



SINGLE


**Efficacy and safety of dolutegravir (DTG) in
treatment-naïve subjects**

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

SINGLE¹ 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



FLAMINGO² 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^{3,4} 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



*Given as 2 x 400 mg tablets

NRTI, nucleoside reverse transcriptase inhibitor

DRV/r, darunavir/ritonavir; QD, once daily; BID, twice daily;

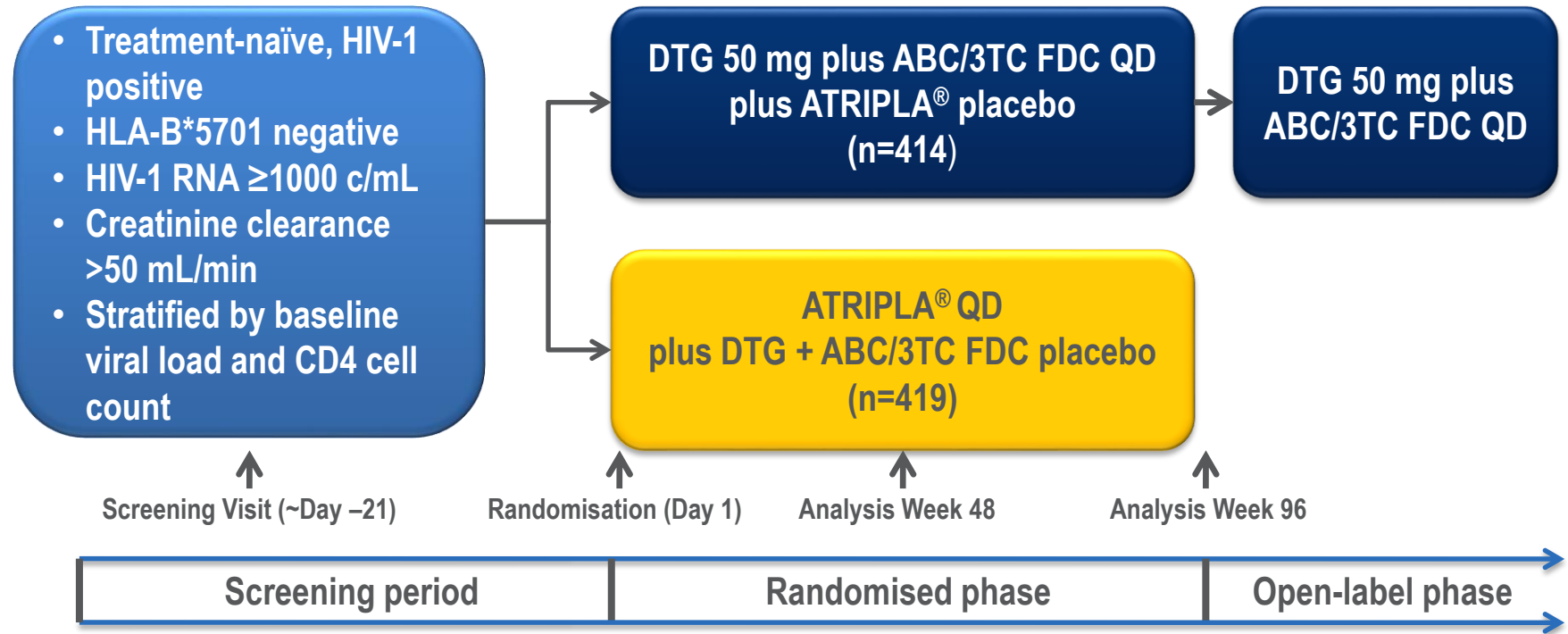
FDC, fixed-dose combination

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

2. Dr Bonaventura Clotet MD et al, *Lancet*. 2014; 383 (9936): 2222-2231

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

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)

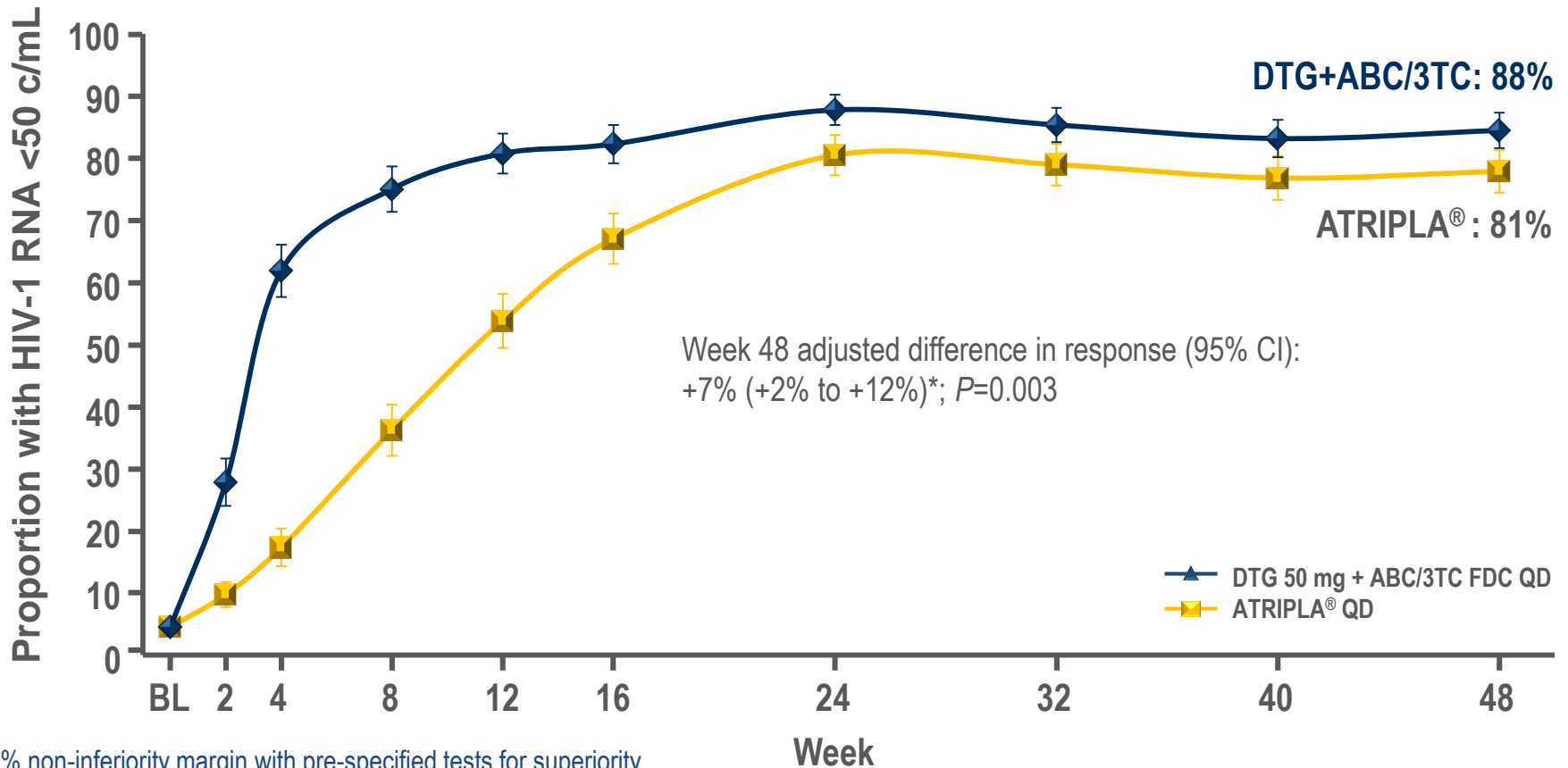
BASELINE CHARACTERISTICS

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/mm³	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
 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 (dolutegravir) Summary of Product Characteristics, 02/2017
2. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18

VIROLOGIC RESPONSE OUTCOMES WITH DTG + ABC/3TC STATISTICALLY SUPERIOR TO ATRIPLA[®] AT WEEK 48

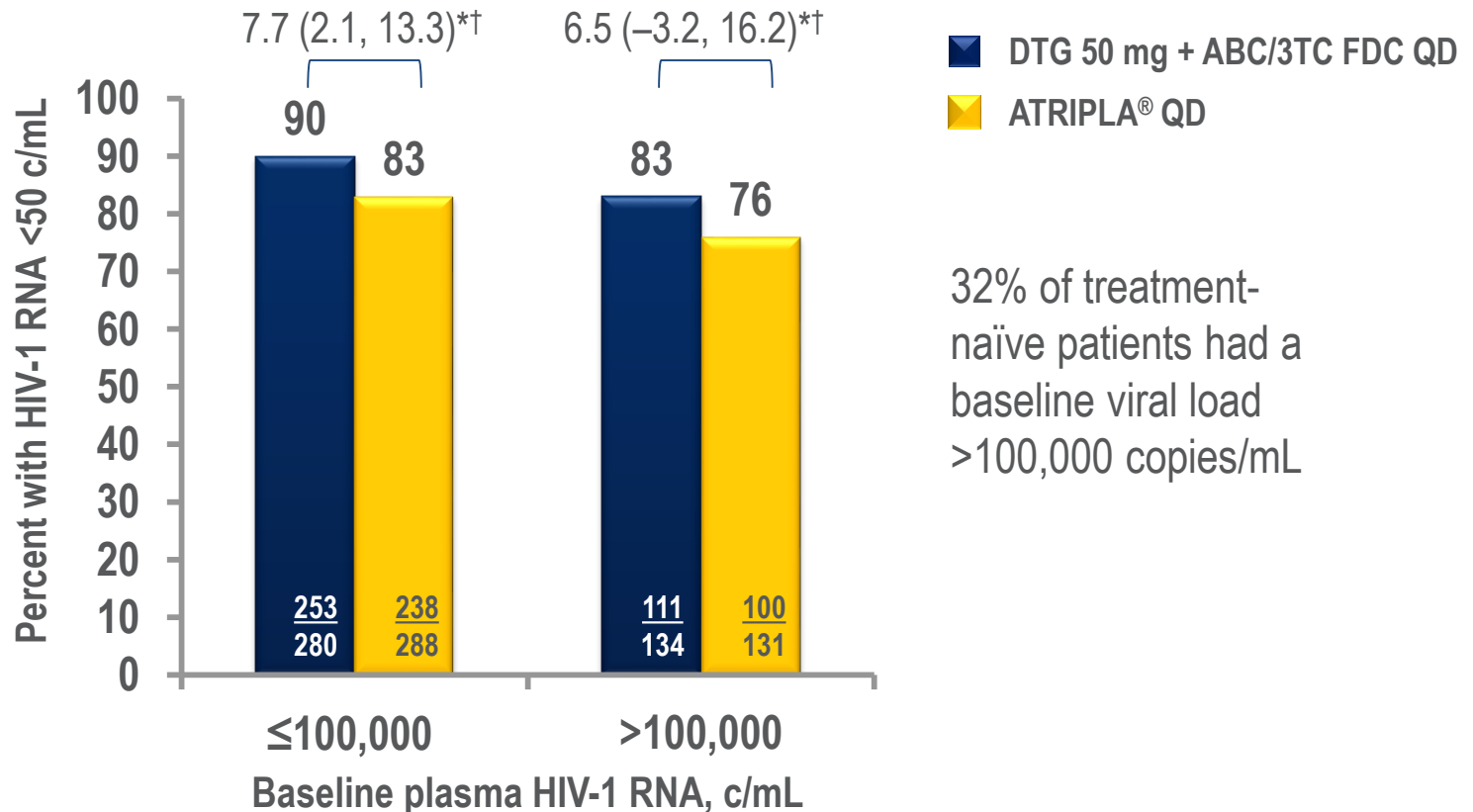
Outcome (Snapshot) at Week 48, n (%)	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA [®] QD (n=419)
Virologic success	364 (88)	338 (81)
Virologic non response	21 (5)	26 (6)
Data in window not <50 c/mL	6 (1)	5 (1)
Discontinued for lack of efficacy	7 (2)	9 (2)
Discontinued for other reason while not <50 c/mL	8 (2)	12 (3)
No virologic data at Week 48	29 (7)	55 (13)
Discontinued because of AE or death*	9 (2)	40 (10)
Discontinued for other reasons	20 (5)	14 (3)
Missing data during window, but on study	0	1 (<1)

*Deaths: n=2, both on Atripla[®]: n=1 primary cause of death (sepsis) judged unrelated to study drug but complicated by renal failure judged possibly related to Atripla[®]; n=1 not related to Atripla[®] (pneumonia)

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
 Data on file. SINGLE STUDY. UK/DLG/0027/13. November 2013

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

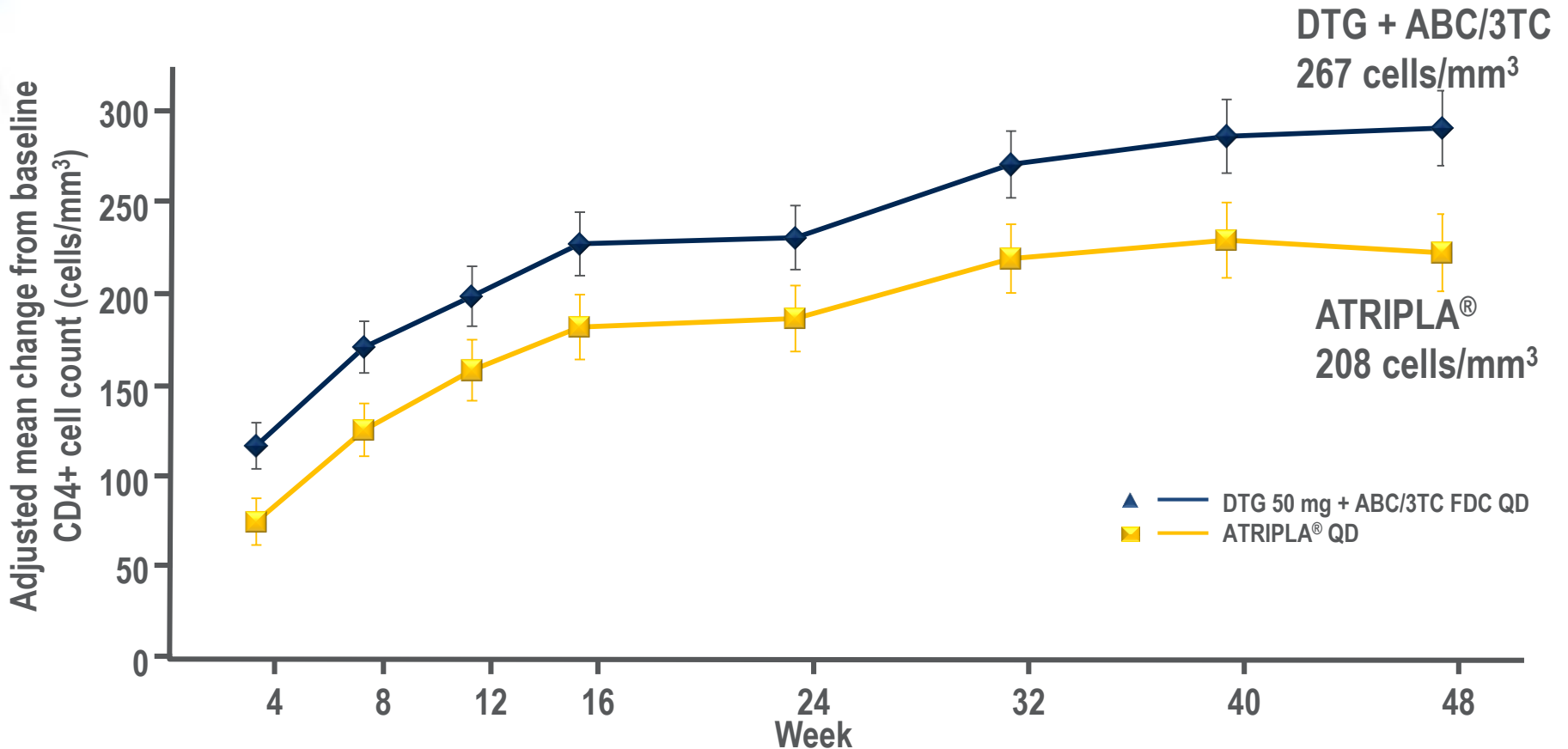
At Week 48, the number of patients achieving virologic response was numerically higher in the DTG + ABC/3TC group vs the Atripla® group, regardless of baseline viral load



*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

NO INI OR NRTI RESISTANCE THROUGH 48 WEEKS WITH DTG

Amongst DTG-treated subjects, no integrase nor NRTI mutations were detected through Week 48¹

	DTG 50 mg +ABC/3TC QD (n=414)	ATRIPLA [®] QD (n=419)
Subjects with PDVF	18 (4%)	17 (4%)
PDVF genotypic population ²	11	9
NRTI major mutations	0	1(K65K/R)
Integrase-resistant major substitution	0 [†]	0
NNRTI major mutations	0	4 (K101E, K103N or K103K/N, G190G/A)*

PDVF was defined as two consecutive plasma HIV-1 RNA values of ≥50 c/mL between weeks 24 and 48

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

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

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

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 48¹

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

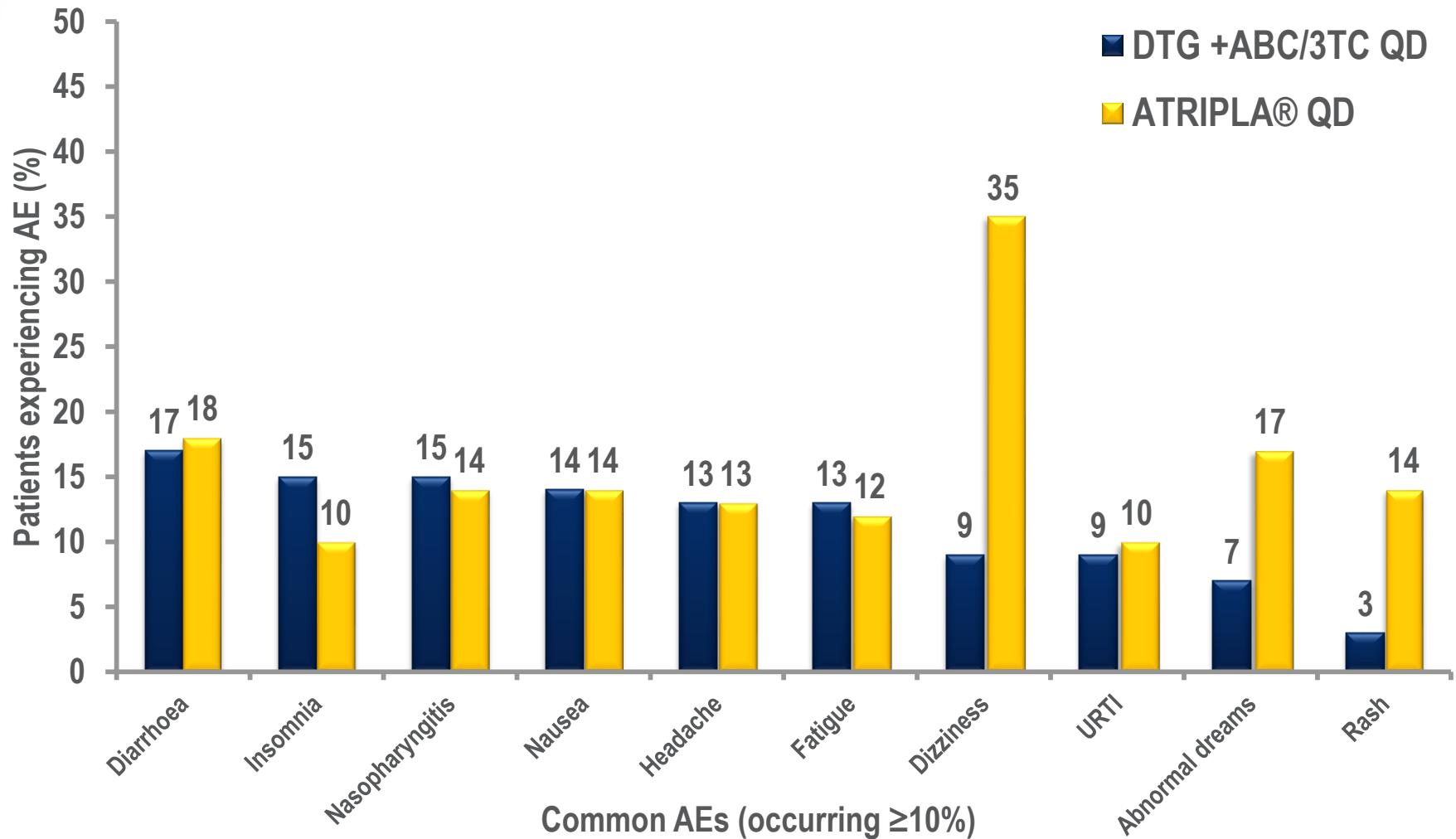
*DTG+ABC/3TC: 1 drug hypersensitivity; [†]Atripla[®]: 4 psychiatric, 2 hypersensitivity reaction, 1 cerebral vascular accident, 1 renal failure; [‡]Deaths: n=1 primary cause of death judged unrelated to study drug but complicated by renal failure judged possibly related to Atripla[®], n=1 not related 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 $\geq 10\%$ IN EITHER REGIMEN)

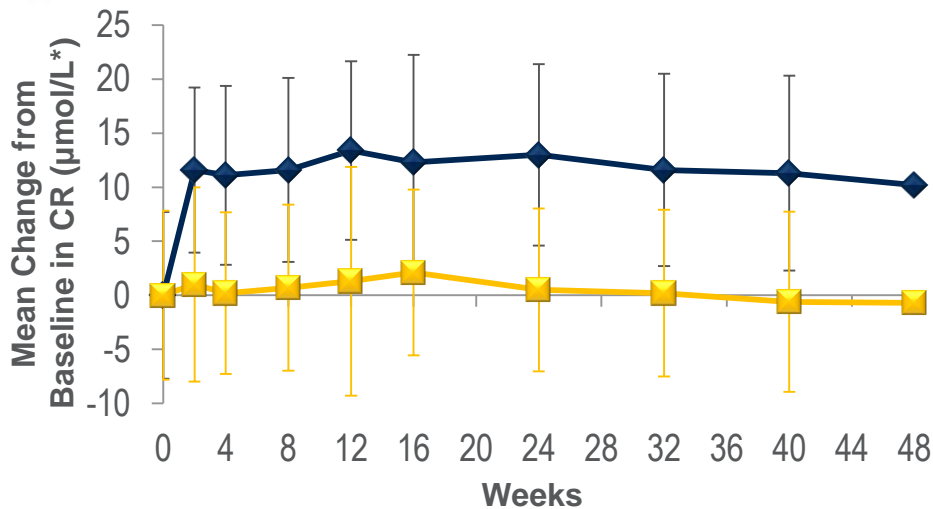


DTG HAD A LOWER IMPACT ON LIVER CHEMISTRY THAN ATRIPLA[®]

Parameter/Criteria, (%)	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA [®] QD (n=419)
Subjects meeting ≥1 FDA stopping criteria	10 (2)	39 (9)
ALT ≥20xULN	0	0
ALT ≥5xULN	1 (<1)	2 (<1)
ALT ≥3xULN	5 (1)	15 (4)
Total bilirubin >1.5xULN	3 (<1)	2 (<1)
Alkaline phosphatase >1.5xULN	1 (<1)	19 (5)
ALT and/or AST >3xULN and total bilirubin >1.5xULN	0	0

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/dL⁵

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. TIVICAY (dolutegravir) Summary of Product Characteristics, 02/2017
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.

SINGLE: SUMMARY

- DTG + ABC/3TC had statistically superior efficacy vs Atripla®
 - 88% vs 81% reached undetectability through 48 weeks ($P=0.003$)
- DTG was effective regardless of baseline viral load
 - 83% of treatment-naïve patients with HIV-1 RNA >100,000 copies/mL reached undetectability
- No INI or NRTI resistance through 48 weeks with DTG
- DTG + ABC/3TC was better tolerated vs Atripla® with fewer discontinuations
 - 13% vs 27% experienced drug-related AEs (Grades 2 to 4)
 - 2% vs 10% discontinued due to AEs at 48 weeks

ABBREVIATIONS

- 3TC, lamivudine
- ABC, abacavir
- AE, adverse event
- ARF, acute renal failure
- ALT, alanine amino transferase
- AST, aspartate amino transferase
- BID, twice daily
- BL, baseline
- c/mL, copies/mL
- CDC, Centers for Disease Control
- CR, creatinine
- DRV/r, darunavir/ritonavir
- DTG, dolutegravir
- FDA, Food and Drug Administration
- FDC, fixed-dose combination
- FTC, emtricitabine
- HIV, human immunodeficiency virus
- INI, integrase inhibitor
- IQR, inter quartile range
- NRTI, nucleoside reverse transcriptase inhibitor
- PDVF, protocol-defined virologic failure
- QD, once daily
- RAL, raltegravir
- RNA, ribonucleic acid
- TDF, tenofovir
- ULN, upper limit of normal
- URTI, upper respiratory tract infection

TIVICAY® (dolutegravir) Rx, EF, ATC kod J05AX12

Detta läkemedel är föremål för utökad övervakning. Filmdragerade tabletter innehållande 10, 25 eller 50 mg dolutegravir (som natrium).

Indikation: TIVICAY är indicerat i kombination med andra antiretrovirala läkemedel för behandling av humant immunbristvirus (hiv) hos vuxna, ungdomar och barn över 6 år.

Kontraindikationer: Överkänslighet mot dolutegravir eller mot något hjälpämne. Samtidig administrering av dofetilid. **Varningar och försiktighet:** Behandling ska förskrivas av läkare med erfarenhet av behandling av hiv-infektion. Dolutegravir är förenat med en risk för överkänslighetsreaktion och bör omedelbart sättas ut vid tecken eller symtom på överkänslighetsreaktion. *Nedsatt njurfunktion:* Ingen dosjustering krävs. *Nedsatt leverfunktion:* Ingen dosjustering krävs för patienter med lätt eller måttlig leverfunktionsnedsättning. Inga data finns för patienter med svår leverfunktionsnedsättning.

Interaktioner: TIVICAY ska administreras två gånger dagligen vid samtidig administrering med efavirenz, nevirapin, tipranavir/ritonavir eller rifampicin. Till patienter med resistens mot integrashämmare ska TIVICAY tas två gånger dagligen och helst tillsammans med mat för att öka exponeringen samtidigt som faktorer som minskar exponeringen för dolutegravir ska undvikas. Detta inkluderar samtidig administrering med magnesium- och aluminiuminnehållande antacida, järn- och kalciumtillskott och multivitaminer. Dolutegravir ökar koncentrationen av metformin. Dosjustering av metformin ska övervägas vid insättning och utsättning av samtidig administrering av dolutegravir och metformin, för att bevara glykemisk kontroll. Metformin elimineras renalt och det är därför viktigt att kontrollera njurfunktionen vid samtidig administrering av dolutegravir. Denna kombination kan öka risken för laktacidosis hos patienter med måttligt nedsatt njurfunktion..

Biverkningar: De vanligaste rapporterade biverkningarna som ansågs möjligen eller troligen relaterade till dolutegravir var illamående (13%), diarré (18%) och huvudvärk (13%).

För fullständig förskrivarinformation, se www.fass.se Datum för översyn av produktresumén 02/2017.

TIVICAY är ett registrerat varumärke som tillhör företagsgruppen ViiV Healthcare.