Superior Efficacy of Dolutegravir/Abacavir/Lamivudine FDC Compared With Ritonavir-Boosted Atazanavir Plus Tenofovir Disoproxil Fumarate/Emtricitabine FDC in Treatment-Naive Women With HIV-1 Infection: ARIA Study

C. Orrell,[1] D. Hagins,[2] E. Belonosova,[3] N. Porteiro,[4] S. Walmsley,[5] V. Falcó,[6] C. Man,[7] A. Aylott,[8] A. Buchanan,[7] B. Wynne,[9] C. Vavro,[7] M. Aboud,[10] K. Smith[7]

[1]Desmond Tutu HIV Foundation, Cape Town, South Africa; [2]Chatham County Health Department, Savannah, GA, USA; [3]Orel Regional Center for AIDS, Orel, Russia; [4]Fundación IDEAA, Buenos Aires, Argentina; [5]University Health Network, Toronto, Canada; [6]Hospital Vall d'Hebron, Barcelona, Spain; [7,9,10]ViiV Healthcare, [7]Research Triangle Park, NC, USA; [9]Philadelphia, PA, USA; [10] Brentford, UK; [8]GlaxoSmithKline Stockley Park, UK

ARIA: Introduction

- DTG/ABC/3TC (Triumeq) is a complete regimen built around DTG, an unboosted INSTI with a high barrier to resistance
- First approval of DTG/ABC/3TC: August 2014 in North America
- To gain additional data for women, the ARIA study was conducted to evaluate the safety and efficacy of DTG/ABC/3TC versus ATV/r +TDF/FTC in ART treatment-naive women (ClinicalTrials.gov: NCT01910402)
- The study enrolled from September 2013 to September 2014 and is ongoing.

DTG/ABC/3TC, dolutegravir/abacavir/lamivudine, ATV/r+TDF/FTC, ritonavir-boosted atazanavir+tenofovir disoproxil fumarate+emtricitabine; ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor.

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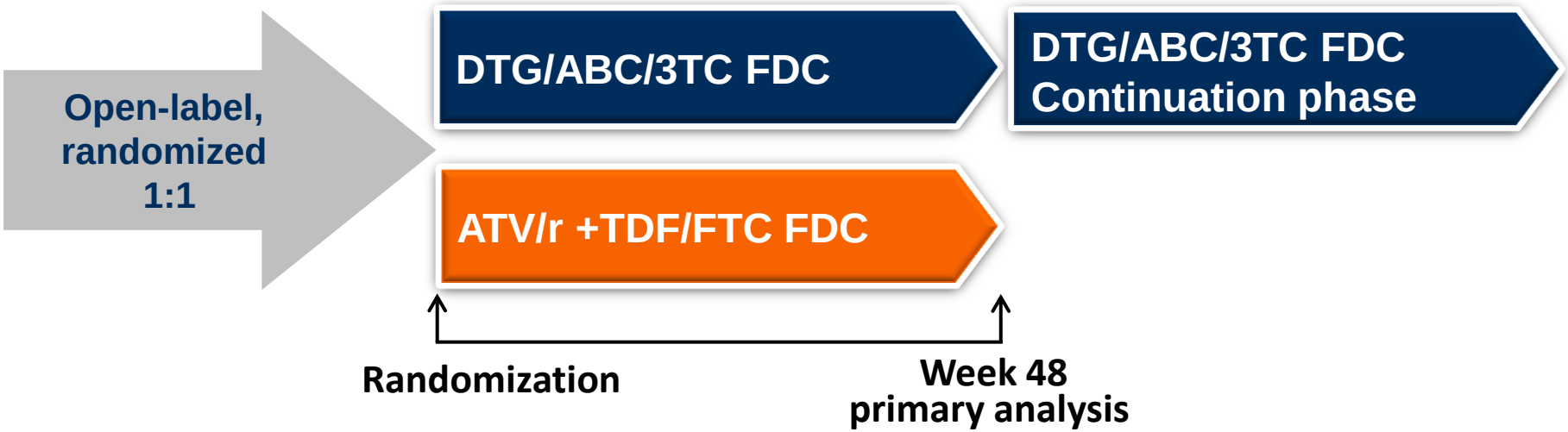
Study Design

Open-label randomised non-inferiority phase 3b study



- **Key eligibility criteria:** women, ART-naive, HLA-B*5701 negative, HIV-1 RNA >500 c/mL, hepatitis B negative
- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), CD4+ count (≤ or >350 cells/mm^3)
- Women who became pregnant were withdrawn and, if possible, offered entry into a DTG/ABC/3TC pregnancy study
- **Primary endpoint:** proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (-12% non-inferiority margin)

ART, antiretroviral therapy; FDA, US Food and Drug Administration; FDC, fixed-dose combination; HLA, human leukocyte antigen.

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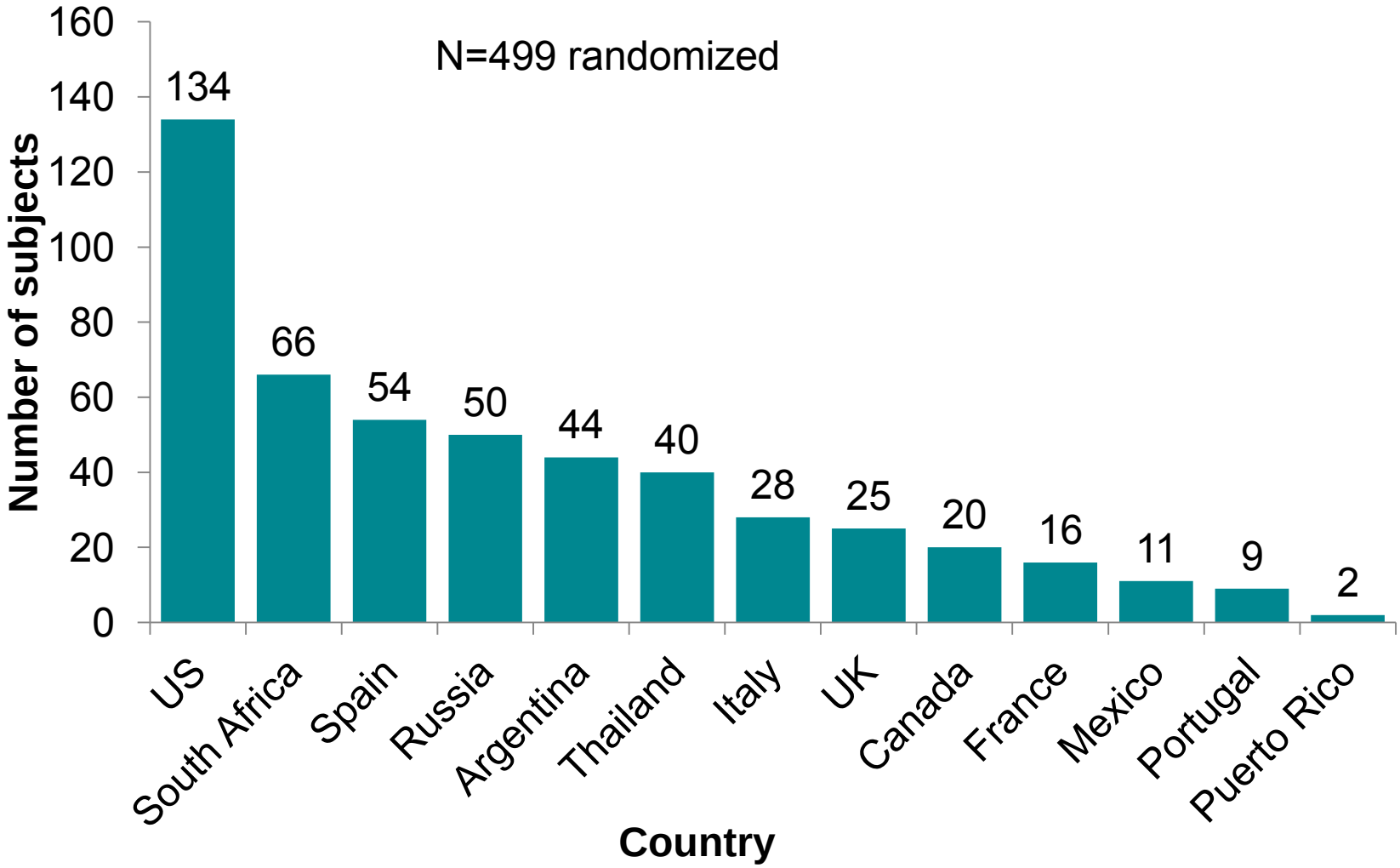
Global Enrollment



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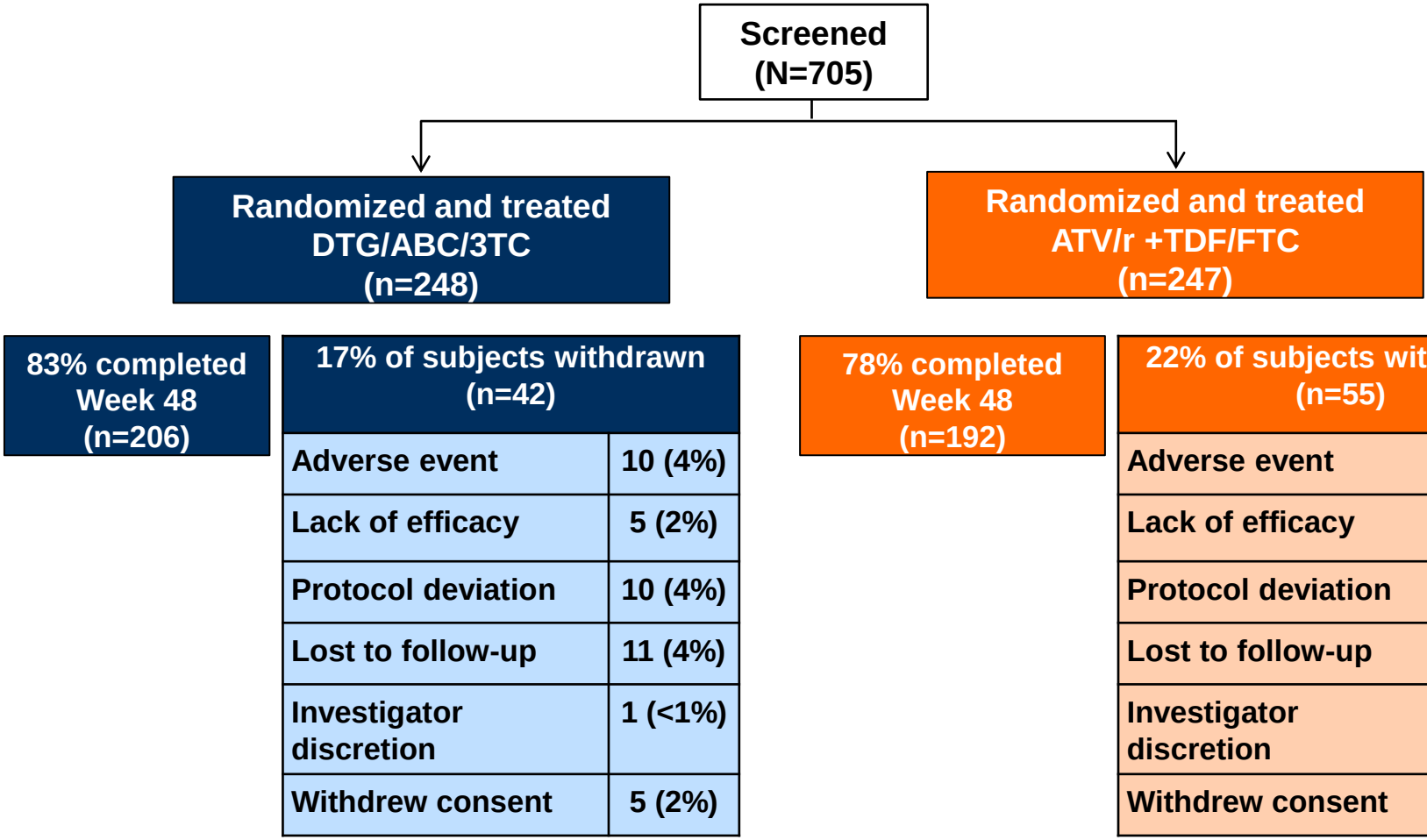
Study Disposition



5 DTG/ABC/3TC subjects (2%) and 8 ATV/r+TDF/FTC subjects (3%) became pregnant and were withdrawn from the study.

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Demographics and Baseline Characteristics

	DTG/ABC/3TC (n=248)	ATV/r +TDF/FTC (n=247)
Age, median (range), y	**37.5 (19-79)**	**37.0 (20-65)**
Race, n (%)		
African heritage	**102 (41)**	**108 (44)**
White	**115 (46)**	**107 (43)**
Asian	**22 (9)**	**23 (9)**
Hepatitis C, n (%)	**16 (6)**	**21 (9)**
CDC category, n (%)		
Asymptomatic	**210 (85)**	**208 (84)**
AIDS	**11 (4)**	**9 (4)**
HIV-1 RNA (log c/mL)	**4.48**	**4.44**
>100,000 (c/mL), n (%)	**69 (28)**	**66 (27)**
CD4+ cell count	**370**	**380**
<350 (cells/mm^3), n (%)	**130 (52)**	**123 (50)**

CDC, Centers for Disease Control.

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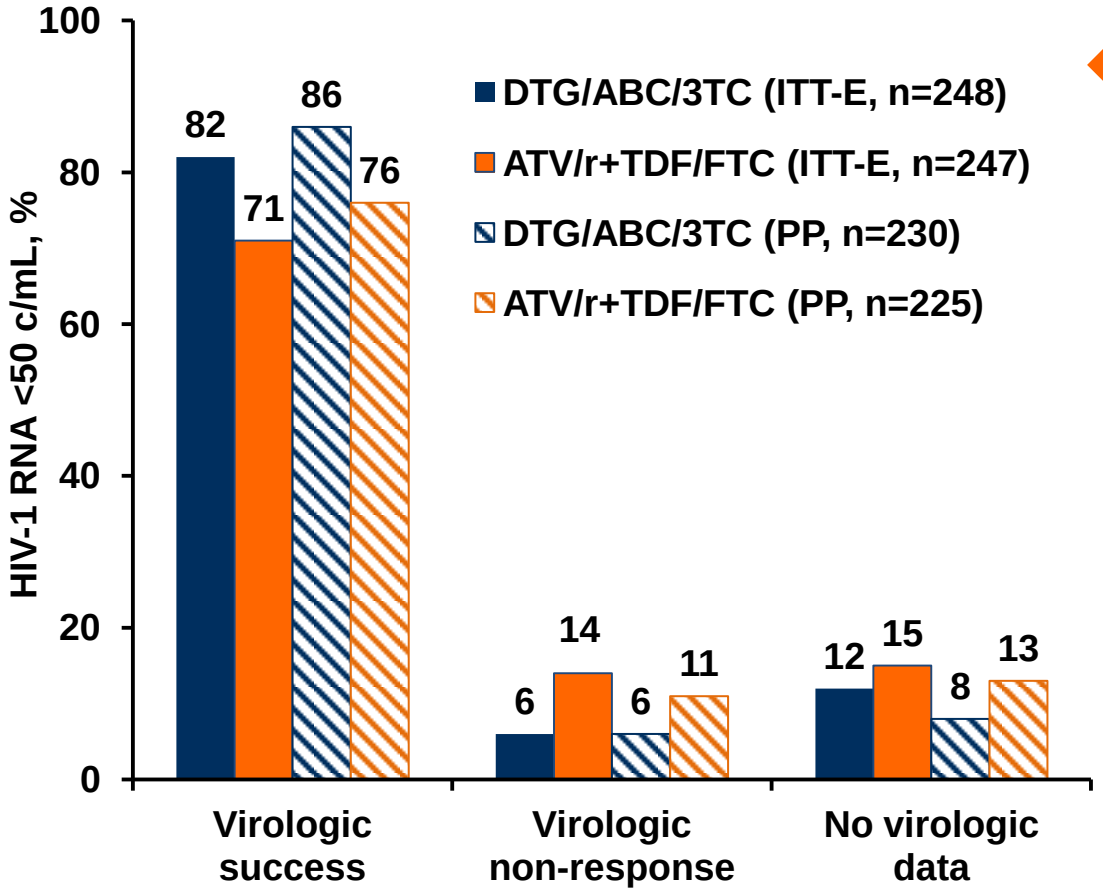
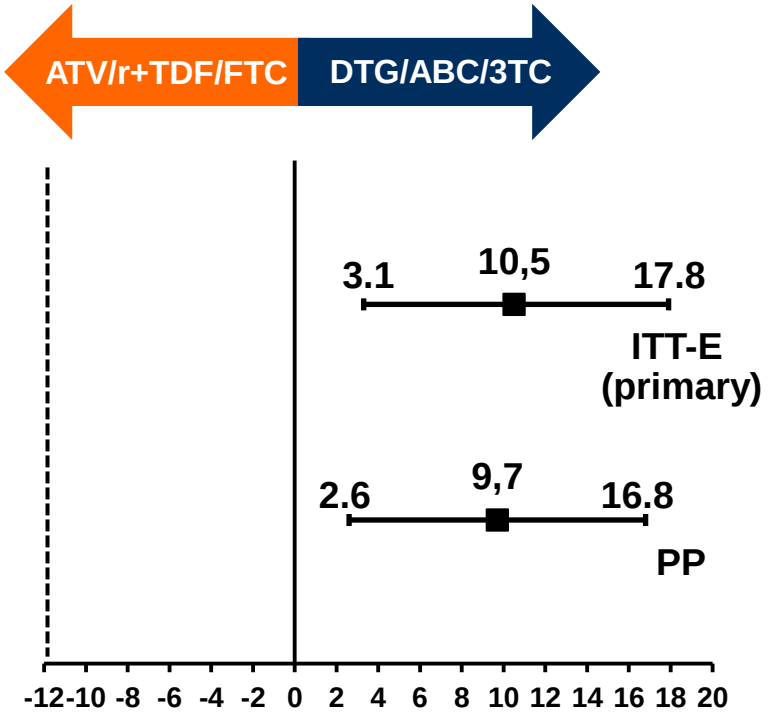
Snapshot Outcomes at Week 48: ITT-E and PP Populations

Virologic outcomes



Treatment differences (95% CI)



- DTG/ABC/3TC is **superior** to ATV/r+TDF/FTC with respect to snapshot in the ITT-E (<50 c/mL) at Week 48, ***P*=0.005**

CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

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Snapshot Outcomes at Week 48: ITT-E

	DTG/ABC/3TC (n=248)	ATV/r+TDF/FTC (N=247)
Virologic response	203 (82%)	176 (71%)
Virologic non-response	16 (6%)	35 (14%)
Data in window not below threshold	4 (2%)	16 (6%)
Discontinued while VL not <50*	12 (5%)	19 (8%)
No virologic data	29 (12%)	36 (15%)
Discontinued study due to AE or death	9 (4%)	18 (7%)
Discontinued study for other reasons	15 (6%)	14 (6%)
Missing data during window but on study	5 (2%)	4 (2%)

Differences in response rates driven by Snapshot virologic non-response and lower rates of both discontinuations due to AEs in the DTG/ABC/3TC group.

*Includes categories: Discontinued for lack of efficacy and Discontinued for other reason while not below threshold

AE, adverse, event; ITT-E, intent-to-treat exposed

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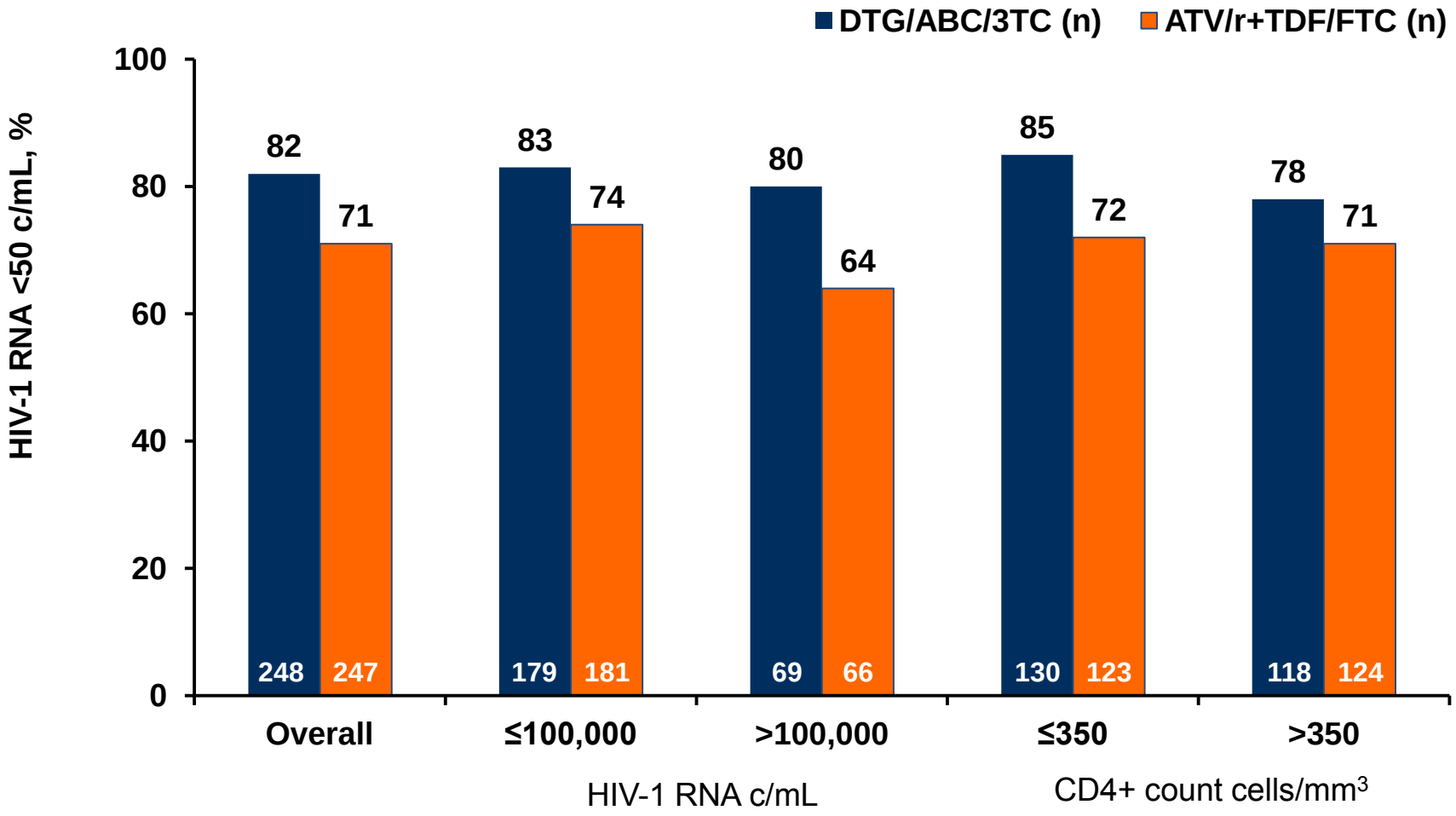
Snapshot Outcomes by Baseline Randomization Strata at Week 48: ITT-E



ITT-E, intent-to-treat exposed.

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Treatment Emergent Mutations in Patients with Confirmed Virologic Withdrawal

- The resistance analysis was performed on subjects meeting confirmed virologic withdrawal (confirmed ≥400 c/mL on or after Week 24)

Resistance Analysis	DTG/ABC/3TC (n=6)	ATV/r +TDF/FTC (n=4)
INSTI	**0**	**0**
NRTI	**0***	**1**
M184V	**0**	**1**
PI	**0**	**0**

*Two subjects receiving DTG/ABC/3TC had either K219K/Q (TAM) or E138E/G at CVW with no reduced susceptibility to DTG/ABC/3TC. K219K/Q is not selected for by ABC or 3TC nor does it affect their fold change

- No subject receiving DTG/ABC/3TC developed INSTI or ABC/3TC resistance-associated mutations

INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

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Summary of Adverse Events: Randomized Phase (up to Week 48)

	DTG/ABC/3TC (n=248)	ATV/r+TDF/FTC (n=247)
Any adverse event, n (%)	195 (79%)	197 (80%)*
Grade 2 to 4 AE	115 (46%)	137(55%)
Drug-related AE (occurring ≥5% of subjects in either arm)	83 (33%)	121 (49%)
Nausea	31 (13)	35 (14)
Diarrhoea	12 (5)	18 (7)
Dyspepsia	4 (2)	15 (6)
Ocular icterus	0	18 (7)
Headache	5 (2)	14 (6)
Jaundice	0	13 (5)
Serious AE	12 (5%)	20 (8%)
Fatal AE	1+	0
Drug-related SAE	0	3 (1%)
Discontinuations due to AEs	10 (4%)	17 (7%)

*Additional AEs identified post-hoc for two ATV+RTV+TDF/FTC subjects at one site are not included in this table. AEs were not considered to impact overall safety findings

+Death certificate noted death due to natural causes. Investigator deemed event unrelated to study drug.

AE, adverse event; SAE, serious adverse event.

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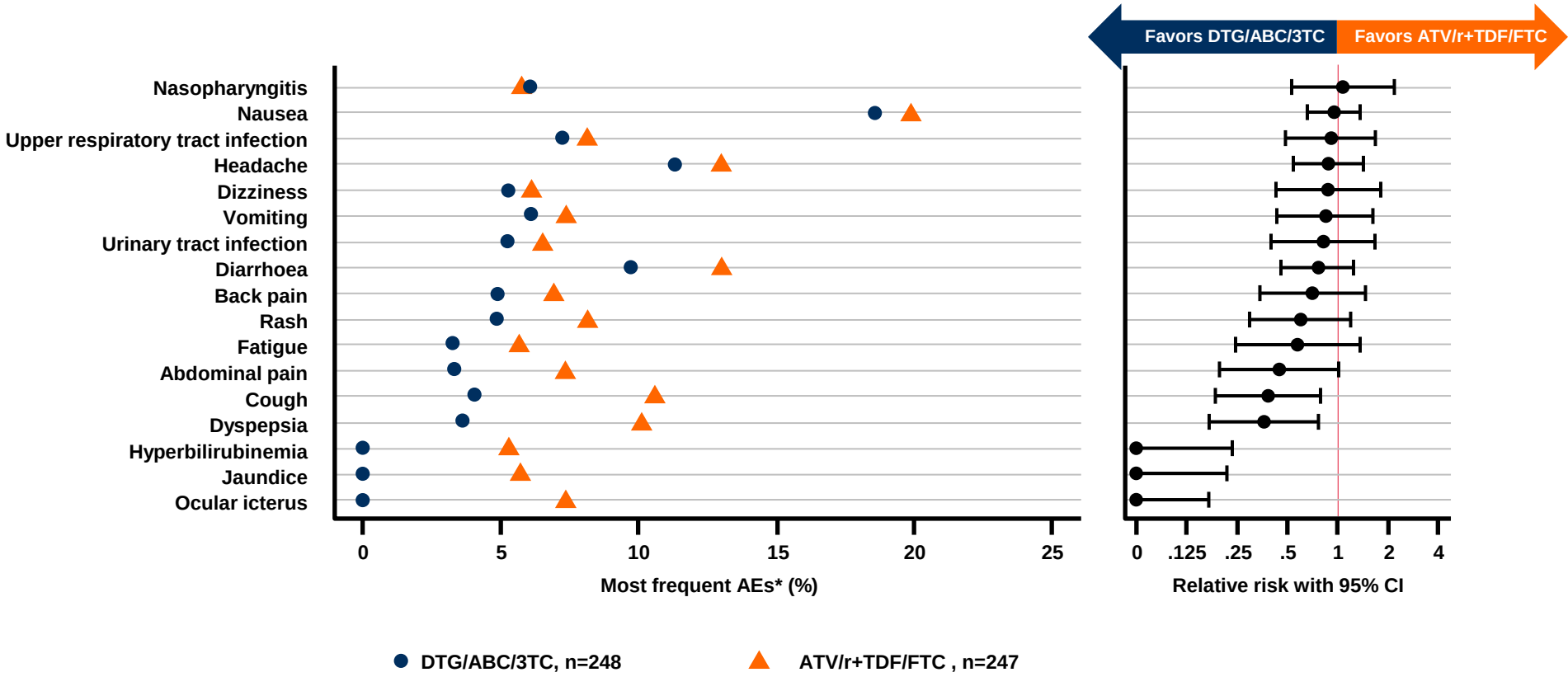
Most Frequent AEs and Relative Risk



* Randomized Phase (up to Week 48); All AEs reported by ≥5% in at least one treatment group.

AE, adverse event; CI, confidence interval.

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Summary of Psychiatric AEs

Event	DTG/ABC/3TC FDC N=248 n (%)	ATV/r+ TDF/FTC FDC N=247 n (%)
Any event	**35 (14)**	**35 (14)**
Insomnia	10 (4)	9 (4)
Anxiety	5 (2)	7(3)
Depression	5 (2)	7 (3)
Suicidal ideation	4 (2)	3 (1)
Depressed mood	3 (1)	4 (2)
Abnormal dreams	2 (<1)	0
Panic attack	2 (<1)	2 (<1)
Agitation	1 (<1)	0
Bipolar disorder	1 (<1)	0
Elevated mood	1 (<1)	0
Mood altered	1 (<1)	2 (<1)
Mood swings	1 (<1)	0
Nightmare	1 (<1)	2 (<1)
Sleep disorder	1 (<1)	2 (<1)

Event	DTG/ABC/3TC FDC N=248 n (%)	ATV/r+ TDF/FTC FDC N=247 n (%)
Acute psychosis	0	1 (<1)
Affect lability	0	1 (<1)
Anxiety disorder	0	1 (<1)
Confusional state	0	1 (<1)
Hallucination, visual	0	1 (<1)
Intentional self-injury	0	1 (<1)
Irritability	0	1 (<1)
Mania	0	1 (<1)
Panic disorder	0	1 (<1)
Stress	0	1 (<1)

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Conclusions

- In treatment-naive women, DTG/ABC/3TC (Triumeq) was superior to ATV/r+TDF/FTC at 48 weeks of treatment
  - Adjusted difference 10.5%, 95% CI: 3.1% to 17.8%, P=0.005
  - Difference driven by lower rate of virologic non-response (Snapshot) and fewer discontinuations due to AEs in DTG arm
- DTG/ABC/3TC had a favorable safety profile compared to ATV/r+TDF/FTC
  - Similar to overall safety profile for DTG from previous studies
- There were no treatment-emergent primary INSTI or ABC/3TC resistance mutations in the DTG/ABC/3TC group
- The study provides important information to help guide treatment decisions in women

AE, adverse event; CI, confidence interval; INSTI, integrase strand transfer inhibitor

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

Acknowledgments

- We thank everyone who has contributed to the success of this study, including
  - All study participants and their families
  - The clinical investigators and their staff
  - The GSK and ViiV Healthcare study teams

Prescribing Information
Triumeq® ▼ dolutegravir 50mg/abacavir 600mg/lamivudine 300mg tablets
See Summary of Product Characteristics before prescribing.
Indication: HIV in over 12 years and ≥ *40kg*. Screen for HLA-B*5701 prior to use. Do not use if HLA-B*5701 positive. **Dose:** one tablet once daily with or without food. *Elderly:* Limited data in 65+ yrs. *Creatinine clearance <50ml/min* or *moderate/severe hepatic impairment:* Not recommended. Monitor closely in mild hepatic impairment.
Contraindications: Hypersensitivity to any ingredient. Co-administration with dofetilide.
Warnings/precautions: Both abacavir and dolutegravir are associated with risk of hypersensitivity reactions (HSR). Do not initiate in HLA-B*5701+ or previous suspected abacavir HSR. Stop Triumeq without delay if HSR suspected. Never reintroduce any dolutegravir- or abacavir-containing product after suspected HSR. Risks of immune reactivation syndrome, osteonecrosis, increased weight, lipids, glucose. Monitor LFTs in Hepatitis B/C co-infection. Inconclusive data on relationship between abacavir and MI; minimise all modifiable CV risk factors (e.g. smoking, hypertension, hyperlipidaemia). Not recommended if dolutegravir required b.d. (with etravirine [without boosted PI], efavirenz, nevirapine, rifampicin, boosted tipranavir, carbamazepine, oxcarbazepine, phenytoin, phenobarbital and St John's Wort). Use with cladribine not recommended. Use with Mg/Al-containing antacids, calcium, multivitamins or iron requires dosage separation. Caution with metformin: monitor renal function and consider metformin dose adjustment.
Pregnancy/lactation: Not recommended. Avoid breast-feeding. **Side effects:** See SPC for details. Headache, insomnia, sleep/dream disorders, GI disturbance, fatigue, hypersensitivity, anorexia, depression, dizziness, somnolence, lethargy, malaise, cough, nasal symptoms, rash, pruritus, alopecia, arthralgia, myalgia, asthenia, fever, elevations of ALT, AST and CPK, blood dyscrasias, suicidal ideation or suicide attempt, rhabdomyolysis, lactic acidosis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. **Basic NHS costs:** 30 tablets: £798.16
EU/1/14/940/001. MA 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 S1A

Triumeq is a registered trademark of the ViiV Healthcare Group of Companies

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Adverse events should be reported. For the UK, reporting forms and information can be found at *www.mhra.gov.uk/yellowcard*. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.

Adverse events should be reported. For Ireland, adverse events should be reported directly to the HPRA; Freepost, Pharmacovigilance Section, Health Products Regulatory Authority, Earlsfort Terrace, Dublin 2, Tel: +353 1 676 4971, *medsafety@hpra.ie*. Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.