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IMPACT OF BASELINE PROTEASE DRUG MUTATIONS ON VIROLOGICAL RESPONSE TO FOSAMPRENAVIR/RITONAVIR-BASED REGIMENS IN ANTIRETROVIRAL-EXPERIENCED PATIENTS (ZEPHIR STUDY)

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OBJECTIVE: To assess the impact of HIV-1 mutations on virological responses to fosamprenavir/ritonavir (FosAPV/r)-based regimens in experienced HIV patients.

METHODS: Antiretroviral-experienced subjects with virological failure (HIV-RNA > 1.7 log₁₀ copies/ml) were included in an observational cohort study and received a FosAPV/r (700 mg/100 mg twice daily)-based regimen. Sequencing of HIV-reverse-transcriptase and protease was performed at baseline. Virological success (VS) at month 3 was defined by HIV-RNA < 1.7 log₁₀ copies/ml. FosAPV/r resistance-related mutations (FosAPV/r-score) were defined according to the French ANRS genotype-interpretation guidelines, that is FosAPV/r resistance if number of mutations was > 6 among L10F/I/V, K20M/R, E35D, R41K, I54V, L63P, V82A/F/T/S, I84V or V32I+I47V or I50V.

RESULTS: FosAPV/r-containing regimen was initiated in 90 patients (M/F=68/22, median [25th–75th] age=45 [40–50] years). The median prior antiretroviral exposure was 9 [7–10] years with a median of 10 [5–16] previous lines of treatment. Eightyseven percent of patients were protease-inhibitor (PI)-experienced. At baseline, median CD4+ and HIV-1-RNA were 284 [150–387]/μl and 3.4 [3.5–4.9] log₁₀ copies/ml, respectively. Median number of PI-resistance mutations and FosAPV/r-score mutations were 8 [3–10] and 4 [2–5] (no I50V at baseline) respectively, and 5 [3–6] NRTI-related mutations. At M3, 24% of patients were considered VS. Median HIV-1-RNA decrease was -0.5 [-2.2;+0.2] log₁₀ copies/ml, CD4+ increase was +24 [-6;+84]/μl. When FosAPV/r-score was < 4 vs ≥ 4 mutations, HIV-1-RNA decrease was -1.7 [-3.1;-0.6] vs -0.07 [-0.4;+0.3]

\log_{10} copies/ml ($P=0.001$) and VS occurred in 47% vs 7% ($P=0.004$) of patients, respectively.

Failure was associated with the number of prior lines of treatment ($P=0.02$), baseline number of PI-resistance mutations ($P=0.01$), FosAPV/r-score ($P=0.006$) and NRTI-related mutations ($P=0.05$). Presence of following protease mutations at baseline were associated with failure: L10I ($P=0.001$), L33F ($P=0.05$), 54L/T/V ($P=0.009$), L63P ($P=0.05$), A71I/T/V/L ($P=0.02$), V82A/F/S/T ($P=0.05$) and L90M ($P=0.008$). Virological failure occurred in the three patients with V32I+I47V baseline PI mutations. The response was significantly reduced in patients with >4 mutations among the seven defined in our study: HIV-1-RNA decrease was -1.8 [-3.0 ; -0.6] vs $+0.07$ [-0.4 ; $+0.3$] \log_{10} copies/ml ($P=5.10^{-4}$) if <4 vs ≥ 4 mutations.

CONCLUSION: In highly experienced patients, FosAPV/r-score was predictive of virological response (<4 vs ≥ 4 mutations) at month 3. We found that L90M PI-mutation was associated with failure.

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31

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