

COVID-19 MORTALITY AMONG PEOPLE WITH DIAGNOSED HIV COMPARED TO THOSE WITHOUT DURING THE FIRST WAVE OF THE COVID-19 PANDEMIC IN ENGLAND

Short title: COVID-19 mortality among people with HIV

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ABSTRACT

Objectives: We describe COVID-19 mortality among people with and without HIV during the first wave of the pandemic in England.

Methods: National surveillance data on adults (aged ≥ 15) with diagnosed HIV resident in England were linked to national COVID-19 mortality surveillance data (02/03/2020-16/06/2020); HIV clinicians verified linked cases and provided information on the circumstances of death. We present COVID-19 mortality rates by HIV status, using negative binomial regression to assess the association between HIV and mortality, adjusting for gender, age and ethnicity.

Results: Overall, 99 people with HIV, including 61 of black ethnicity, died of/with COVID-19 (107/100,000) compared to 49,483 people without HIV (109/100,000). Compared to people without HIV, higher COVID-19 mortality rates were observed in people with HIV of black (188 vs. 122/100,000) and Asian (131 vs. 77.0/100,000) ethnicity, and in both younger (15-59 years: 58.3 vs. 10.2/100,000) and older (≥ 60 years: 434 vs. 355/100,000) people. After adjustment for demographic factors, people with HIV had a higher COVID-19 mortality risk than those without (2.18; 95%CI: 1.76-2.70). Most people with HIV who died of/with COVID-19 had suppressed HIV viraemia (91%) and at least one co-morbidity reported to be associated with poor COVID-19 outcomes (87%).

Conclusions: In the first wave of the pandemic in England, COVID-19 mortality among people with HIV was low, but was higher than in those without HIV, after controlling for demographic factors. This supports the strategy of prioritising COVID-19 vaccination for people with HIV and strongly encouraging its uptake, especially in those of black and Asian ethnicity.

INTRODUCTION

Reliable ascertainment and description of mortality is critical to inform the public health response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which can lead to coronavirus disease (COVID-19). Examining the disparities in outcomes between population sub-groups provides critical insight into which are most severely affected, enabling the development of specific health policies to protect these populations.

In England, an estimated 96,200 people live with HIV, with 6% unaware of their infection.⁽¹⁾ Of those diagnosed, 98% receive antiretroviral treatment (ART) and of those on treatment, 97% are virally suppressed; this is equivalent to at least 89% of all people living with HIV in England having an undetectable viral load.⁽¹⁾ While ART is effective in restoring immunity and uptake is high,⁽²⁾ persistent immune dysfunction and chronic inflammation may put people with HIV at increased risk of COVID-19 mortality due to a reduced ability to mount a protective immune response. Additionally, in England, people with HIV are more likely to be male and belong to communities known to experience socioeconomic deprivation, both of which are predictors of adverse COVID-19 outcomes.^(3, 4) Evidence on the risk of death from COVID-19 among people with HIV compared to the general population is mixed, with some studies suggesting higher mortality rates ⁽⁵⁻⁸⁾ but others reporting little difference in mortality.⁽⁹⁻¹¹⁾

We use comprehensive national surveillance data to provide an epidemiological description of COVID-19 mortality among all people with diagnosed HIV during the first wave of the COVID-19 pandemic in England and compare the mortality burden to people without HIV.

METHODS

Data sources

People with HIV

As part of the national HIV surveillance programme, clinical and epidemiological information on all people accessing HIV care in England is submitted to the HIV and AIDS Reporting System (HARS) at Public Health England (PHE) by National Health Service (NHS) specialist outpatient clinics.⁽¹²⁾ Individual follow-up begins at diagnosis; data collected for each subsequent attendance for HIV outpatient care include: CD4 count (where indicated), HIV treatment status, HIV viral load and the presence of AIDS-defining illnesses.

Information on deaths among people with HIV (date and cause of death) are reported through routine surveillance, as well as through matching to mortality data from the Office for National Statistics (ONS). In 2019, PHE introduced enhanced surveillance of deaths among people

with HIV (Annual National HIV Mortality Review) in collaboration with the British HIV Association (BHIVA).(13) Briefly, HIV clinicians complete an online modified Causes of Death in HIV (14) reporting form for all deaths among their patients, which captures information on HIV clinical profile, co-morbidities, lifestyle risk factors, causes of death and end-of-life care. Data are usually submitted annually and retrospectively. However, to better understand the impact of COVID-19 on people with HIV, clinicians were contacted through the BHIVA network and asked to submit a mortality review form following each death of/with COVID-19 in a person with HIV.

General population

In England, COVID-19 deaths in the general population are reported to PHE daily through four sources: a) the COVID-19 Patient Notification System (hospital deaths) (15); b) local PHE Health Protection Teams (deaths in non-hospital settings); c) NHS Demographic Batch Service matching of all laboratory confirmed COVID-19 cases against records of registered deaths; and d) ONS death registration records. Data from each source are merged and de-duplicated, creating a single dataset (COVID-19 Specific Mortality Surveillance System (COSMOSS)). Data are matched to ONS death registrations using NHS number (16) to ascertain cause and place of death, and to Hospital Episode Statistics to identify ethnicity, and linkage to area-level data on socioeconomic status (index of multiple deprivation (IMD)).(17) In England, COVID-19 was first detected on 30th January 2020, with the first death of/with COVID-19 occurring on 2nd March 2020.

Data linkage

The general population COVID-19 mortality dataset (data to 16th June 2020) was linked to the national HIV surveillance dataset using a combination of pseudo-anonymised identifiers (Soundex (scrambled surname),(18) first initial, date of birth, gender and lower super output area of residence) (PHE Caldicott approval: NISCRP552020). Two epidemiologists reviewed all matches independently, with disparities reviewed by an HIV clinician and consensus agreed. For matches deemed to be definite (exact matches for all information) or probable (matches for most information), clinicians were contacted by PHE and asked to confirm that the HIV patient had died and to submit the mortality review form (Supplementary Figure 1). Where clinical information collected through the mortality review form conflicted with that collected in HARS (e.g. ART start date), the clinician reported data were prioritised. For the five people with no mortality review form completed, HARS clinical profile data were used, where available.

Definition of COVID-19 mortality

People were considered to have died of/with COVID-19 if their death occurred within 60 days of a positive COVID-19 test, with COVID-19 included on the ONS death registration form (death certificate) or if COVID-19 was reported as a cause of death by the reporting clinician.

Analyses

We present a descriptive analysis of adults (aged ≥ 15 years) with and without HIV resident in England who died of/with COVID-19 between 2nd March and 16th June 2020 (3.5 months). There were no deaths among children aged < 15 with HIV over this time period.

Crude mortality rates were calculated as the number of COVID-19 deaths per 100,000 population for those with and without HIV, comparing those aged 15-59 with those aged ≥ 60 . The number of adults living with diagnosed HIV in England at the end of 2019 ($n=92,643$) was estimated as the number of people who accessed HIV outpatient care in 2019 ($n=88,341$), plus (i) people last seen for HIV outpatient care in 2018 and not known to have died by the end of 2019 ($n=3,580$) and (ii) those newly diagnosed with HIV in 2018 and 2019 but not yet seen for outpatient care ($n=722$). The number of people without HIV was calculated by subtracting the number of people with HIV from the number of people in the general population (ONS).(19) Latest available mid-year ONS population estimates were used: 2019 for IMD and region of residence and 2017 for ethnicity. Data were available by gender, age at death (five-year age-bands) and ethnicity, region or IMD.

Multivariable negative binomial regression was used to assess the association between HIV and death of/with COVID-19, adjusting firstly for age at death and subsequently for gender, age at death and ethnicity. Interaction terms were added to assess effect modification by age and ethnicity. Separate models were built to describe associations between mortality and region of residence and IMD, adjusting for gender, age at death and HIV status.

We also describe the clinical profile of people with HIV who died of/with COVID-19 overall and by gender, age and ethnicity. Co-morbidities reported to increase the risk of COVID-19 death include: cardiovascular disease (CVD) (including hypertension), diabetes mellitus, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obesity and dementia/cognitive impairment.(20) Detailed information on co-morbidities was available for those people with a completed mortality review form ($n=94$); for the remainder, information on co-morbidities was taken from the death certificate. Viral suppression was defined as a viral load of < 200 copies/mL. HIV viral load and CD4 count measurements were considered to be "at death" if within a year of death.

All analyses were carried out using Stata v15.0 (Stata Corp, USA).

RESULTS

Mortality among people with and without HIV

As of 16th June 2020, there were 99 COVID-19 deaths reported among the 92,643 adults with diagnosed HIV in England, equivalent to a crude mortality rate of 107/100,000 population (Table 1). In comparison, there were 49,483 COVID-19 deaths reported among the 45,565,024 people without HIV over the same period, equivalent to a crude rate of 109/100,000.

Overall, the median age of death among people with HIV who died of/with COVID-19 was 60 years [interquartile range (IQR): 51-72], with 53% (52/99) aged ≥ 60 . By comparison, median age of death among people without HIV who died with/of COVID-19 was 83 years [IQR: 74-89], with 93% (46,195/49,582) aged ≥ 60 . Sixty-nine percent (n=68) of all COVID-19 deaths in people with HIV were among men compared to 55% (n=27,204) of those among people without HIV (Table 1). These differences largely reflect variation in the structure of the populations, whereby 13% (11,974/92,643) of all people with HIV were aged ≥ 60 and 69% (n=63,585) were men compared to 29% (13,016,372/45,565,024) and 49% (n=22,539,107) of those without HIV, respectively. Supplementary Figure 2 shows the age and sex structure of both populations compared to the age and sex structure of those who died of/with COVID-19 and of any cause.

Higher crude mortality rates were observed among people aged ≥ 60 compared to younger individuals (434 vs. 58.3/100,000 among people with HIV vs. 355 vs. 10.1/100,000 among those without) (Table 1). Crude mortality rates among people with HIV of black and Asian ethnicity were higher compared to those among people of equivalent ethnicity without HIV, and lower in the most deprived residential areas.

Risk factors for dying of/with COVID-19

After adjustment, the risk of COVID-19 death was 2.18 (95% confidence interval (CI): 1.76-2.70) times higher in people with HIV compared to those without (Table 2). Regardless of HIV status, risk of death increased with increasing age (adjusted risk ratio (aRR) per increasing five-year age-band: 1.79; 1.77-1.81) and was higher in those of black (3.44; 3.06-3.87), Asian (2.24; 2.00-2.52) and other/mixed (3.23; 2.86-3.65) ethnicity, compared to those of white ethnicity. Women were less likely to die compared to men (0.55; 0.51-0.60). There was no statistical evidence of interaction between HIV status and age or ethnicity. Separate models

describing the association between region of residence and IMD on mortality can be found in Supplementary Table 1.

Clinical characteristics of people with HIV who died of/with COVID-19

Table 3 shows the demographic and clinical characteristics of the 99 people with HIV who died of/with COVID-19; comparable data from the 96,243 people living with diagnosed HIV can be found in Supplementary Table 2. Eighty percent (n=79) of people had a positive COVID-19 test prior to death; of whom 99% (n=78) died within a month (28 days) of their positive test. This compares to 77% (n=38,056) and 72% (n=35,481) for deaths among those without HIV, respectively. Most people with HIV died in hospital (85% (84/99) vs. 64% (29,544/46,176) among those without HIV), whilst fewer died in a nursing home (9% (n=9) vs. 30% (n=13,664)).

The median time between HIV diagnosis and COVID-19-related death was 15 years [IQR: 10-19]; three people died within three months of their HIV diagnosis and five within one year (Table 3). Access to outpatient specialist HIV care was high, with 95% (n=94) attending at least once since their HIV diagnosis. Among those who accessed HIV care, 94% (n=88) were last seen between 2018-2020, 5% (n=5) were last seen between 2016-2017 and one person was last seen in 2002. ART coverage was 99% (n=98) overall, with 95% (90/95) documented as receiving ART at death or in the preceding year (median time since ART initiation: 14 years [IQR: 9-18]). Of the 69 people with a CD4 count reported in the year prior to death, 1.4% (n=1), 16% (n=11) and 42% (n=29) had a CD4 count <50, <200 and <350 cells/mm³, respectively. Of those with a CD4 <350 cells/mm³, all were aged ≥40, 83% (n=24) were ≥50 and 62% (n=18) were ≥60. Of the 92 people with any CD4 count available, 14% (n=13), 53% (n=49) and 86% (n=79) had a CD4 nadir <50, <200 and <350 cells/mm³, respectively. Overall, 91% (83/91) of people were virally suppressed. There were no significant differences by gender or ethnicity with regard to HIV clinical markers and ART uptake.

Ninety percent (89/99) of people with HIV who died had at least one reported co-morbidity; 87% (n=82) had at least one documented co-morbidity known to be associated with higher risk of poor COVID-19 outcomes (65% at least two).⁽²⁰⁾ The prevalence of CVD (including hypertension) was 69% (57/83), diabetes mellitus 48% (40/83), CKD 41% (32/78), COPD 10% (8/77) and dementia/cognitive impairment 17% (9/51). Among those with height and weight available (n=70), 49% (n=34) had a body mass index (BMI) >30 kg/m² indicating obesity, a further 26% (n=18) were overweight (BMI 25-30 kg/m²). While diabetes mellitus was more common in men, obesity and dementia/cognitive impairment were more common in women.

CVD, diabetes mellitus, CKD and obesity were more common among people of black ethnicity compared to those of white ethnicity (Table 3).

Table 4 presents the burden of co-morbidities known to be associated with poor COVID-19 outcomes among people with diagnosed HIV who died of/with COVID-19 by gender, age at death and ethnicity. Of the 47 people who died aged <60, 74% had at least one documented co-morbidity associated with poor COVID-19 outcomes; 55% had ≥ 2 co-morbidities and 19% one. This compares to 96% among the 25 people who died age 60-69 (80% ≥ 2 and 16% one) and 85% among the 27 people who died aged ≥ 70 (70% ≥ 2 and 15% one). Among the 12 people aged <60 with no documented co-morbidities, three were not virally suppressed within a year of death. The prevalence of co-morbidities was high for both men and women, and across ethnicities.

DISCUSSION

We describe COVID-19 mortality among people with diagnosed HIV during the first wave of the pandemic in England. The overall mortality rate due to COVID-19 among people with HIV was low, at approximately 0.1%. Whilst this low death rate is reassuring, it is possible that a relatively small proportion of the population (particularly those with HIV) was exposed to the virus during the first three and a half months of the pandemic.(21) United Kingdom (UK) government advice to “stay at home” and “socially distance” was released in March and specific groups of the population, identified as clinically extremely vulnerable, were asked to “shield” by staying home for three months and avoid all non-household contacts.(22) People with HIV were initially included in the government’s shielding advice; however this was subsequently changed in line with advice issued by BHIVA in late April recommending that only individuals with CD4 counts < 50 cells/mm³, a recent AIDS diagnosis and/or multiple co-morbidities should “shield”.(23) Consequently, the risk of death among those most clinically vulnerable with HIV may be underestimated in our study.

While mortality was low overall, COVID-19 mortality among people with HIV in England was more than double that of people without HIV after differences in the population age structure were taken into consideration. This is consistent with other published studies.(5-8) Primary care data from the OpenSAFELY platform showed people living with HIV had higher risk of COVID-19 death (hazard ratio 2.90; 95% CI: 1.96-4.30) than those without HIV after adjusting for age and sex.(5) The ISARIC study of a subset of patients hospitalised with COVID-19 in the UK found a 63% increased risk of mortality among those with HIV compared to HIV-negative individuals after adjusting for sex, ethnicity, age, baseline date, co-morbidities and disease severity at presentation.(8) Similar to these other studies, our findings should be

interpreted with caution.(24) Unlike OpenSAFELY and ISARIC, which were restricted to analysis of specific subgroups (e.g. people registered at general practice or in hospital), we utilised comprehensive national HIV surveillance data including all people living with diagnosed HIV and had access to data on all people who died of/with COVID-19 in the general population. Nevertheless, we were limited by a lack of available data on co-morbidities for those without HIV to adjust our analyses; this is particularly important as people with HIV are known to have higher levels of co-morbidities than the general population.(3, 25)

Our analyses show that among people with HIV who died of/with COVID-19, the large majority (88%) were either aged ≥ 60 (53%) or had at least one documented co-morbidity known to be a risk factor for COVID-19 death (87%). There were very few deaths among people with diagnosed HIV aged < 60 without a documented co-morbidity. The co-morbidities commonly reported among people with HIV who died of/with COVID-19 in England included: CVD (69%), obesity (49%), diabetes mellitus (48%), CKD (41%) and hypertension (39%). These rates are higher than those reported among all people living with diagnosed HIV (Supplementary Table 2) (3, 25), higher than those documented among people with HIV who died pre-COVID-19 and higher than the general population as a whole.(26, 27) These findings are consistent with the literature and highlight the importance of ensuring optimal care of co-morbidities alongside HIV care.(28-31)

Over two-thirds of the people with HIV who died of/with COVID-19 were from black, Asian or ethnic minority populations; only 35% of people living with diagnosed HIV in England are of these ethnicities. We observed a higher risk of COVID-19 mortality in people of an ethnic minority with HIV, compared to those without, remained after adjustment for age and gender. Higher COVID-19 diagnosis rates have been observed amongst people of black ethnic groups in England compared to other ethnic groups, as well as higher mortality rates.(20, 32) This disparity may be partially explained by socioeconomic factors, co-morbidities and occupational exposure to COVID-19, with a relatively high proportion of people of black ethnicity employed in health and social care roles.(31, 33) Our ability to characterise the relationship between ethnicity and mortality was limited by a lack of data on underlying COVID-19 testing and diagnosis rates and an inability to adjust for occupational exposure. Furthermore, despite finding that an increased risk of death was seen among those in London and those living in areas of higher deprivation (Supplementary Table 1), we could not adjust for ethnicity, IMD and region of residence in the same model, due to a lack of available general population data.

This is the first population-level national study of COVID-19 mortality among people with HIV in the UK, capturing all deaths during the first wave. We linked the national cohort of people diagnosed with HIV to national COVID-19 death data, including people not linked to HIV care

and those lost to clinical follow up, groups that may be particularly vulnerable to COVID-19. Additional clinical data were collected on those who died to ascertain the treatment and immunosuppression levels, as well as better understand co-morbidities and cause of death. PHE reports to date have focussed on people who have died within 28 days and 60 days of a positive COVID-19 test or linked to a death registration certificate.(34) We also included deaths where COVID-19 was entered on the death certificate of individuals that were not linkable to a positive COVID-19 test; most of these deaths occurred at the start of the pandemic where testing was not widely available.

However, our study has several additional limitations. Mortality rates among people with HIV presented here exclude deaths among the 5,900 people estimated to have undiagnosed infection in England; however, this is a relatively low proportion (6%) among all people with HIV in the country.(1) We are not yet able to calculate excess mortality as surveillance of deaths among people with HIV in 2020 is still underway. We cannot calculate case fatality or account for any differences in exposure to COVID-19 comparing HIV to those without.(35) Despite HIV surveillance being comprehensive and of high quality, there were some missing data which may have affected our findings. Notably, CD4 counts in the year preceding death were only available for 70% of people who died of/with COVID-19; this reflects current UK monitoring guidelines which do not require annual CD4 testing for those with well-controlled HIV.(36) COVID-19 is known to dysregulate the immune system and lower CD4 cell counts;(37) in our analysis we included at least 17 people with a CD4 measured within two weeks of or after their COVID-19 diagnosis. However, this should have minimal impact as the distribution of these counts was equitable across CD4 strata (Table 3). Where clinical information collected through the mortality review form conflicted with that collected in HARS, clinician reported data were prioritised. However, clinicians may not have been aware of previous clinical history if patients died in hospitals where they did not receive HIV outpatient care. Our analysis includes data until June 2020. In England, deaths remained at low sustained levels through the summer months of 2020 before rising again in late September.(38) Over 65,000 additional COVID-19 deaths in the general population were reported to PHE as of 15th February 2021. However, the age, sex and ethnic profile of people who died has not changed substantially over this period and thus we believe the results presented remain representative and relevant across the pre-vaccination era.(38)

Conclusions

In England, where 94% of people with HIV are diagnosed and on suppressive ART, the rate of COVID-19 death in the first wave of the COVID-19 pandemic among people with HIV was low but higher than among those without HIV after controlling for age. Few people with HIV

who died of/with COVID-19 were aged <60 and did not have a documented co-morbidity associated with worse outcomes. Most people with HIV who died of/with COVID-19 had risk factors similar to those identified in the general population; male, older age, non-white ethnicity, co-morbid conditions and residential deprivation are important risk factors for COVID-19 mortality regardless of HIV status. People with HIV in the UK are currently being prioritised for COVID-19 vaccination.(39) Our findings highlight that uptake of vaccination in people with HIV of all ages should be strongly encouraged.

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CONTRIBUTION STATEMENT

VD, DB, AB, AS and SEC conceived this research study. AB extracted data on COVID-19 deaths in the general population. JK and SN extracted the HIV data and JK performed the data linkage. SEC and AB reviewed all matches; AS reviewed all discrepancies. SEC and AS coordinated mortality review form follow-up. FP, RM and SEC reviewed all causes of death. SEC and AB carried out the majority of analyses and drafted and finalised the paper; SN carried out the descriptive analysis of people with HIV. CS and PK input into the research methods and provided statistical support. MK, DB, CS, RM, FP, RH, SC, LW, DA, DC, VD and AS provided important intellectual content to the discussion and conclusions. All authors critically appraised the manuscript and approved its submission.

CONFLICT OF INTEREST STATEMENT

SEC, SN, MK, AS, PK, JK and SC have no conflicts of interest to declare. DB reports grants from ViiV Healthcare and Gilead Sciences outside the submitted work. LW reports speaker/advisory fees from Gilead Sciences, Viiv Healthcare, Merck Sharp & Dohme (MSD), Janssen-Cilag, Cipla, Mylan and Theratechnologies and funding for clinical trials from Gilead Sciences and Janssen-Cilag outside the submitted work. FP reports grants and personal fees from Gilead Sciences, Viiv Healthcare, Janssen-Cilag and MSD outside the submitted work. RM reports personal fees from Gilead Sciences for conference attendance and non-promotional talks outside the submitted work. CS reports funding from Gilead Sciences and Janssen-Cilag for participation in advisory panels and for the preparation of educational

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