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)

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Introduction
Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg (DTG/ABC/3TC) fixed-dose combination (Tzido®) is a complete regimen built around at least one unboosted integrase strand transfer inhibitor (INSTI) with a high barrier to resistance.7-10 The safety and efficacy of DTG has been demonstrated in 3 phase 3 studies (FLAMINGO,11 SPARTAN-2 and SINGLE-1), an antifungal therapy and ART-naive patients with HIV-1 infection and 2 phase 3 studies (SALVIA2 and VIKING3-1) in ART-experienced patients. The proportion of women enrolled in phase 3 DTG trials has ranged between 14% and 32%.11-13 More data on the safety 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 vs ritonavir 100 mg (ATV) plus lamivudine+emtricitabine (TDF) 300 mg and emtricitabine (FTC) 200 mg.

Objectives
To demonstrate the noninferior antiviral activity of DTG/ABC/3TC compared with ATV+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 in ART-naive women.

To compare noninferiority of DTG/ABC/3TC vs ATV+r+TDF/FTC on time to virologic nonresponse.

Methods
ARIA is an ongoing, randomised, open-label, parallel-group, multinational, phase 3b study of the safety and efficacy of once-daily DTG/ABC/3TC in ART-naive women with HIV-1 infection.

The study enrolled women from 24 August 2013 to 21 March 2014. Women who were not pregnant were enrolled at 13 countries in Phase 3 and 11 countries in Phase 4. Key eligibility criteria: women, ART naive, ≥18 years (≤100,000 or >100,000 c/mL) and CD4+ cell count (≤350 or >350 cells/mm$^3$).

Results
Women who became pregnant were withdrawn and, if possible, offered entry into a DTG/ABP/3TC study.

Methods
After 4 to 28 week 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 (1%-12% non-linearity 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$^3$).

Safety
Adverse events were reported by 79% of patients treated with DTG/ABC/3TC and 80% of patients treated with ATV+r+TDF/FTC once daily over time.

Factors that influenced the differences in response rates included:
- Snapshot virologic nonresponse (DTG/ABC/3TC: 5% vs. ATV+r+TDF/FTC: 14%).
- No virologic data because of discontinuations due to adverse events (AEs) or death (DTG/ABC/3TC: 4% vs. ATV+r+TDF/FTC: 7%).
- Viral suppression in subgroups stratified by baseline HIV-1 RNA values
- HIV-1 RNA <100,000: DTG/ABC/3TC: 60% vs. ATV+r+TDF/FTC: 74%.
- HIV-1 RNA ≥100,000: DTG/ABC/3TC: 26% vs. ATV+r+TDF/FTC: 39%.

Among patients with confirmed HIV-1 RNA >100,000 c/mL at or after Week 24, none assigned to treatment with DTG/ABC/3TC developed INSTI or ABC/3TC resistance–associated mutations.

Factors that influenced the differences in resistance rates included:
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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.

Similar to overall safety profile for DTG from previous studies.

Conclusions
In treatment-naive women, DTG/ABC/3TC was superior to ATV+r+TDF/FTC at 48 weeks of treatment.

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No virologic data because of discontinuations due to adverse events (AEs) or death (DTG/ABC/3TC: 4% vs. ATV+r+TDF/FTC: 7%).

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.

Comparable rates of neurocognitive AEs between treatments.

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Conclusions
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Adjusted difference 10.5%, 95% CI: 3.1% to 17.8%, P=0.005

Â Reckless treatment emergence of INSTI or ABC/3TC resistance mutations

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Comparable rates of neurocognitive AEs between treatments.