Tivicay (dolutegravir) 50 mg tablets

gsk ViiV Healthcare

WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

SINGLE

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

IL/DLG/0038/14 June 2014
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PHASE III DTG TRIALS IN TREATMENT-NAÏVE ADULT SUBJECTS WITH HIV

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

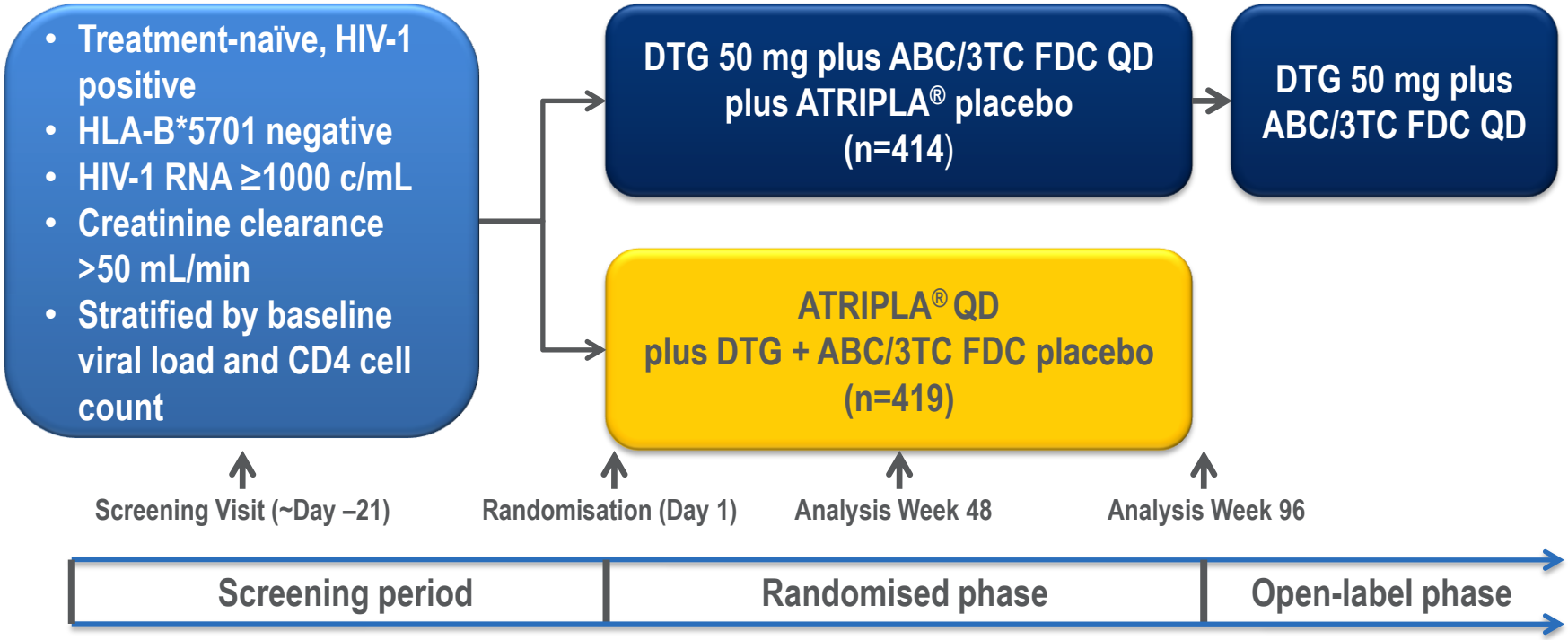
SPRING-2[3,4] — N=822

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. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35

SINGLE STUDY DESIGN



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

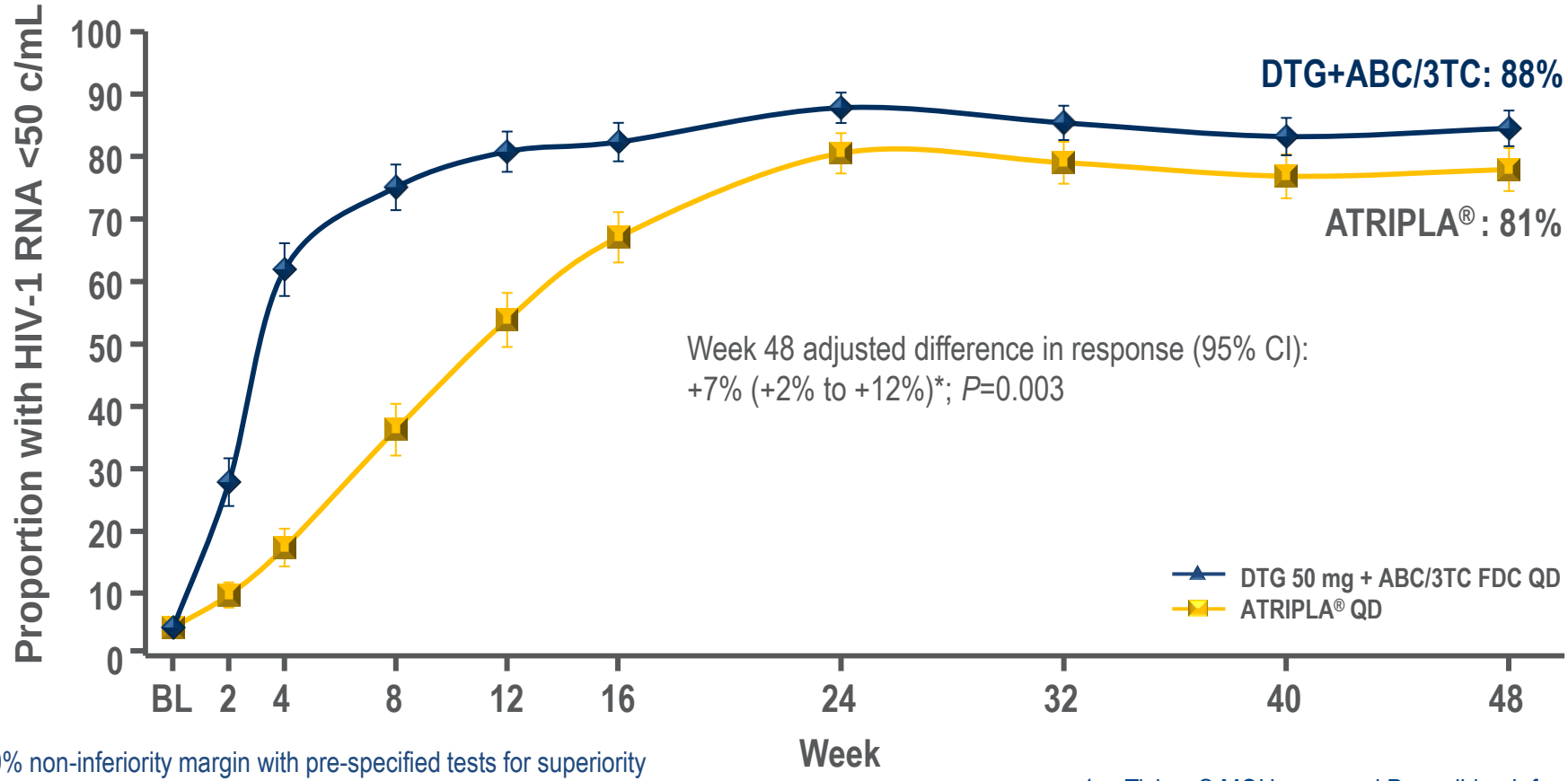
Characteristic	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Median age, years	36	35
Female, %	16	15
African American / African Heritage, %	24	24
CDC class C, %	4	4
Baseline HIV-1 RNA		
Median (log_{10} c/mL)	4.7	4.7
>100,000 c/mL, %	32	31
Median CD4 cell count, cells/mm^3	335	339
<200, %	14	14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

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

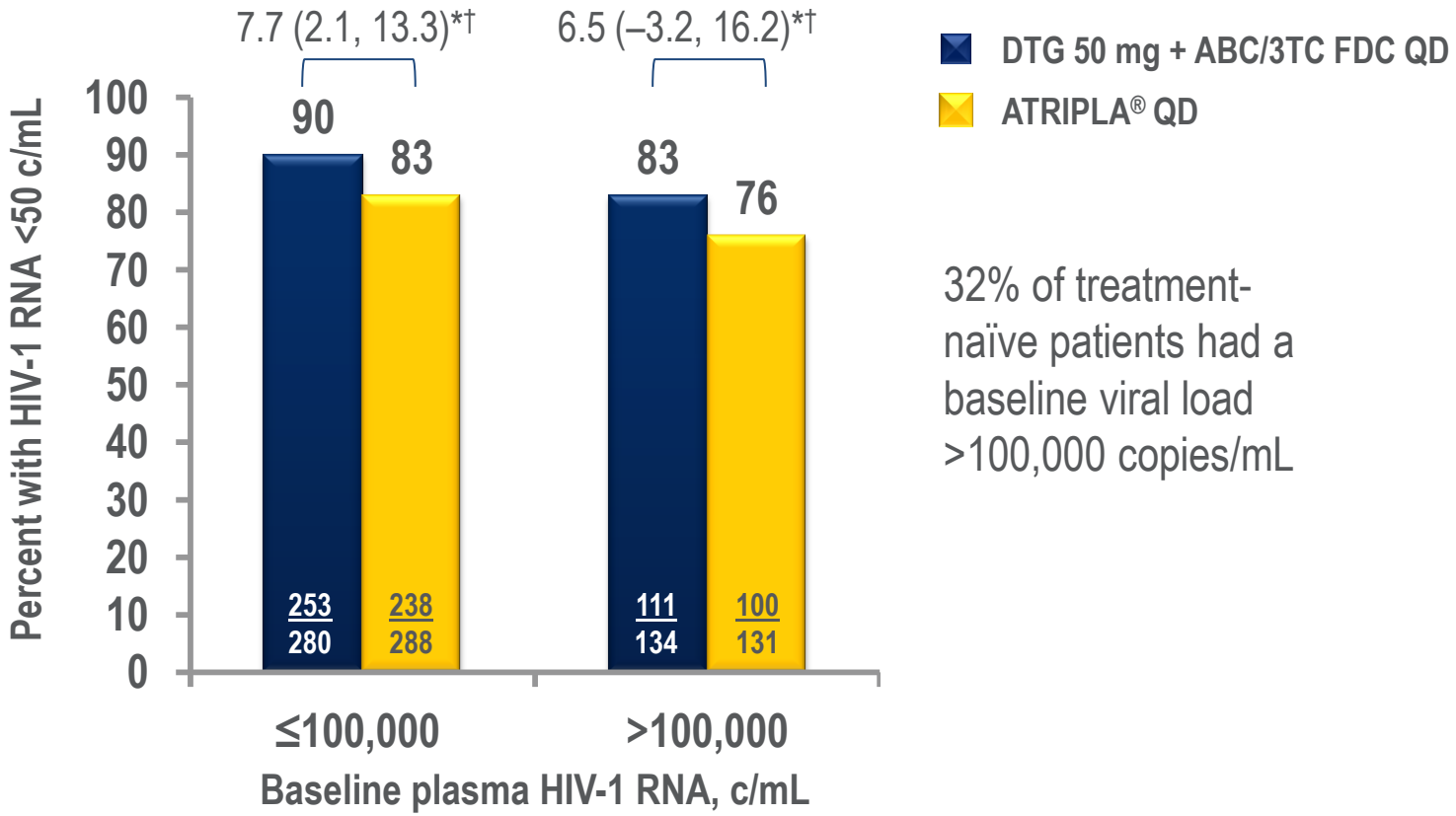
Outcome (Snapshot) at Week 48, n (%)	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Virologic success	364 (88)	338 (81)
Virologic non response	21 (5)	26 (6)
Data in window not <50 c/mL	6 (1)	5 (1)
Discontinued for lack of efficacy	7 (2)	9 (2)
Discontinued for other reason while not <50 c/mL	8 (2)	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

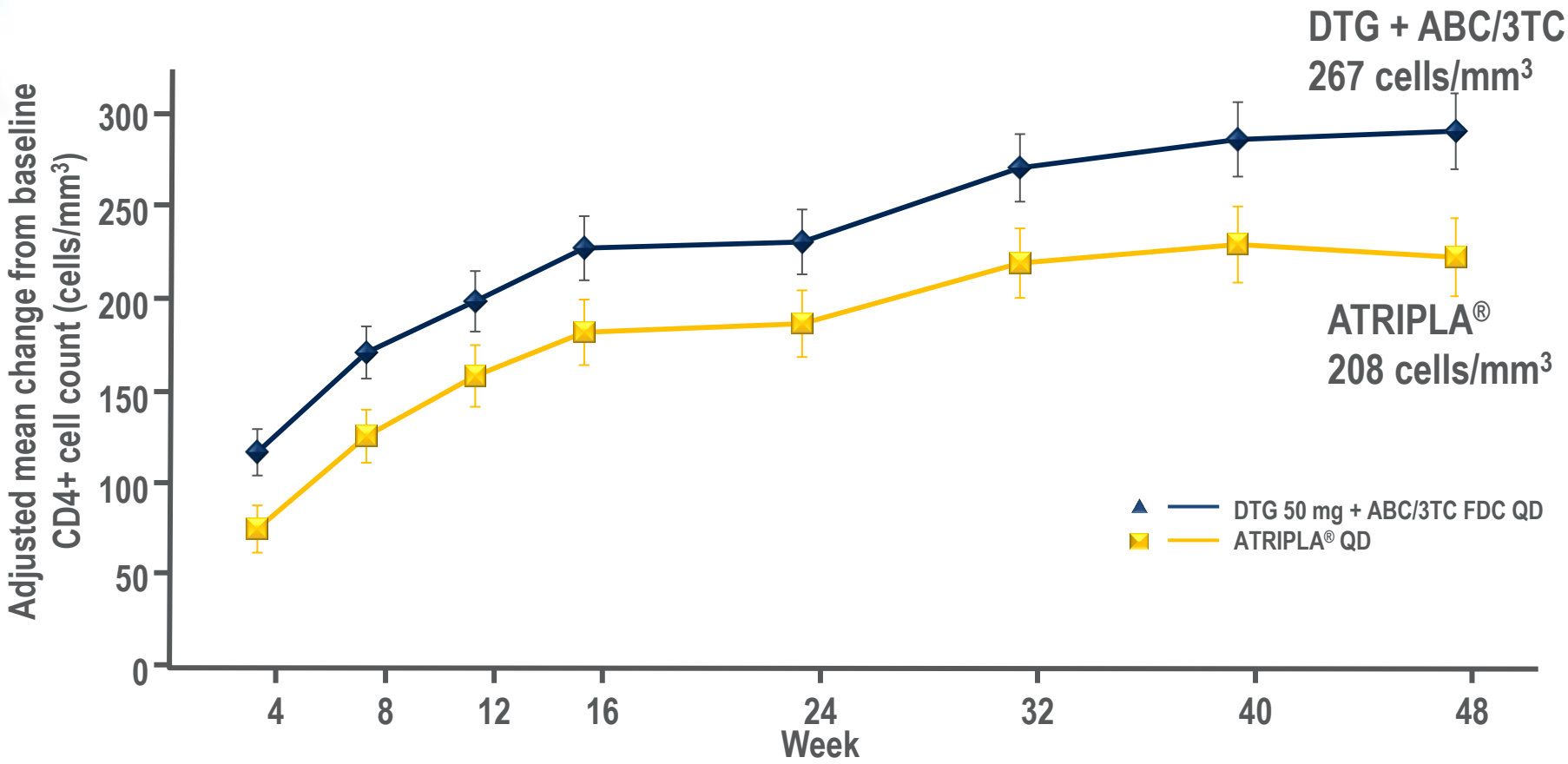


32% of treatment-naïve patients had a baseline viral load >100,000 copies/mL

*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

NO INI OR NRTI RESISTANCE THROUGH 48 WEEKS WITH DTG

Amongst DTG-treated subjects, no integrase nor NRTI mutations were detected through Week 48[1]

	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 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)‡

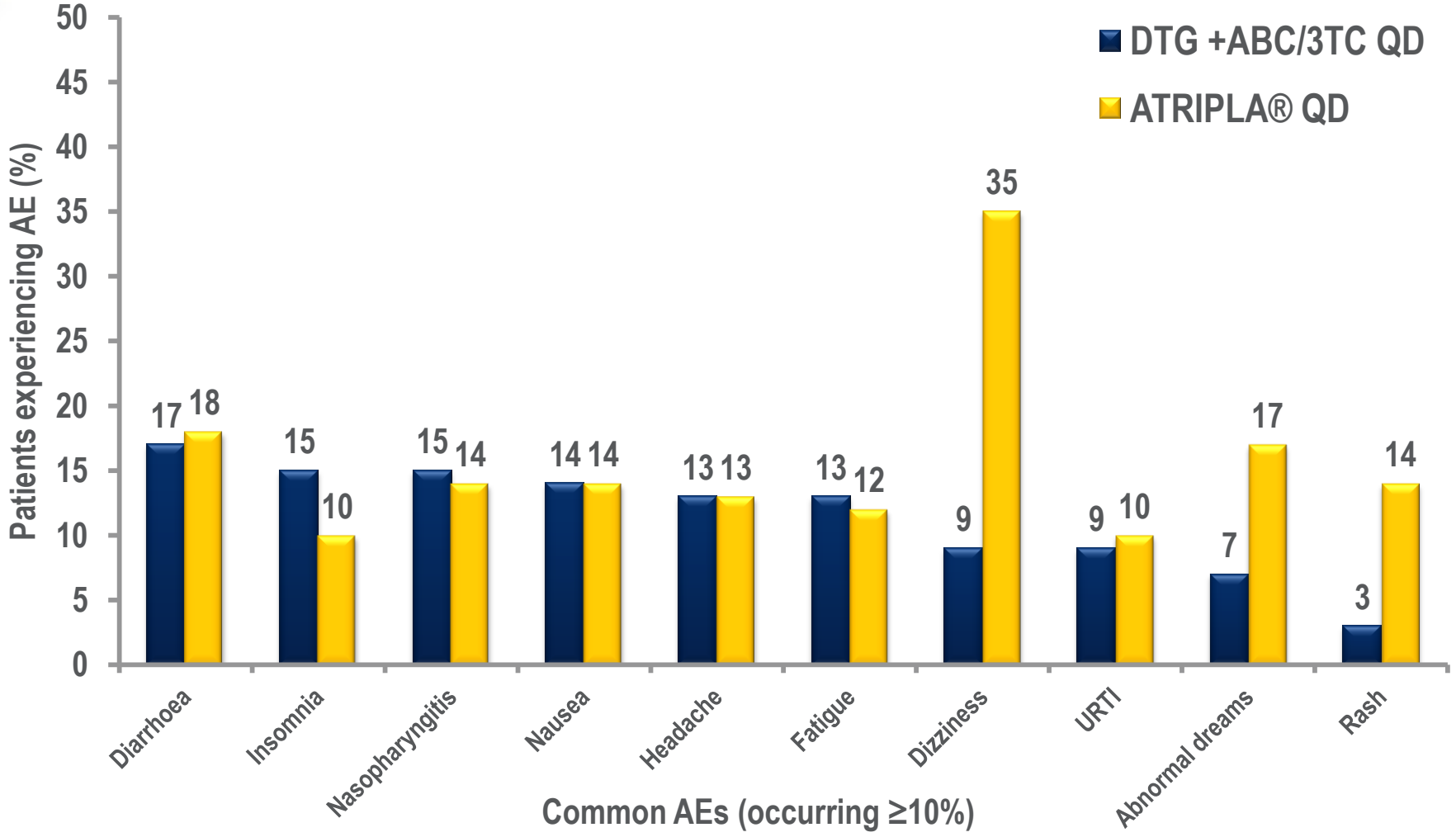
Drug-related Grade 2 to 4 AEs (any event) were 13% (53/414) for DTG + ABC/3TC and 27% (114/419) for Atripla®[2]

*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)

DTG HAD A LOWER IMPACT ON LIVER CHEMISTRY THAN ATRIPLA®

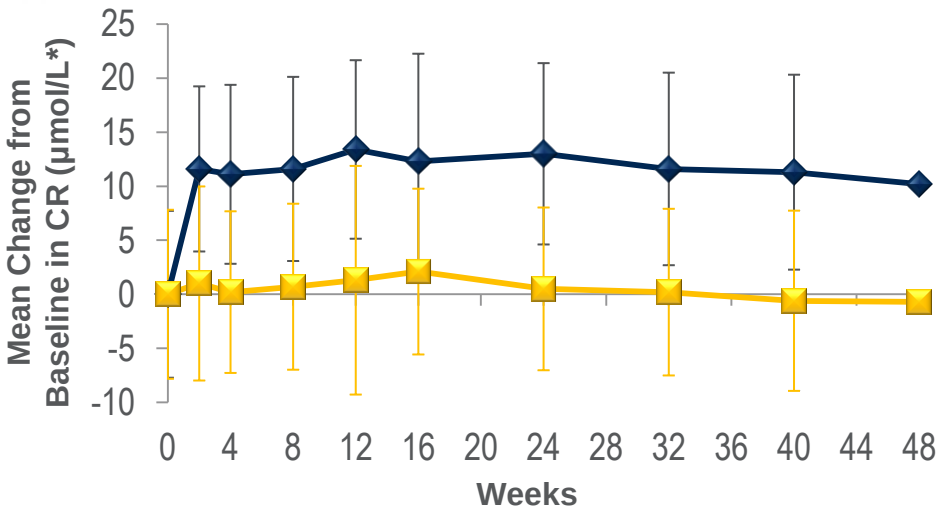
Parameter/Criteria, (%)	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Subjects meeting ≥1 FDA stopping criteria	10 (2)	39 (9)
ALT ≥20xULN	0	0
ALT ≥5xULN	1 (<1)	2 (<1)
ALT ≥3xULN	5 (1)	15 (4)
Total bilirubin >1.5xULN	3 (<1)	2 (<1)
Alkaline phosphatase >1.5xULN	1 (<1)	19 (5)
ALT and/or AST >3xULN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

ULN, upper limit of normal

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

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 (dolutegravir) Summary of Product Characteristics, 11/2013
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

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

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

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

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