Review 2: "HIV infection and COVID-19 death: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform"

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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:

Bhaskaran and colleagues present the results of an analysis of routinely collected electronic primary care data linked to national death registrations to investigate the potential impact of HIV infection on mortality from coronavirus disease-19 (COVID-19). This is an important topic – reported associations between HIV and COVID-19 in the literature have been inconsistent, and there are hypothesized rationales for either an *increased* or a *decreased* risk of mortality in those with HIV. The authors' findings suggest a 2.3-fold increase in the hazard of mortality after adjustment for a range of potential confounders (age, sex, ethnicity, socio-economic status [as measured through an index of multiple deprivation], obesity, smoking and several key comorbidities), although the confidence interval around the estimate is relatively wide (1.55-3.41) reflecting the small number of deaths among people with HIV in the dataset (n=25). The results are, however, consistent with UK results from the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) Clinical Characterisation Protocol (CCP), which were published in pre-print format at a similar time¹ in which people with HIV hospitalised with COVID-19 had a 1.49-1.63-fold higher mortality risk after adjustment for a similar range of confounders.

Whilst linkage with national death registrations ensures a fairly complete picture of the mortality outcomes, the robustness of Bhaskaran's findings depends heavily on an accurate assessment of both the main exposure (HIV infection) as well as the confounders. In the present analysis, individuals were required to have at least 1 year of continuous GP registration prior to 1st February 2020. Whilst people living with HIV in the UK are encouraged to register with a GP, a substantial minority do not, many may not have a fixed place of abode, and even where people do register with a GP, they may choose not to disclose their HIV status. HIV remains a highly stigmatized condition and there is likely to be some systematic bias in terms of who does and doesn't register with a GP and/or disclose their status. Whilst the authors correctly argue that the number of such people who are incorrectly assumed to be HIV-negative in the analysis is likely to be tiny as a proportion of this group, and speculate that those with higher underlying mortality risk may be less likely to register with a GP, biasing their

findings, if anything, to the null, it is equally possible that those with the most serious non-HIV health problems may be the people who are most strongly encouraged to register and disclose to their GP, potentially introducing bias in the other direction.

Comorbidities may also be selectively reported – because of the potential for some antiretroviral drugs to lead to serious adverse events, blood pressure, renal function and diabetes are routinely monitored in people with HIV within the HIV clinic – indeed, monitoring may be *more* regular and people with HIV with comorbidities may be diagnosed *sooner* than in the general population – but results may not always be shared with an individual's GP, particularly if this could then result in disclosure of status. From a statistical modelling perspective, the association of diagnosed diabetes, say, with mortality might be different in those with HIV compared to other people.

As discussed, the authors were unable to account for COVID-19 infection in their analyses, as testing was not routinely undertaken over the study period. An increased risk of COVID-19 mortality may therefore indicate either a higher risk of initial infection but with similar associated mortality or a higher risk of mortality once infected (or a combination of these). People with HIV are likely to be disproportionately drawn from occupations at greater risk of COVID-19 infection (e.g. those working in the hospitality, travel and healthcare industries) and it may be this increased risk of exposure/infection to COVID-19 rather than a poorer mortality outcome *per se*, that is truly to blame.

Unfortunately, as the authors recognise, the available data did not permit any assessment of associations with immunosuppression, exposure to viraemia and/or antiretroviral therapy, all of which may have helped to clarify whether the association seen with HIV was likely to be a causal one. Finally, many people living with HIV belong to under-served populations with high levels of socioeconomic deprivation – although the authors adjusted for an index of multiple deprivation to attempt to remove this confounding, this is unlikely to fully remove the potential confounding with socio-economic status that may be present. In this regard, the stronger association with HIV infection among those of black ethnicity is intriguing, although the pooling of a range of different ethnic groups within this broad category, each with a potentially different risk for infection and mortality, limits the interpretation of this finding.

In summary, this paper is to be welcomed as it adds to our knowledge about the potential association between HIV infection and COVID-19 outcomes. However, given the small number of deaths among people with HIV in the dataset, the results should be interpreted with caution until clearer evidence is available to support a causal association. In the meantime, the results should provide further motivation to ensure that those at risk of HIV infection are tested regularly, and started on antiretroviral therapy rapidly if diagnosed.

References

1. Geretti AM, Stockdale A, Kelly S, Cevik M, Collins S, Waters L, Villa G, Docherty AB, Harrison EM, Turtle L, Openshaw PJM, Baillie K, Sabin C, Semple MG. Outcomes of COVID-19 related hospitalisation among people with HIV in the ISARIC WHO Clinical Characterisation Protocol UK Protocol: prospective observational study. <https://www.medrxiv.org/content/10.1101/2020.08.07.20170449v1>