



COVID-19 death in people with HIV: interpret cautiously

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Since the start of the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we have sought to understand the predictors of severe COVID-19 and mortality. Data show that age and chronic comorbidities are major risk factors, but what about immunosuppression? Patients with malignant disease and recipients of solid-organ transplants might be at increased risk, but evidence is less clear for people with other types of immunocompromise, including HIV.¹ Are people with HIV, even those with well controlled viraemia and immune reconstitution, at risk of more severe COVID-19 and death or is the risk associated with overlapping demographic and comorbidity characteristics?

In *The Lancet HIV*, Krishnan Bhaskaran and colleagues² have analysed COVID-19 deaths in people with HIV from OpenSAFELY, a UK primary care database of 17·3 million adults. Mortality among the 27 480 people with HIV (0·16% of the study population) was higher than the general population with an adjusted hazard ratio of 2·59 (95% CI 1·74–3·84; $p < 0·0001$). Unfortunately, due to lack of SARS-CoV-2 testing in the UK at the time of the study, there is no denominator of people with infection or people with symptoms but no confirmatory test. London, which has almost half of the UK's HIV cases, was under-represented, and missing data for ethnicity was generated by multiple imputations.

An analysis of people hospitalised with COVID-19 in the UK (ISARIC)³ also found a higher risk of mortality among people with HIV, albeit to a lesser degree, with an adjusted hazard ratio of 1·69 (95% CI 1·15–2·48; $p = 0·008$). Neither study was able to fully adjust for confounders, and Bhaskaran and colleagues excluded people with missing age, sex, or index of multiple deprivation.

The “particularly marked” HIV association with COVID-19 death in people of Black ethnicity (HR 4·31 [95% CI 4·2–7·65] vs 1·84 [1·03–3·26] in non-Black individuals) is in discord with the Public Health England data, which suggest a much smaller excess mortality among Black ethnic groups.⁴ Some key occupations seem to be at higher risk of COVID-19 in the UK⁵ and have a high proportion of workers from Black and minority ethnic groups,⁶ but Bhaskaran and colleagues could not adjust for occupation. This could account for some of the apparent mortality risk

associated with ethnicity and is a potential confounder for the association between mortality and HIV.

People with HIV and no comorbidities might be less likely to be registered or to have shared their HIV status with their general practitioner, meaning those who are included in this analysis are more likely to have comorbidities and, thus, already at greater risk of worse COVID-19 outcomes. The role of comorbidities is further highlighted by this study's finding that there was no increased risk of COVID-19 death among people with HIV but no additional comorbidities, a crucial result in our view. The attenuation of effect when restricting the analysis with known, as opposed to imputed, body-mass index and smoking data shows that people with HIV might disproportionately have negative prognostic features.

Additionally, there is uncertainty as to the role of severe immunosuppression or uncontrolled viraemia in the risk for severe COVID-19 and death. A study from the Western Cape, South Africa,⁷ found an association, but data were not complete, because many participants had no recent viral load or CD4 count. Similar to ISARIC,³ the analysis of OpenSAFELY could not adjust for HIV treatment or surrogate markers of HIV control, which is a major limitation.

Although the authors claim that research is hampered by policy guidance that restricts the flow of HIV data, we are not aware of any policy guidance that cautions against sharing HIV-associated information in primary care. On the contrary, there is referenced guidance that encourages data sharing.⁸

Understanding who is at high risk of worse COVID-19 outcomes, and why, is essential to guiding advice and prevention efforts. Bhaskaran and colleagues have brought important findings into the public domain about the risk of death from COVID-19 in people with HIV and are frank about the strengths and weaknesses of their study. Nevertheless, they draw a strong conclusion on risk, stating that HIV was associated with increased risk of COVID-19 death. This statement might overshadow their other findings of a low absolute mortality of less than 0·1% and that 23 (92%) of 25 people with HIV who died had comorbidities and the remaining two (8%) were not of increased risk of death. An interpretation of this study

that might better serve people living with HIV in the UK and the clinicians that treat them is that their findings are important, but their conclusion should be taken with caution until we have more specific controlled data to assess the effects of HIV on COVID-19 outcomes.

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Lessons from dolutegravir and neural tube defects



The relatively uncommon neural tube defects (NTDs) are among the most severe birth defects that affect an estimated 300 000 births annually.¹ Although the causes of NTDs are multifactorial and difficult to study, folate supplementation is well established in their prevention. In this context, the 2018 announcement that preconception use of dolutegravir was associated with four NTDs in a population-based surveillance study in Botswana generated immediate and massive concern.² Dolutegravir was at that time poised to become the preferred first-line antiretroviral agent throughout international guidelines; the announcement sent shockwaves through the HIV world, as regulators, scientists, policy makers and people living with HIV sought to grapple with this possible association.³

In response, scientists and policy makers in Brazil launched a retrospective chart review of all women with pregnancies and possible dolutegravir exposure included in the national antiretroviral therapy (ART) database, reported by Gerson Peirera and colleagues in this issue of *Lancet HIV*.⁴ The results found no NTDs during the study period in women conceiving on either dolutegravir or efavirenz as a comparator; however two NTDs were reported post-hoc in women conceiving on dolutegravir, bringing the estimated NTD prevalence with dolutegravir exposure to a level slightly higher

than the NTD occurrence in the Brazilian general population. The study is impressive in its scope but not without limitations, particularly as a retrospective review with a relatively small sample and limited statistical power to detect associations between NTD and dolutegravir.

Nonetheless, Peirera and colleagues' findings help advance our insights into whether and how dolutegravir might increase the risk of NTDs, and two trends seem increasingly evident from the literature on this question. First, in global comparisons, countries with routine folate fortification have low levels of NTDs, thus any association with dolutegravir would be extremely difficult to detect. For example, the findings from Brazil (where maize and wheat flours are fortified with folate by law) parallel those from other settings with fortification programs.^{5,6} Hence, detecting an association might be difficult if dolutegravir does increase NTD risk through a mechanism related to folate deficiency, or simply because the rarity of NTDs with folic acid food fortification makes associations impossible to discern.

Second, any association between dolutegravir and NTDs is small in absolute terms and highly likely to be outweighed by the benefits of dolutegravir as an agent to treat HIV infection in women. Further data