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Safety and efficacy of doravirine as first-line therapy in adults with HIV-1: week 192 results from the open-label extensions of the DRIVE-FORWARD and DRIVE-AHEAD phase 3 trials

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Abstract

Background: In two phase 3 trials for first-line therapy in adults with HIV-1, doravirine showed non-inferior efficacy, a favourable safety profile, and a superior lipid profile to darunavir and efavirenz through to 48 and 96 weeks. Here we report 192-week results from both studies.

Methods: DRIVE-FORWARD and DRIVE-AHEAD are multicentre, double-blind, randomised, active comparator-controlled, phase 3 trials of first-line antiretroviral treatment in adults with HIV-1. Eligible participants (aged ≥ 18 years) were naive to antiretroviral therapy, had plasma HIV-1 RNA 1000 copies per mL or more at screening, had no known resistance to any of the trial drugs, and had creatinine clearance 50 mL per min or more. DRIVE-FORWARD was conducted at 125 sites in 15 countries and compared doravirine (100 mg) with ritonavir-boosted darunavir (ritonavir [100 mg] and darunavir [800 mg]), each administered orally once daily with two nucleoside or nucleotide reverse transcriptase inhibitors (tenofovir disoproxil fumarate [300 mg] and emtricitabine [200 mg] or abacavir sulfate [600 mg] and lamivudine [300 mg]). DRIVE-AHEAD was conducted at 126 sites in 23 countries and compared doravirine (100 mg), lamivudine (300 mg), and tenofovir disoproxil fumarate (300 mg) with that of efavirenz (600 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg), all administered orally once daily. DRIVE-FORWARD enrolment was between Dec 1, 2014, and June 1, 2020, and DRIVE-AHEAD enrolment was between June 10, 2015, and Aug 10, 2020. After the 96-week double-blind phase, eligible participants could enter an open-label extension and either continue doravirine or switch from comparator to doravirine for an additional 96 weeks. Efficacy (HIV-1 RNA < 50 copies per mL) and safety assessments (adverse events and changes in laboratory parameters) were pooled. The DRIVE-FORWARD and DRIVE-AHEAD trials were registered with ClinicalTrials.gov, [NCT02275780](#) and [NCT02403674](#).

Findings: Of 1494 participants treated in the double-blind phase (1261 [84%] male and 233 [16%] female), 550 continued doravirine and 502 switched to doravirine in the extension. Using the FDA snapshot approach, HIV-1 RNA less than 50 copies per mL was maintained in 457 (83%) of 550 participants who continued doravirine and 404 (80%) of 502 participants who switched to doravirine. Protocol-defined virological failure and development of resistance were low, occurring mainly before week 96. Two ($< 1\%$) of 550 participants who continued doravirine reported serious drug-related adverse events, and three (1%) who continued doravirine and one ($< 1\%$) of 502 who switched to doravirine discontinued due to drug-related adverse events. Participants continuing or switching to doravirine showed generally favourable lipid profiles, little weight gain, and small decreases in estimated glomerular filtration rates, with no discontinuations due to increased creatinine or renal adverse events.

Interpretation: Favourable efficacy and safety profiles for doravirine at week 96 were maintained through to week 192 in participants who continued or switched to doravirine, supporting use of doravirine for long-term first-line HIV-1 treatment and for virologically suppressed adults switching therapy.

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