460 TDF/FTC FOR HIGH-RISK PATIENTS WITH COVID-19: THE PANCOVID RANDOMIZED CLINICAL TRIAL

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Background: Some in vitro, animal, and epidemiological data suggest that tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) might be an efficacious treatment for COVID-19

Methods: In a multicenter open-label, pragmatic, randomized trial in 25 hospitals in Spain we included participants with symptomatic SARS-CoV-2 detected by PCR or antigenic test, with a creatinine clearance > 60 mL/min, > 60 years or younger if they had at least 2 comorbidities (hypertension, obesity, diabetes, cirrhosis, chronic neurologic disease, active cancer, heart failure, coronary heart disease or COPD). Participants were randomized to receive or not TDF/FTC. Randomization was stratified by age group, symptoms duration (< or $\geq$ 5 days) and health care setting (hospitalized, long-term care facility, ambulatory). Primary outcome was 28 days mortality. Secondary outcomes were disease progression (increased O2 requirements, need for mechanical ventilation or increase in medical therapy: steroid dose, need for tocilizumab). At any moment during the trial participants with room air O2 saturation < 95% and $\geq$ 1 increased inflammatory biomarker could be randomized to dexamethasone (D) or dexamethasone plus baricitinib (DB)

Results: 355 participants included (TDF/FTC n=177, no TDF/FTC n=178), median age 67 years (IQR 62-73), male (64.5%), median days of symptoms 8 (IQR 5-10), 29% with < 5 days of symptoms, 96.9% hospitalized, 35.5% with 1 and 36.6 % with $\geq$ 2 comorbidities (62.8% hypertension, 9.3% diabetes, 1.7%

obesity), median room air SaO2 95% (IQR 94-96), 63% receiving O2 and 11.8% Remdesivir. 74% of participants were simultaneously randomized to D or DB. There were not statistically significant differences in endpoints in participants not treated vs.treated with TDF/FTC: mortality 2.2%/4.0%, disease progression 23.6%/22.0%, deferred randomization to D or DB 6.7%/6.2%, mechanical ventilation (invasive or noninvasive) 22.5%/20.3%, days since randomization until discharge (median [IQR]) 7 [5,14]/6 [4,12], discharge before 28 days 91.9%/89.7%. By Cox regression Hazard Ratio (95% CI) of 28-day mortality was 1.96 (0.55-7.01) for participants treated with TDF/FTC. Serious adverse events occurred in 6.18%/5.65% of participants not treated/treated with TDF/FTC. Adverse events leading to TDF/FTC discontinuation occurred in 2.26%.

Conclusion: In this clinical trial of high-risk patients with COVID-19 TDF/FTC did not improve disease outcomes. Overall mortality was unexpectedly low