# Superior Efficacy of Dolutegravir/Abacavir/Lamivudine Fixed Dose Combination Compared With Ritonavir Boosted Atazanavir Plus Tenofovir/Emtricitabine in Treatment-Naive Women With HIV-1 Infection (ARIA Study)

136

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## Introduction

- Dolutegravir 50 mg/abacavir 600 mg/lamividune 300 mg (DTG/ABC/3TC) fixed-dose combination (Triumeq®) is a complete regimen built around DTG, an unboosted integrase strand transfer inhibitor (INSTI) with a high barrier to resistance[1-2]
- The safety and efficacy of DTG has been demonstrated in 3 phase 3 studies (FLAMINGO,[3] SPRING-2,[4] and SINGLE[5]) in antiretroviral therapy (ART)-naive patients with HIV-1 infection and 2 phase 3 studies (SAILING[6] and VIKING-3[7]) in ART-experienced patients
- The proportion of women enrolled in phase 3 DTG trials has ranged between 14% and 32%[3-7]
  - More data on the safety and efficacy of DTG-based regimens in women is needed
- The ARIA study (ClinicalTrials.gov: NCT01910402) evaluated the safety and efficacy of DTG/ABC/3TC in treatment-naive women with HIV-1 versus atazanavir 300 mg boosted with ritonavir 100 mg (ATV/r) plus tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg

## Objectives

- To demonstrate the noninferior antiviral activity of DTG/ABC/3TC compared with ATV/r + TDF/FTC, each administered once daily over 48 weeks in HIV-1–infected ART-naive women
- To compare the safety and tolerability and virologic and resistance outcomes of DTG/ABC/3TC with ATV/r + TDF/FTC once daily over time

## Methods

- ARIA is an ongoing randomised, open-label, multicentre, active-controlled, parallel-group, noninferiority phase 3b study of the safety and efficacy of once-daily DTG/ABC/3TC in ART-naive women with HIV-1 infection
- The study was initiated on August 22, 2013, and participants were enrolled at 86 sites in 13 countries
- Key eligibility criteria: women, ART naive, *HLA-B*5701* negative, HIV-1 RNA >500 c/mL, hepatitis B negative
- Women who became pregnant were withdrawn and, if possible, offered entry into a DTG/ABC/3TC pregnancy study
- After a 14- to 28-day screening period, eligible patients were randomly assigned 1:1 to receive DTG/ABC/3TC or ATV/r + TDF/FTC once daily for 48 weeks
- The primary endpoint was the proportion of patients with plasma HIV-1 RNA <50 c/mL at Week 48 in the intent-to-treat exposed (ITT-E) population using the FDA snapshot algorithm (-12% noninferiority margin)
- Random treatment group assignment was stratified by screening levels of plasma HIV-1 RNA (≤100,000 or >100,000 c/mL) and CD4+ cell count (≤350 or >350 cells/mm$^3$)
- Patient safety was monitored by recording the incidence, duration, severity, and causality of all adverse events throughout the study

## Results

### Participants

- Of 705 patients screened, 499 were randomly assigned to receive either DTG/ABC/3TC or ATV/r + TDF/FTC for 48 weeks; 495 received at least one dose of study medication
- 398 patients completed the study through Week 48
  - 206 (83%) patients were randomized to DTG/ABC/3TC and 192 (78%) patients were randomized to ATV/r + TDF/FTC in the ITT-E population
- Key baseline characteristics in the ITT-E population were similar between the treatment groups (Table 1)

**Table 1. Patient Demographics and Baseline Disease Characteristics (ITT-E Population)**

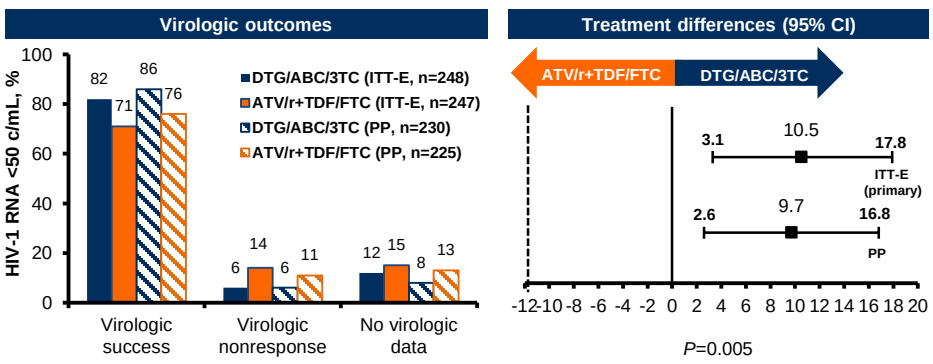
| | DTG/ABC/3TC (n=248) | ATV/r + TDF/FTC (n=247) |
|---|---|---|
| Age, median (range), y | 37.5 (19-79) | 37.0 (20-65) |
| Race, n (%) | | |
| African heritage | 102 (41) | 108 (44) |
| White | 115 (46) | 107 (43) |
| Asian | 22 (9) | 23 (9) |
| Hepatitis C, n (%) | 16 (6) | 21 (9) |
| CDC category, n (%) | | |
| Asymptomatic | 210 (85) | 208 (84) |
| AIDS | 11 (4) | 9 (4) |
| HIV-1 RNA, median, log c/mL | 4.41 | 4.43 |
| >100,000 c/mL, n (%) | 69 (28) | 66 (27) |
| CD4+ cell count, median, cells/mm$^3$ | 340 | 350 |
| <350 cells/mm$^3$, n (%) | 130 (52) | 123 (50) |

ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; CDC, Centers for Disease Control and Prevention; DTG, dolutegravir; FTC, emtricitabine; ITT-E, intent-to-treat exposed; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

### Virologic Efficacy

- Treatment with DTG/ABC/3TC was superior to ATV/r + TDF/FTC in achieving HIV <50 c/mL in the ITT-E population in the Week 48 snapshot analysis (82% vs 71%; adjusted difference, 10.5%; 95% CI, 3.1% to 17.8%; *P*=0.005; Figure 1)

**Figure 1. Virologic Efficacy at Week 48**




ABC, abacavir; ATV/r, atazanavir with ritonavir; CI, confidence interval, DTG, dolutegravir; FTC, emtricitabine; ITT-E, intent-to-treat exposed; 3TC, lamivudine; PP, per protocol, TDF, tenofovir disoproxil fumarate.

- Factors that influenced the differences in response rates included
  - Snapshot virologic nonresponse (DTG/ABC/3TC, 6%; ATV/r + TDF/FTC, 14%)
  - No virologic data because of discontinuations due to adverse events (AEs) or death (DTG/ABC/3TC, 4%; ATV/r + TDF/FTC, 7%)
- Viral suppression in subgroups stratified by baseline HIV-1 RNA viremia
  - HIV-1 RNA ≤100,000 c/mL: DTG/ABC/3TC, 83%; ATV/r + TDF/FTC, 74%
  - HIV-1 RNA >100,000 c/mL: DTG/ABC/3TC, 80%; ATV/r + TDF/FTC, 64%
- Viral suppression in subgroups stratified by baseline CD4+ cell counts
  - CD4+ cell counts ≤350: DTG/ABC/3TC, 85%; ATV/r + TDF/FTC, 72%
  - CD4+ cell counts >350: DTG/ABC/3TC, 78%; ATV/r + TDF/FTC, 71%
- Among patients with confirmed HIV-1 RNA ≥400 c/mL at or after Week 24, none assigned to treatment with DTG/ABC/3TC developed INSTI or ABC/3TC resistance–associated mutations
  - One patient treated with ATV/r + TDF/FTC developed a treatment-emergent mutation associated with resistance (M184V; NRTI)
  - Two patients treated with DTG/ABC/3TC had either K219K/Q or E138E/G substitutions at withdrawal but no reduced susceptibility to any antiretroviral drug tested

### Safety

- Adverse events were reported by 79% of patients treated with DTG/ABC/3TC and 80% of patients treated with ATV/r + TDF/FTC (Table 2)

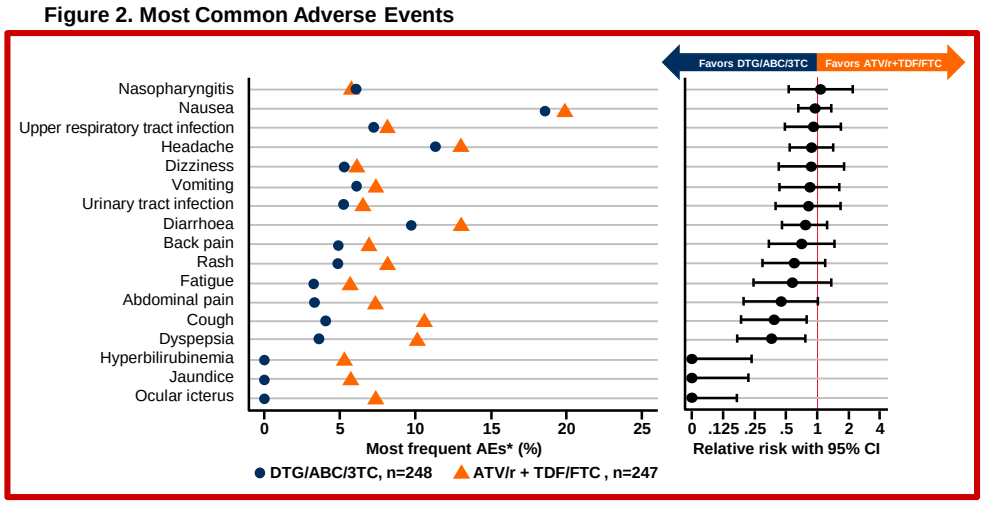
**Table 2. Adverse Events**

| Number of patients with AE | DTG/ABC/3TC n=248 n (%) | ATV/r + TDF/FTC n=247 n (%) |
|---|---|---|
| Any AE | 195 (79) | 197 (80) |
| Grade 2 to 4 AE | 115 (46) | 137(55) |
| SAE | 12 (5) | 20 (8) |
| Drug-related AE | 83 (33) | 121 (49) |
| (occurring ≥5% of subjects in either arm) | | |
| 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) |
| Drug-related SAE | 0 | 3 (1) |
| Any neuropsychiatric AE | 35 (14) | 35 (14) |
| (occurring ≥3% of subjects in either arm) | | |
| Insomnia | 10 (4) | 9 (4) |
| Anxiety | 5 (2) | 7 (3) |
| Depression | 5 (2) | 7 (3) |
| Fatal AE | 1 (<1)[a] | 0 |
| Discontinuations due to AE | 10 (4) | 17 (7) |

ABC, abacavir; AE, adverse event; ATV/r, ritonavir-boosted atazanavir; DTG, dolutegravir; FTC, emtricitabine; 3TC, lamivudine; SAE, serious adverse event; TDF, tenofovir disoproxil fumarate. [a]Death certificate noted death due to natural causes. Investigator deemed event unrelated to study drug.

- Neuropsychiatric events occurred at a comparable rate between treatment groups (14% in each arm)
- The most commonly reported AEs were nasopharyngitis, nausea, upper respiratory infection, headache, and dizziness, which occurred at similar rates in the two treatment groups (Figure 2)

**Figure 2. Most Common Adverse Events**




*Occurring ≥5% of subjects in either arm. ABC, abacavir; AE, adverse event; ATV/r, ritonavir-boosted atazanavir; CI, confidence interval, DTG, dolutegravir; FTC, emtricitabine; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

## Conclusions

- In treatment-naive women, DTG/ABC/3TC 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 nonresponse (snapshot) and fewer discontinuations due to AEs in DTG/ABC/3TC group
  - Virologic outcomes in stratification analyses were consistent with overall results
- There were no treatment-emergent primary INSTI or ABC/3TC resistance mutations in the DTG/ABC/3TC group
- DTG/ABC/3TC had a favourable safety profile compared to ATV/r + TDF/FTC
  - Fewer grade 2 to 4 AEs and drug-related AEs in the DTG/ABC/3TC group
  - Comparable rates of neuropsychiatric AEs between treatments
  - Similar to overall safety profile for DTG from previous studies[3-7]

**Acknowledgments:** Study supported by ViiV Healthcare. We thank everyone who has contributed to the success of this study, including study participants and their families, the clinical investigators and their staff, and the GSK and ViiV Healthcare study teams. Medical writing support and editorial support were provided by MedThink SciCom and funded by ViiV Healthcare. These data were previously presented at the 21st International AIDS Conference; July 18-22, 2016; Durban, South Africa. Abstract THAB0205LB.

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