Review 1: "HIV infection and COVID-19 death: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform"

Norman Hearst¹

¹UCSF: University of California San Francisco, Family Medicine

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

This is a well done secondary analysis of large health system data sets to evaluate whether persons with HIV infection are at increased risk of death from COVID-19. The results are important and deserve to be published. I have some concerns about how the authors present and interpret their results.

The authors seem intent on exaggerating the strength and public health importance of their findings. They summarize their findings as showing a "markedly raised risk of COVID-19 death among persons with HIV." In fact, the crude risk ratio is 1.05 (2.34/2.22), a number that the authors don't even present. After adjustment for just age and sex, this goes up to 2.90. After adjusting for other available covariates, this goes down to 2.30 and to 1.93 for those with complete data.

Although this is a study of millions of people and almost 15,000 COVID-19 deaths, the results are entirely based on only 25 deaths among persons with HIV. Of these 25, 23 had other known risk factors for COVID mortality. The point estimate for risk of death for persons with HIV and no comorbidities was 1.02; there were only two such deaths. The authors gloss over this finding and don't even mention it in the text, saying instead that they lack statistical power to prove an interaction. But that is a sample size problem, and this is the best estimate of risk according to their data.

The authors suggest a need for targeted policies for persons with HIV, such as priority for a future vaccine. The correct conclusion from this study is that persons with HIV but without other comorbidities are at little or no additional risk compared to their peers without HIV. Those with HIV and other comorbidities do appear to be at increased risk, but it is not clear if and how this should alter policy. A hazard ratio of somewhere between 1.05 and 2.90, depending on how many factors one adjusts for, is

of scientific interest, but it is a relatively weak risk factor compared to others.

I particularly object to their figure 2. It presents smoothed out modeled data (instead of presenting the real data that they have), apparently in an attempt to create a false impression of strong rigorous data. In fact, it conveys no additional information beyond the hazard ratios that were already presented.