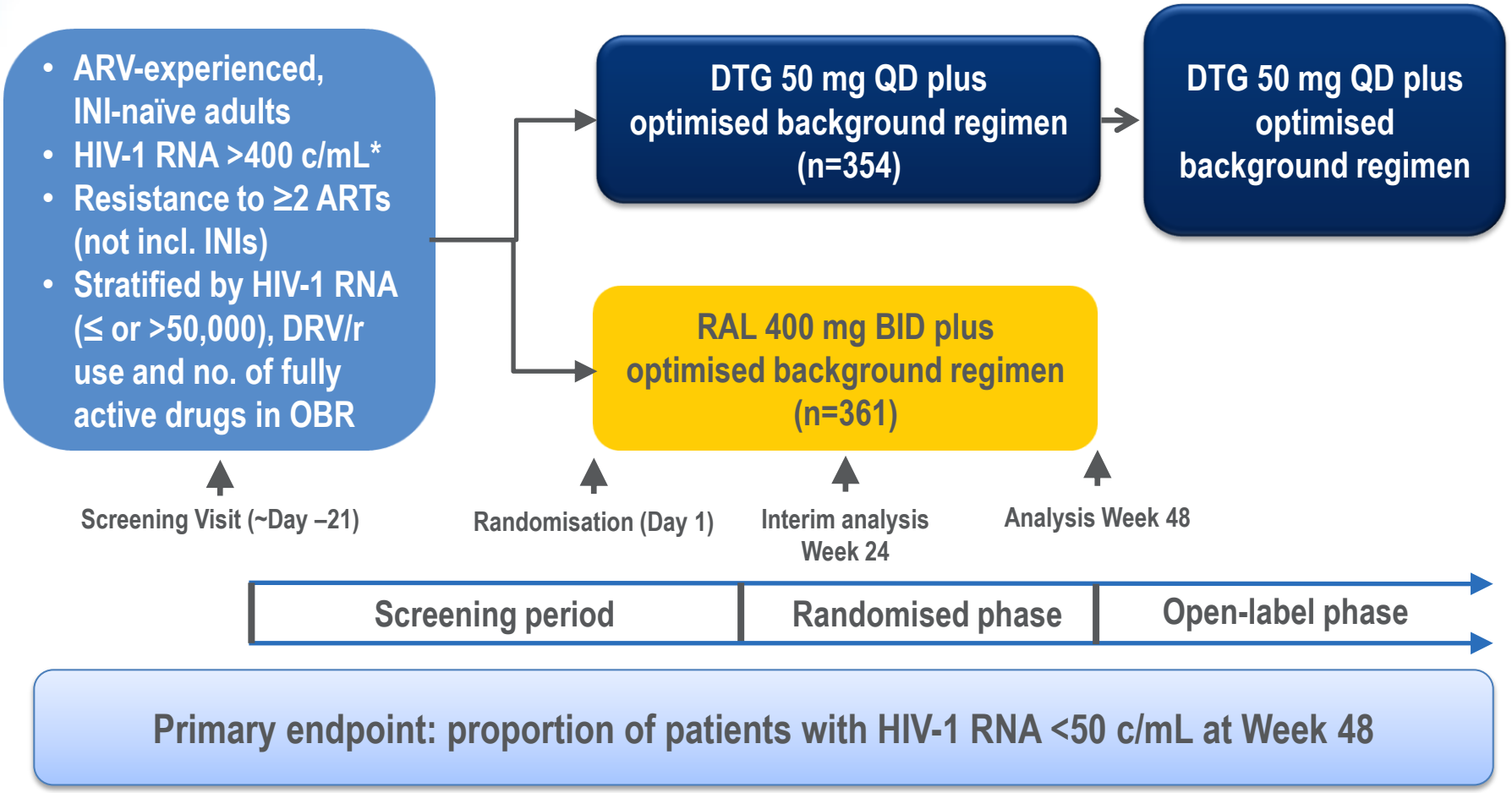
Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

PROVEN CD4+ T-CELL RESPONSE



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

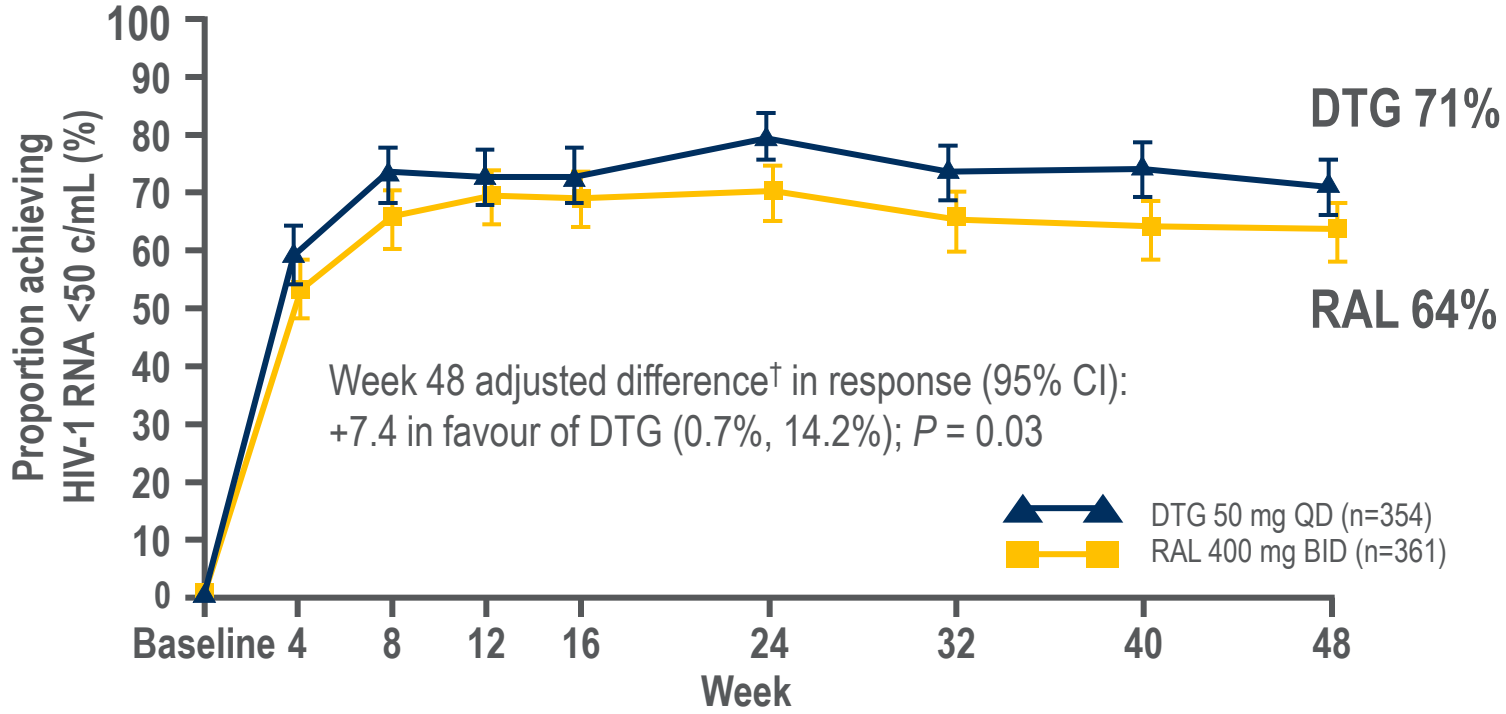
Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708
Pozniak A, et al. CROI 2013. Abstract 179LB

BASELINE CHARACTERISTICS

	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
Age, median (years)	42	43
Gender, female (%)	30	34
Race		
White (%)	49	48
African American or African heritage (%)	40	44
HIV-1 RNA, median (log_{10} c/mL)	4.17	4.21
>50,000 c/mL (%)	30	30
CD4+ count, median (cells/mm^3)	205	193
HBV coinfection (%)	5	4
HCV coinfection (%)	9	13
Duration prior ART, median (months)	80	72
≥3 class resistance (%)	47	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



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)

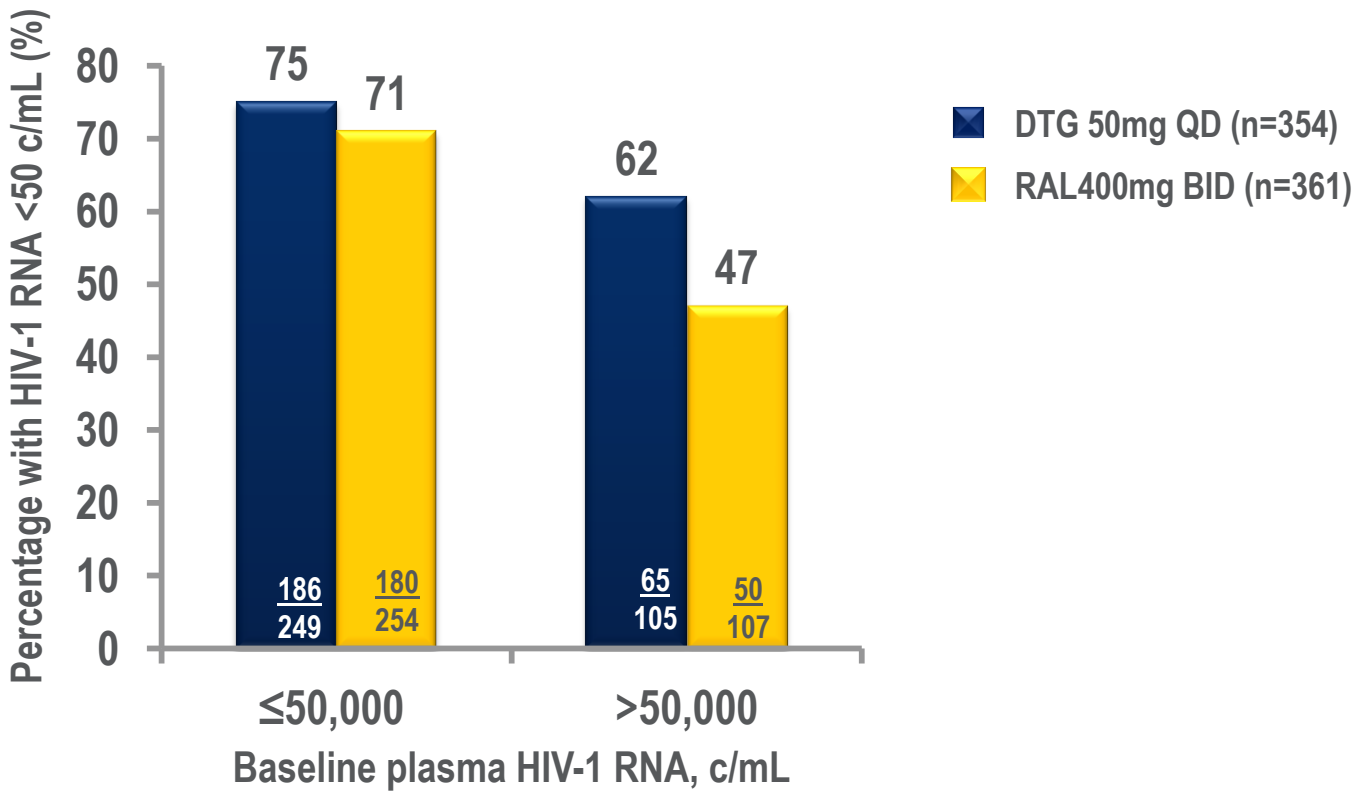
Mean (SD) CD4+ change from baseline to Week 48 was similar between arms: DTG: +162 (151) cells/mm^3; RAL: +153 (144) cells/mm^3

*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



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

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

EFFICACY SUMMARY: IN INI-NAÏVE PATIENTS, DTG-BASED REGIMENS DEMONSTRATED STATISTICALLY SUPERIOR EFFICACY TO RAL, DRV/R AND ATRIPLA®

SINGLE

ART-naïve patients (n=833)[1]

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

- 88% vs 81% reached undetectability through 48 weeks (*P*=0.003)

SPRING-2

ART-naïve patients (n=822)[2,3]

DTG was non-inferior to RAL

- 88% vs 85% reached undetectability through 48 weeks
- 81% vs 76% reached undetectability through 96 weeks

FLAMINGO

ART-naïve patients (n=484)[4]

DTG had **statistically superior efficacy vs darunavir/r**

- 90% vs 83% reached undetectability at Week 48 (*P*=0.025)

SAILING

Treatment-experienced, INI-naïve (n=715)[5]

DTG had **statistically superior efficacy vs raltegravir**

- 71% vs 64% reached undetectability at Week 48 (*P*=0.03)

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Raffi F et al. *Lancet* 2013;381:735–43
3. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
4. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
5. 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)[1,2]

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

NO INI OR NRTI RESISTANCE THROUGH 48 WEEKS WITH DTG

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=234)	DRV/r 800/100 mg QD (n=234)
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¶	0	0[a]	0
NNRTI-resistant mutations	–	–	0	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

¶E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility
‡n=1 with K101E, n=1 with K103K/N, n=1 with G190G/A and n=1 with K103N+G190G/A

[a]One subject in the DTG treatment group had phenotypic resistance to nelfinavir. This subject had secondary PI resistance mutations L10V, I13V, K20R, E35D, M36I, I62I/V, L63T and L89M at baseline and at PDVF

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

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. *Lance*t 2013;382(9893):700-708

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

DTG HAS A HIGH BARRIER TO RESISTANCE: SUMMARY

SINGLE

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

No INI or NRTI resistance through 48 weeks with DTG

SPRING-2

ART-naive patients (n=822)[2,3]

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

FLAMINGO

ART-naive patients (n=484)[4]

No emergent INI, NRTI or PI mutations through 48 weeks with DTG

SAILING

Treatment-experienced, INI-naïve (n=715)[5]

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. Raffi F et al. *Lancet* 2013;381:735–43
3. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
4. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
5. 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. Nichols G, et al. IAS 2013. Poster TULBPE19; 8. Hightower KE, et al. *Antimicrob Agents Chemother* 2011;55:4552–9

TOLERABILITY AND SAFETY PROFILE OF DOLUTEGRAVIR

DTG + ABC/3TC WAS BETTER TOLERATED VS ATRIPLA® WITH FEWER DISCONTINUATIONS

Discontinuations due to AEs were 2% for DTG + ABC/3TC vs 10% for Atripla® at week 48[1]

AEs, n (%)	DTG 50 mg +ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Subjects with AEs leading to withdrawal, n (%)	10 (2)	42 (10)
Serious drug-related AE	1 (<1)*	8 (2)†
Fatal AEs	0	2 (<1)‡

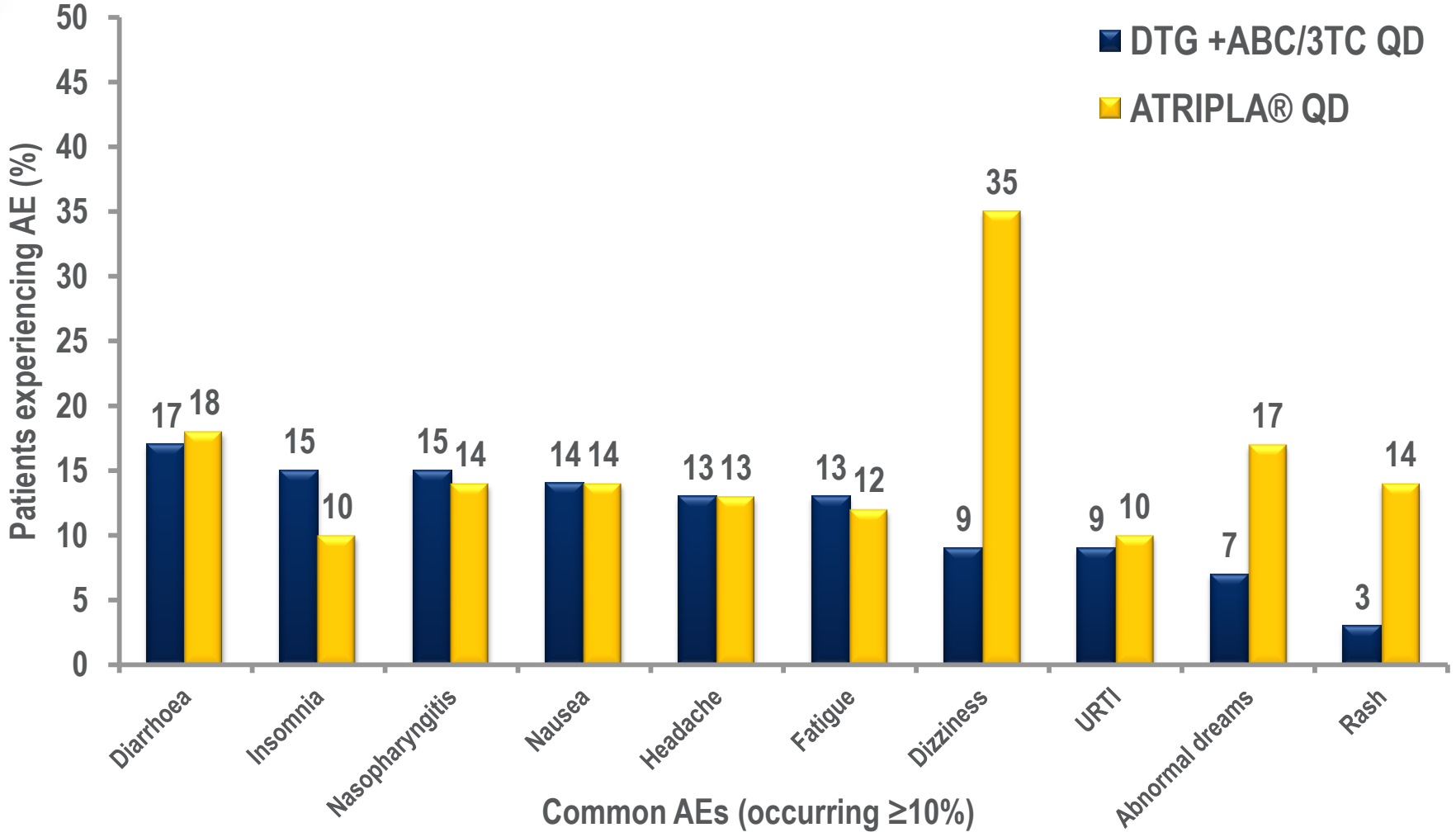
Drug-related Grade 2 to 4 AEs (any event) were 13% (53/414) for DTG + ABC/3TC and 27% (114/419) for Atripla®[2]

*DTG+ABC/3TC: 1 drug hypersensitivity; †Atripla®: 4 psychiatric, 2 hypersensitivity reaction, 1 cerebral vascular accident, 1 renal failure; ‡Deaths: n=1 primary cause of death judged unrelated to study drug but complicated by renal failure judged possibly related to Atripla®, n=1 not related to Atripla® (pneumonia).

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Data on file. UK/DLG/0026/13,01/11/13

DTG + ABC/3TC WAS BETTER TOLERATED VS ATRIPLA®

RATES OF MOST COMMON AEs (ALL GRADES ≥10% IN EITHER REGIMEN)



URTI , upper respiratory tract infection

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

AT WEEK 48 DTG WAS WELL TOLERATED WITH FEW DISCONTINUATIONS

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 OFFERED 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 WELL TOLERATED WITH FEW DISCONTINUATIONS THROUGH 48 WEEKS

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

	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)
Overall, n (%)	**206 (85)**	**205 (85)**
Common AEs (≥10% in either arm)		
Diarrhoea	41 (17)	70 (29)
Nausea	39 (16)	43 (18)
Headache	37 (15)	24 (10)
Discontinuations due to AE/ stopping criteria met	**4 (2)**	**10 (4)**
Drug-related Grade 2–4	**23 (10)**	**30 (12)**
Serious – any event*	**26 (11)**	**13 (5)**
Serious drug-related – any event	**1 (<1)†**	**0**
Fatal AEs	**0**	**0**

*Each individual SAE was reported in <1% of subjects in each treatment group

†DTG + ABC/3TC: 1 suicide attempt (subject with a history of suicidality)

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

DTG WAS WELL TOLERATED WITH FEW DISCONTINUATIONS

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

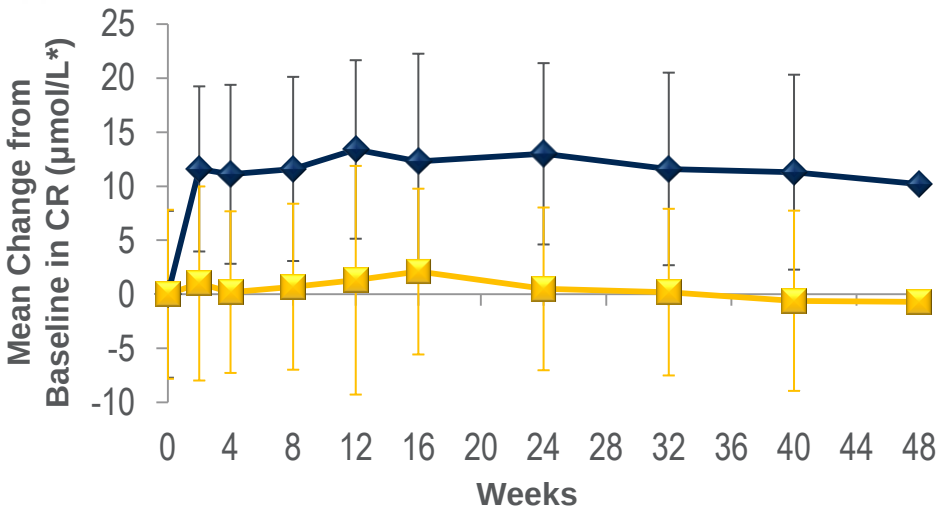
DTG OFFERED SIMILAR TOLERABILITY TO RAL THROUGH 48 WEEKS

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 ON SERUM CREATININE IS NOT CLINICALLY RELEVANT

Small increases in serum creatinine occurred in the first week and remained stable through 48 weeks.[1,2] These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged.[3]



Creatinine clearance by Cockcroft-Gault, mean (SD)[4]	DTG 50 mg + ABC/3TC QD		ATRIPLA® QD	
	n	mL/min	n	mL/min
Baseline	414	129.7 (36.4)	419	130.5 (30.8)
Week 24	384	-18.2 (15.0)	362	-1.2 (14.6)
Week 48	366	-13.1 (15.6)	339	2.1 (15.7)

Urine albumin/creatinine (mg/mmol CR)[1]	DTG 50 mg+ABC/3TC QD	ATRIPLA® QD
Median change (IQR) from baseline to Week 48	0.00 (-0.30, 0.30)	+0.05 (-0.20, 0.30)

*10 µmol/L=0.11mg/dL[5]

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Tivicay® MOH approved Prescribing Information.
3. Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996
4. Adapted from Curtis LD, et al. IAS 2013. Poster TUPE282
5. Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

RENAL ADVERSE EVENTS WERE RARELY REPORTED AND NONE WERE ATTRIBUTED TO DTG

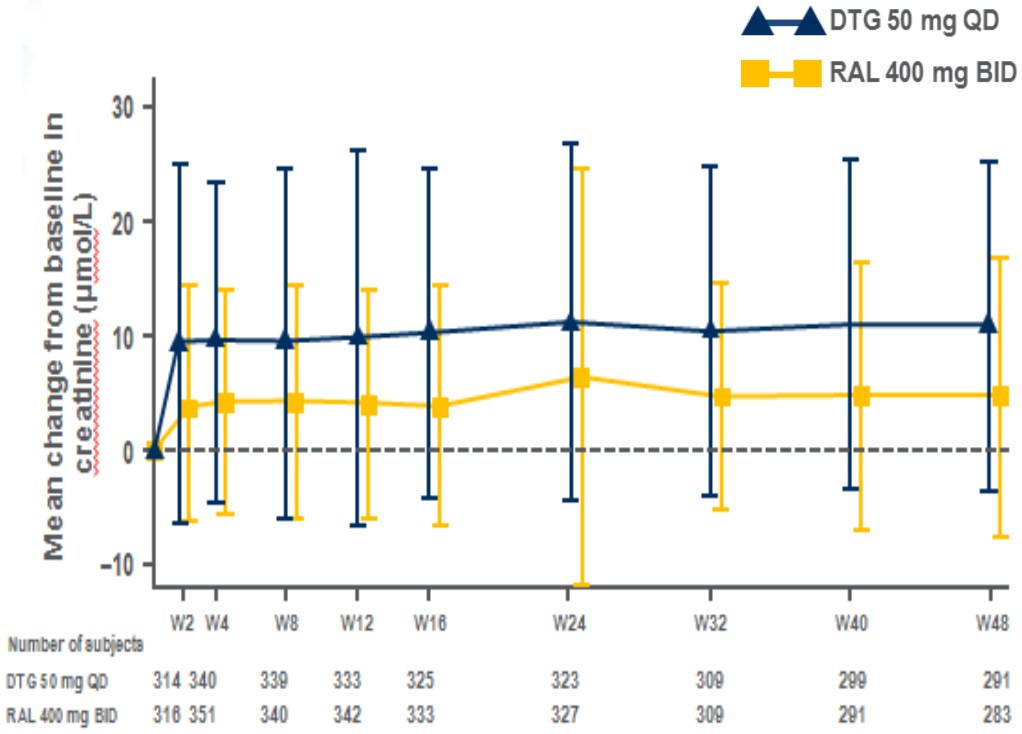
Group	Gender	Age	Description	Related	Withdrawn
DTG	M	38	Poorly controlled diabetes and hypertension and proteinuria at baseline. Withdrawn with Grade 1 elevation of creatinine	N	Y
EFV	M	40	Died of fungal sepsis with renal failure part of terminal event	Y	Y
EFV	M	51	Transient increase in creatinine related to ibuprofen	N	N
EFV	F	39	Transient worsening of chronic renal failure attributed to pre-existing cryoglobulinemia	N	Y
EFV	M	33	Episode of acute renal failure resolved	N	N

- One subject on DTG and four subjects on Atripla® had a renal AE.
  - The AE in the DTG subject was judged not to be related to DTG, but the subject was withdrawn from the study.
  - The AE in the subject who died of fungal sepsis in the Atripla® arm was judged to be related to study medication; one other Atripla® subject was withdrawn due to a renal AE, although none of the other AEs were considered related to study drugs.

Curtis LD, et al. IAS 2013. Poster TUPE282

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

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

TOLERABILITY DATA: SUMMARY

SINGLE

ART-naïve patients (n=833)[1,2]

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

- 13% vs 27% experienced drug-related AEs (Grades 2 to 4)[1]
- 2% vs 10% discontinued due to AEs at 48 weeks[2]

SPRING-2

ART-naïve patients (n=822)[3,4]

DTG offers 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 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]

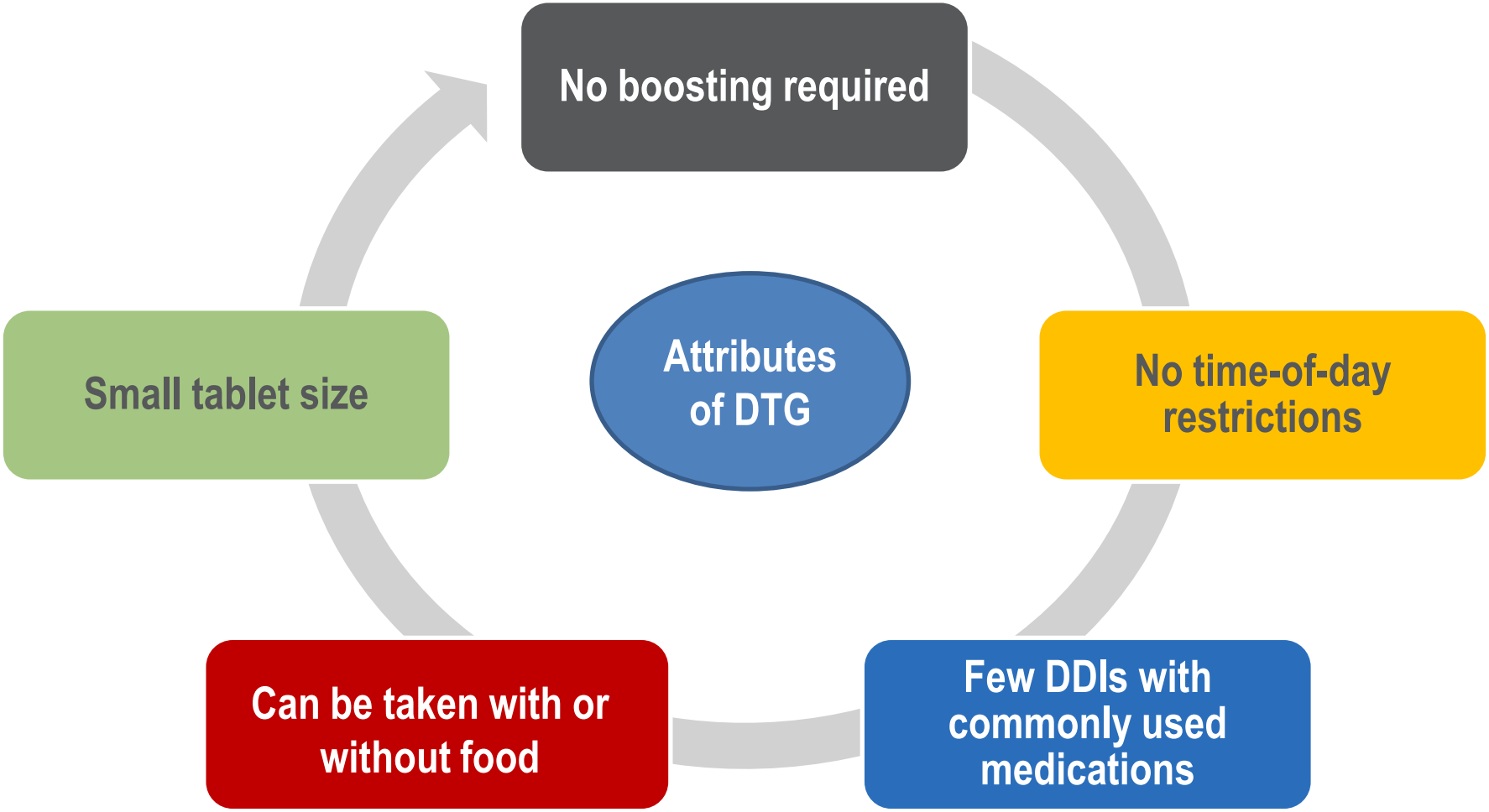
DTG offers similar tolerability to RAL

- 1% vs 3% discontinued due to AEs

1. Data on file. UK/DLG/0026/13,01/11/13
2. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
5. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
6. Cahn P, et al. *Lancet* 2013;382(9893):700-708

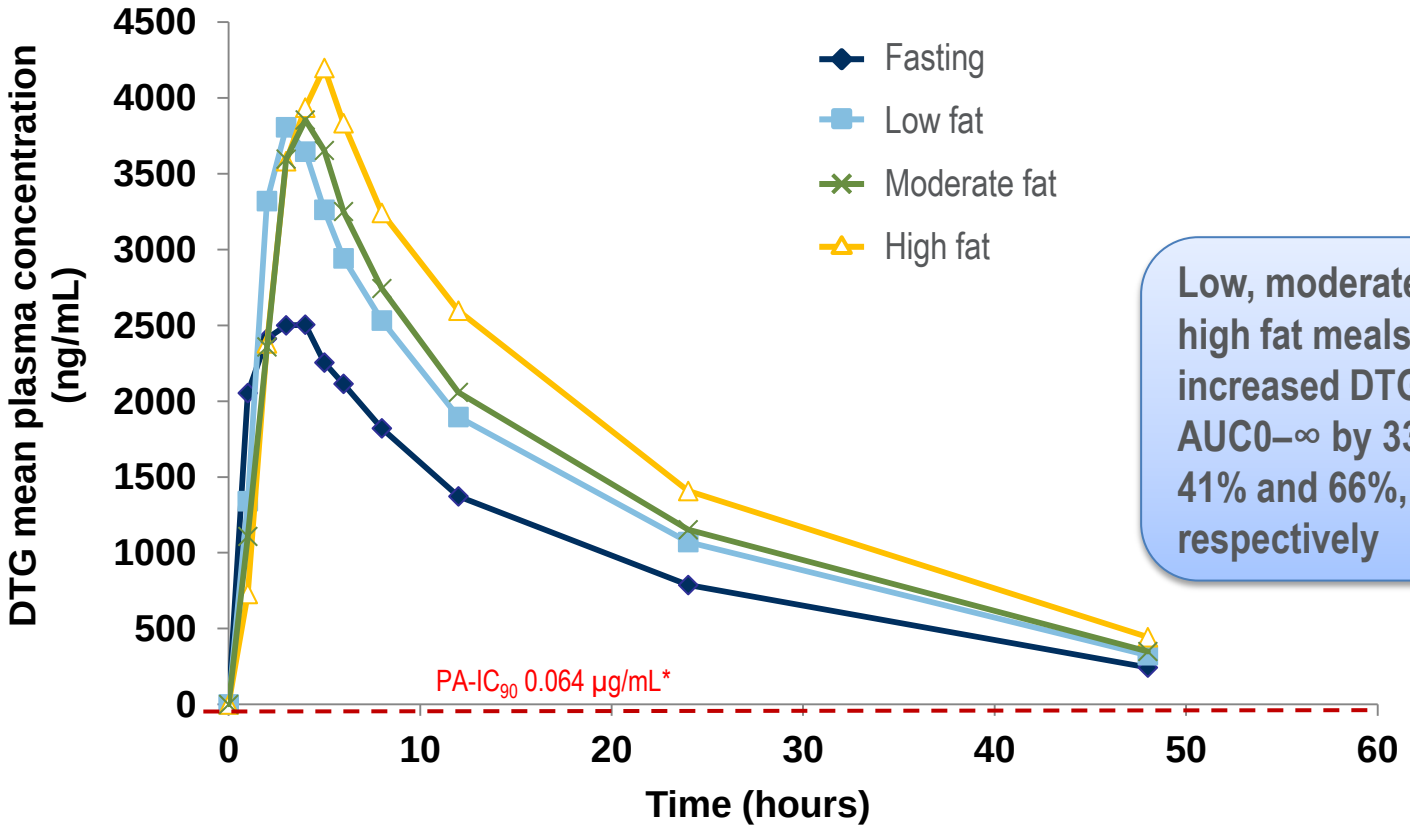
CONVENIENCE AND DRUG-DRUG INTERACTIONS

CONVENIENCE BEYOND ONCE-DAILY DOSING



Tivicay® MOH approved Prescribing Information.

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

*PA-IC_{90} is the protein-adjusted 90% inhibitory concentration;
†Phase III (50 mg) formulation

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

DTG HAS FEW 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 separate 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 at a dose of 50 mg QD

- 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 MOH approved Prescribing Information 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® MOH approved Prescribing Information.
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)

Patients without documented or clinically suspected resistance to the integrase class	**One 50 mg tablet, QD*†¥**

- Dolutegravir can be taken with or without food ¶

*Must be taken in combination with other antiretroviral agents
†For patients with resistance to the integrase class (documented or clinically suspected), the recommended dose of DTG is one 50 mg tablet twice-daily
¥DTG should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/r or rifampicin)
¶In the presence of INI-class resistance, DTG should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations)

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® MOH approved Prescribing Information.
2. Min S, et al. *Antimicrob Agents Chemother* 2010;54:254–8
3. Min S, et al. *AIDS* 2011;25:1737–45; 4. Isentress prescribing information (April 2013)
5. Stribild prescribing information (August 2012); 6. Ramanathan S, et al. *Clin Pharmacokinet* 2011;50:229–44

ABBREVIATIONS

- AE, adverse event
- ALT, alanine aminotransferase
- ART, antiretroviral therapy
- ARV, antiretroviral
- BID, twice daily
- c/mL, copies/mL
- CDC, Centers for Disease Control
- CR, creatinine
- DRV/r, darunavir/ritonavir
- DTG, dolutegravir
- ENF, enfuvirtide
- ETR, etravirine
- EVG, elvitegravir
- FC, fold change
- HIV, human immunodeficiency virus
- INI, integrase inhibitor
- IQR, interquartile range
- ITT-E, intent-to-treat-exposed
- MVC, maraviroc
- NNRTI, non-nucleoside reverse transcriptase inhibitors
- NRTI, nucleoside reverse transcriptase inhibitor
- OBR, optimised background regimen
- OCT2, organic cation transporter 2
- OSS, overall susceptibility score
- PI, protease inhibitor
- PSS, phenotypic sensitivity score
- QD, once daily
- RAL, raltegravir
- RNA, ribonucleic acid
- SD, standard deviation

Indication(s): Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents aged 12 years and older and weighing at least 40 kg.

Succinct safety information:

Contraindications: Coadministration with dofetilide. Hypersensitivity to dolutegravir or to any of the excipients. **Warnings and Precautions**: Integrase class resistance of particular concern: The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring . Hypersensitivity reactions: Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect agents should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop. Immune Reactivation Syndrome: An inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Drug interactions: Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. Metformin concentrations may be increased by dolutegravir. Patients should be monitored during therapy and a dose adjustment of metformin may be required. Osteonecrosis: Although the aetiology is considered to be multifactorial, cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. **Undesirable effects:** Very common: Headache, nausea, diarrhoea. Common: Insomnia, abnormal dreams, dizziness, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort, rash, pruritus, fatigue, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations, creatine phosphokinase (CPK) elevations.

Dosage and administration: Adults: 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. Tivicay should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). 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. Co-administration of Tivicay with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Adolescents aged 12 and above: In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily. Method of administration: Oral use. Tivicay can be taken with or without food . In the presence of integrase class resistance, Tivicay should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations).

For full information please refer to MOH approved Prescribing Information