Comparative Neuropsychiatric Profile of Dolutegravir and Efavirenz After 48w in Treatment Naive Patients: Data From ING114467 SINGLE Study

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Introduction

- Dolutegravir (DTG, S/GSK1349572) is a new integrase inhibitor with a 14-hour plasma half-life that enables once-daily dosing without pharmacokinetic boosters.[1,2] Regulatory review of DTG for the treatment of HIV-1 infection in adults and adolescents is ongoing globally.
- DTG 50 mg once daily was non-inferior to twice-daily raltegravir 400 mg at 48 weeks in naïve patients, both in combination with coformulated TDF/FTC or ABC/3TC, in SPRING-2 study.[3]
- Atripla is a first-line antirretroviral therapy in HIV-infected naïve patients. CNS toxicity is the most common reason for Atripla discontinuations.[4]
- Both approved integrase strand transfer inhibitors, raltegravir and elvitegravir, have shown non-inferiority in terms of efficacy and better CNS and psychiatric tolerability compared with Atripla.[5,6]

1. Min S, Song I, Borland J, et al. *Antimicrob Agents Chemother. 2010;54(1):254-258;* **2.** Powderly WG. *J Antimicrob Chemother. 2010;65(12):2485-2488;* ***3.*** *Raffi F, et al. Lancet 2013; 381: 735–43*; **4.** Scourfield A, et al. AIDS 2012, 26*:1399–1401* **5.** Lenox et al Lancet 2009; 374: 796–806; **6.** Sax PE et al. *Lancet 2012; 379: 2439–48.*

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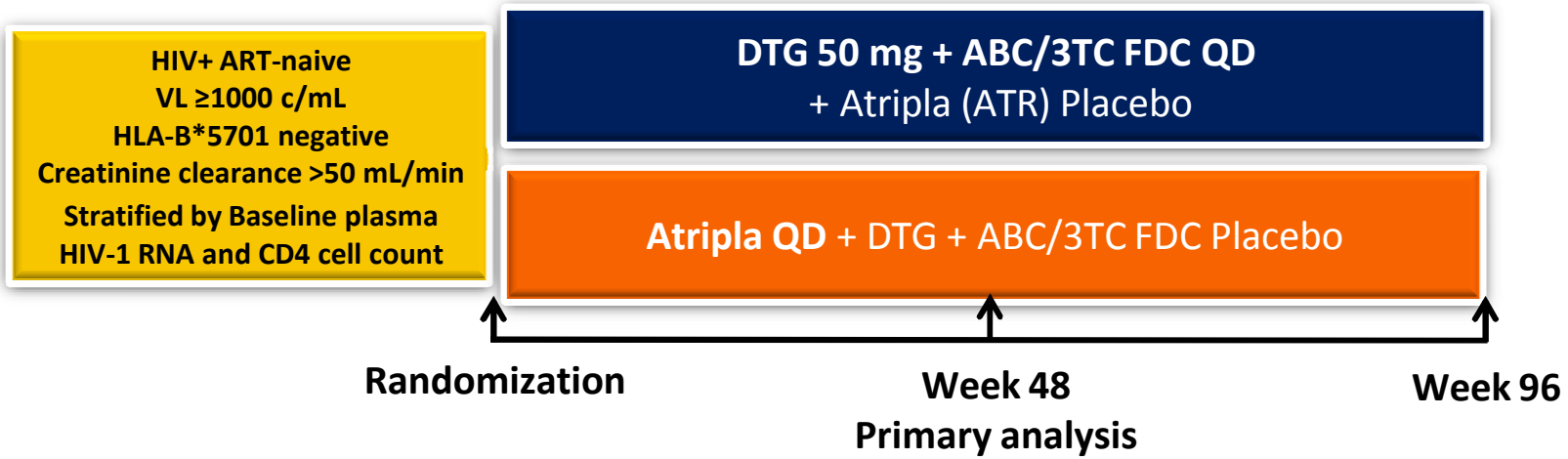
Study Design



Primary endpoint:

Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis, -10% noninferiority margin with prespecified tests for superiority

Secondary endpoints:

Tolerability, long-term safety, immunologic, health outcome and viral resistance

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Baseline Characteristics

	DTG 50 mg + ABC/3TC QD (N=414)	Atripla QD (N=419)	Total (N=833)
Age (y), median	36	35	35
Female (%)	16%	15%	16%
African American/African heritage (%)	24%	24%	24%
CDC class C (%)	4%	4%	4%
HIV-1 RNA (log_{10} c/mL), median	4.67	4.70	4.68
>100,000	32%	31%	32%
CD4+ (cells/mm^3) median	335	339	338
<200	14%	14%	14%
200 to <350	39%	38%	39%
350 to <500	32%	31%	31%
≥500	15%	17%	16%

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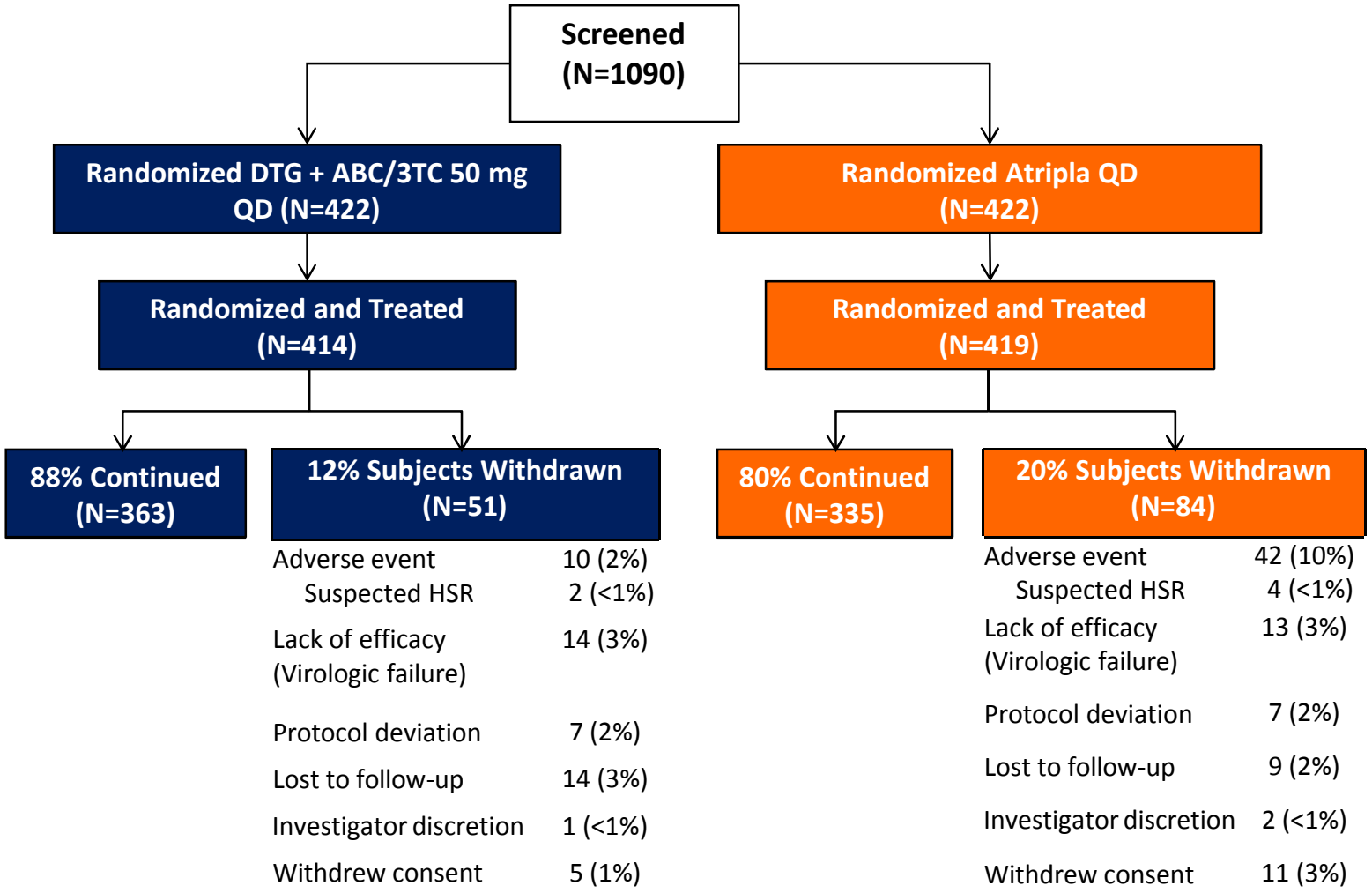
Subject Disposition



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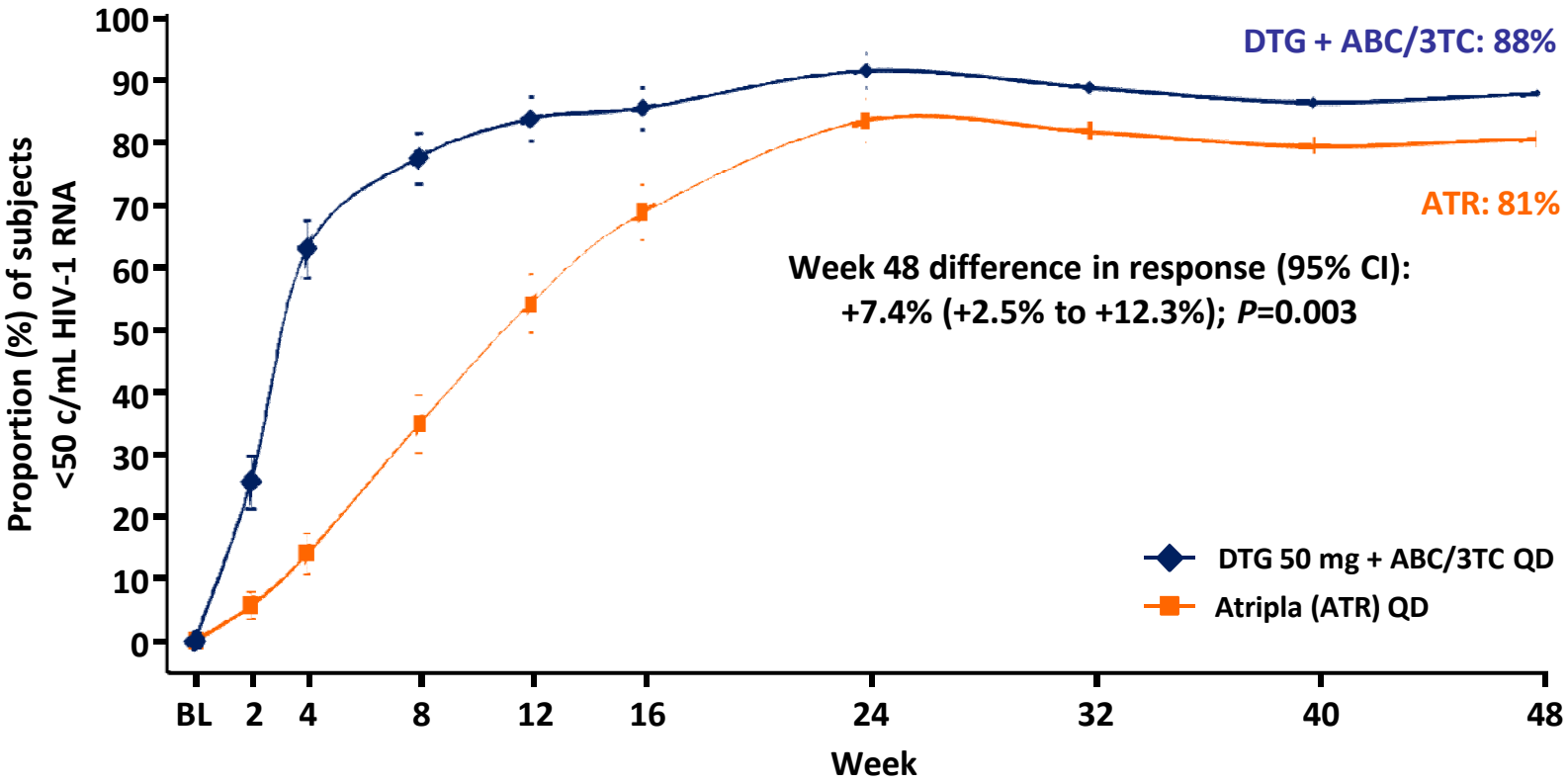
Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)



- DTG 50 mg + ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint).
- Subjects receiving DTG + ABC/3TC achieved virologic suppression faster than Atripla; median time to HIV-1 RNA <50 c/mL of 28 days (DTG + ABC/3TC) versus 84 days (Atripla), *P*<0.0001.

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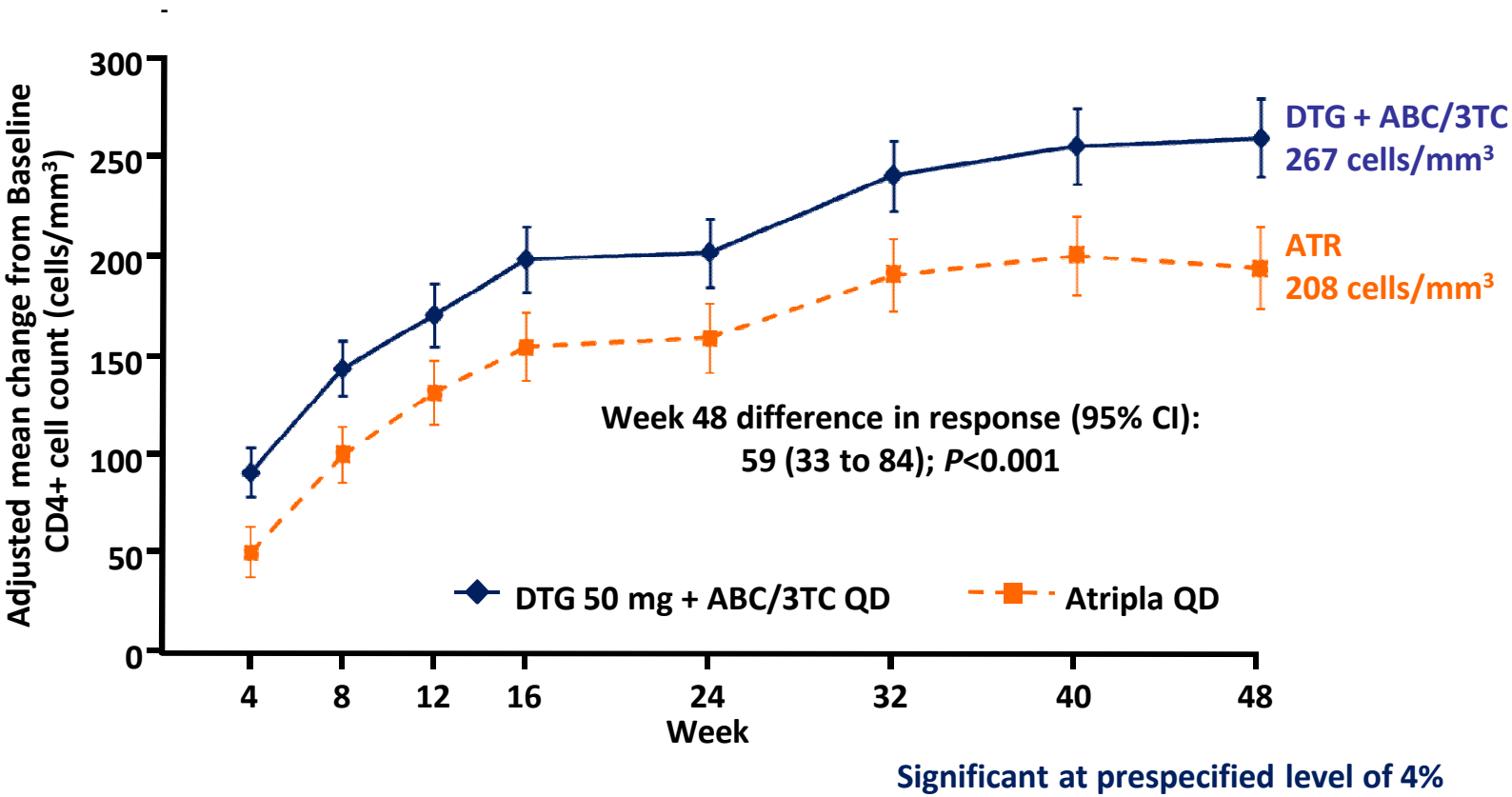
Absolute Change From Baseline in CD4+ Cell Count Repeated Measures Mixed Model Analysis



Significant at prespecified level of 4%

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Most Common Adverse Events (≥10%)

Adverse Event	DTG 50 mg + ABC/3TC QD (N=414), %	Atripla QD (N=419), %
Any event	369 (89)	387 (92)
Dizziness	37 (9)	148 (35)
Abnormal dreams	30 (7)	72 (17)
Insomnia	64 (15)	43 (10)
Headache	55 (13)	56 (13)
Fatigue	54 (13)	50 (12)
Diarrhea	72 (17)	75 (18)
Nausea	59 (14)	57 (14)
Nasopharyngitis	62 (15)	60 (14)
Upper respiratory tract infection	36 (9)	43 (10)
Rash	14 (3)	58 (14)

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Select Adverse Events

	DTG 50 mg + ABC/3TC QD (N=414), %	Atripla QD (N=419), %
Subjects with events leading to withdrawal	10 (2)	42 (10)*
Serious drug-related – any event	1 (<1)**	8 (2)^
Fatal AEs	0	2(<1)[¥]

*Atripla: Most commonly reported events were CNS, gastrointestinal and rash

**DTG + ABC/3TC: 1 drug hypersensitivity

^Atripla: 4 psychiatric, 2 drug hypersensitivity, 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 ATR, n=1 not related to ATR (pneumonia)

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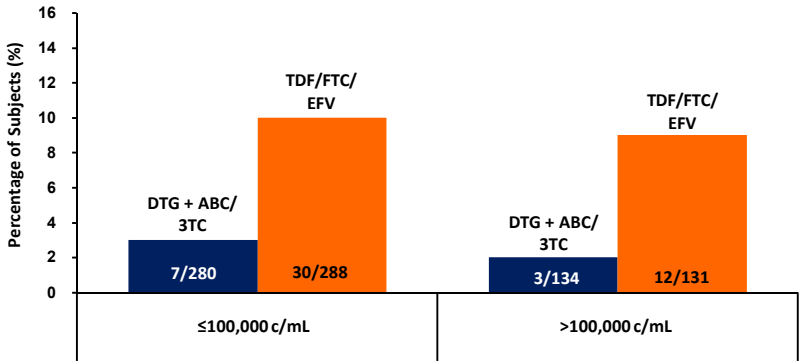
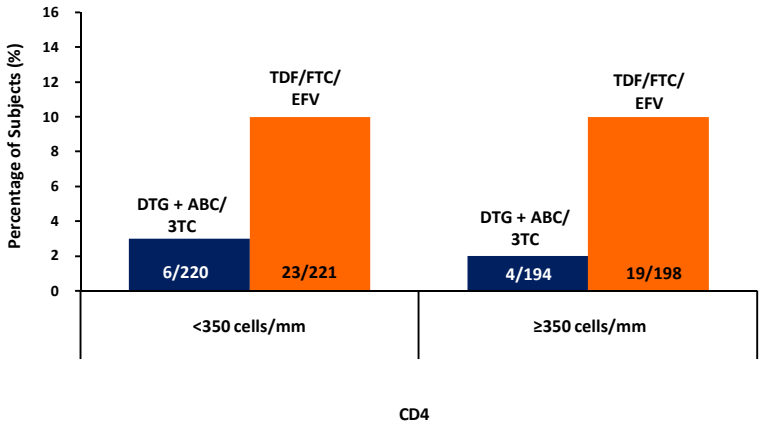
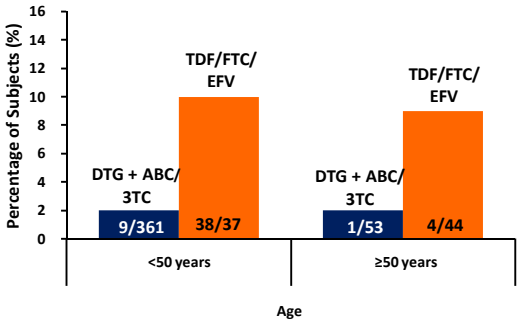
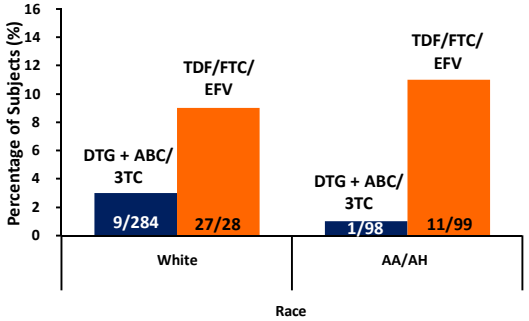
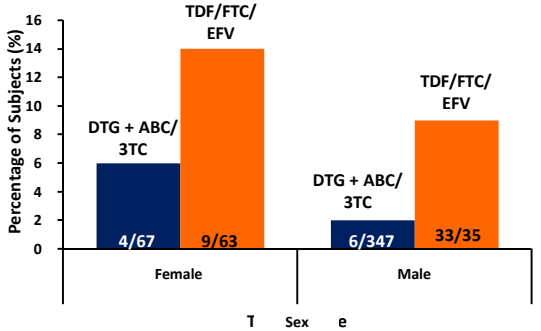
Events Leading to Withdrawal by Key Subgroups











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Predefined Adverse Events: Neuropsychiatric AEs of Interest

System Organ Class Preferred Term	DTG 50 mg + ABC/3TC QD (N=414), %	Atripla QD (N=419), %	Difference in percentage (95% CI)	Fisher's exact *P* value
Any event	**169 (41)**	**260 (62)**		
Nervous system disorders	**91 (22)**	**196 (47)**	**-24.8 (-31.0, -18.6)**	**<0.001**
Dizziness	37 (9)	148 (35)	-26.4 (-31.7, -21.0)	<0.001
Headache	55 (13)	56 (13)	-0.1 (-4.7, 4.5)	1.000
Somnolence	9 (2)	23 (5)	-3.3 (-5.9, -0.7)	
Psychiatric disorders	**120 (29)**	**158 (38)**	**-8.7 (-15.1, -2.3)**	**0.008**
Insomnia	64 (15)	43 (10)	5.2 (0.7, 9.7)	0.029
Abnormal dreams	30 (7)	72 (17)	-9.9 (-14.3, -5.5)	<0.001
Nightmare	9 (2)	17 (4)	-1.9 (-4.2, 0.5)	
Sleep disorder	6 (1)	11 (3)	-1.2 (-3.1, 0.7)	
Depression	23 (6)	26 (6)	-0.6 (-3.8, 2.5)	
Depressed mood	3 (<1)	7 (2)	-0.9 (-2.4, 0.5)	
Anxiety	14 (3)	27 (6)	-3.1 (-6.0, -0.1)	

Only AEs of interest occurring in at least 2% of subjects in either group are presented.
P value only derived if more than 10% of subjects in either group experienced this AE.

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Conclusions

- DTG 50mg+ABC/3TC is superior to Atripla with respect to snapshot (<50 c/mL) at Week 48
  - 88% on DTG were virologically suppressed (<50 c/mL) vs 81% on Atripla
  - 95% CI: (2.5%, 12.3%), lower end above pre-specified -10% non-inferiority limit
  - DTG 50mg+ABC/3TC statistically superior to Atripla in CD4 change from baseline

- DTG + ABC/3TC safety & tolerability generally favorable vs Atripla
  - Fewer rash and discontinuations due to AEs
  - Lower rate of liver chemistry elevations

- DTG + ABC/3TC was associated with lower rate of CNS events, than efavirenz.

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