Dose-dependent influence of didanosine on immune recovery in HIV-infected patients treated with tenofovir

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BACKGROUND: Antiretroviral therapy (ART) containing tenofovir disoproxil fumarate (TDF) and didanosine (ddI) has been associated with poor immune recovery despite virologic success. This effect might be related to ddI toxicity since ddI exposure is substantially increased by TDF. OBJECTIVE: To analyze whether immune recovery during ART with TDF and ddI is ddI-dose dependent.

DESIGN AND METHODS: A retrospective longitudinal analysis of immune recovery measured by the CD4 T-cell slope in 614 patients treated with ART containing TDF with or without ddI. Patients were stratified according to the tertiles of their weight-adjusted ddI dose: low dose (< 3.3 mg/kg), intermediate dose (3.3-4.1 mg/kg) and high dose (> 4.1 mg/kg). Cofactors modifying the degree of immune recovery after starting TDF-containing ART were identified by univariable and multivariable linear regression analyses.

RESULTS: CD4 T-cell slopes were comparable between patients treated with TDF and a weight-adjusted ddI-dose of < 4.1 mg/kg per day (n = 143) versus TDF-without-ddI (n = 393). In the multivariable model the slopes differed by -13 CD4 T cells/microl per year [95% confidence interval (CI), -42 to 17; P = 0.40]. In contrast, patients treated with TDF and a higher ddI dose (> 4.1 mg/kg per day, n = 78) experienced a significantly impaired immune recovery (-47 CD4 T cells/microl per year; 95% CI, -82 to -12; P = 0.009). The virologic response was comparable between the different treatment groups.

CONCLUSIONS: Immune recovery is impaired, when high doses of ddI (> 4.1 mg/kg) are given in combination with TDF. If the dose of ddI is adjusted to less than 4.1 mg/kg per day, immune recovery is similar to other TDF-containing ART regimen.