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LETTER TO THE EDITOR

Response to 'The use of tenofovir in patients with COVID-19'

We thank Kow et al. [1] for their response to the findings of the RECEDE-C19 study on clinical outcomes between people living with and without HIV hospitalized with coronavirus disease 2019 (COVID-19) [2]. The authors suggest the inclusion of antiretroviral therapy (ART) in the multivariable model, particularly those who received tenofovir-based ART, to investigate the effectiveness of these medications in patients with COVID-19.

As only five (7.4%) people living with HIV not receiving ART were included, this study was not powered to compare the effect of ART on clinical outcomes in hospitalized patients. Tenofovir disoproxil fumarate (TDF) is associated with renal and bone density-related adverse effects, and UK national guidelines [3] recommend avoiding TDF in people with impaired renal function or osteoporosis. As a result, the population receiving TDF is biased, and its inclusion in the multivariable model risks multicollinearity with the comorbidities, frailty and age factors that were already included. The small sample size and lack of a suitable denominator for people living with HIV across all clinics receiving tenofovir-based ART were other limitations in evaluating the effectiveness of tenofovir in the prevention of severe COVID-19 hospitalisation outcomes. Therefore, we considered that inclusion of tenofovir-based ART in the multivariable model would be of limited value, and the antiretroviral data were presented descriptively to avoid overinterpretation in this paper.

As the authors have summarized, tenofovir has been hypothesized to be potentially effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, evidence to support the use of tenofovir-based strategies for the treatment or prevention of COVID-19 remains sparse. Evidence from two open-labelled randomized trials have provided mixed results. Participants randomized to TDF/emtricitabine following a recent diagnosis (<7 days) of non-severe COVID-19 showed a mean real-time polymerase chain reaction cycle threshold difference of 2.9 (95% confidence interval [CI] 0.1–5.2, $p = 0.044$) but no difference in time to symptom recovery, and the study was not powered to collect other clinical outcomes [4]. Although a larger pragmatic randomized trial of TDF/emtricitabine, rosuvastatin plus colchicine, or a combination of the four medications showed lower mortality in participants receiving all four medications (hazard ratio [HR] 0.53; 95% CI 0.29–0.96; $p = 0.038$), TDF/emtricitabine alone was not associated with a reduction in 28-day mortality in the TDF/emtricitabine arm compared with standard of care (HR 0.69; 95% CI 0.39–1.20; $p = 0.187$) [5]. Two ongoing randomized controlled trials investigating TDF/emtricitabine as treatment for COVID-19 are registered in the clinicaltrials.gov database at the time of writing (NCT04712357, NCT04890626).

Effective treatments for COVID-19 are available, but the search continues for effective, lower cost, alternative treatments and remains relevant, particularly for settings with limited resources and/or access to vaccines. However, we advise caution in the interpretation of the effectiveness of ART including tenofovir for the treatment of COVID-19 from retrospective cohorts because of the contribution of confounding overlapping factors that may not be possible to adequately adjust for. The findings of the ongoing suitably powered and blinded randomized controlled trials are anticipated to provide more robust answers as to whether tenofovir is effective in the treatment of COVID-19.

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AUTHOR CONTRIBUTIONS

MJL drafted the letter, AN, SF, RK, JF, CS reviewed and contributed to the final draft.

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