Does HIV impact susceptibility to COVID-19 (SARS-CoV-2) infection and pathology? A review of the current literature

Running Title: HIV and susceptibility to COVID-19

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Abstract

Objectives

Giving appropriate guidance to people living with HIV (PLWH) during the COVID-19 pandemic depends on having adequate data to inform recommendations. Several studies have now been published which inform such advice. The objective of this study was to collate this information and review the implications of emerging data.

Methods

We performed a systematic literature search of studies relating COVID-19 to HIV infection from the beginning of the pandemic to end of November 2020. We included both published and pre-published manuscripts and analysed papers according to whether they primarily informed risk of infection or risk of adverse outcome.

Results

68 papers (including 11 pre-prints) were identified. In terms of risk of infection, it appears that PLWH are no more or less likely to become infected with COVID-19. In terms of outcomes and mortality, most early small studies did not demonstrate an increase in mortality compared to background populations. However, several larger, more recent studies from South Africa, New York and two from the UK demonstrate higher mortality among PLWH when results are adjusted for other risk factors, giving relative risks of 2.1, 1.2, 1.7 and 2.3 respectively. Apparently conflicting results may arise from differences between studies in their power to account for cofactors and confounding variables. HIV-positive non-survivors tend to be younger and have fewer comorbidities than their HIV-negative counterparts; mortality may be higher in PLWH with low CD4 counts.

Conclusions

Although the literature appears conflicting, large studies which account for covariates strongly suggest that HIV infection increases COVID-19 mortality.
Introduction.

The ongoing coronavirus disease-2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has emerged as a major global health threat. Two striking features of this disease are, firstly, its often high but variable infectivity and, secondly, the striking range in its clinical consequences. In terms of infectivity, even remote and pre-symptomatic contact may result in infection, (1) whereas highly-exposed household contacts may remain uninfected. Similarly, pathology is highly variable; some infected individuals remain asymptomatic, whereas others develop life-threatening multi-organ failure. Given that the virus is relatively stable, and that this spectrum seems largely independent of the immediate environment, such variability must derive predominantly from host factors. Several host susceptibility factors were recognised early in the pandemic and our understanding of risk factors for serious pathology has evolved rapidly over the last six months. We now recognise that the disease disproportionally affects older people, those with obesity and those with underlying health conditions such as diabetes, renal and cardiovascular disease. (2) This information has allowed the identification of highly-susceptible individuals and driven national and regional guidelines for “shielding” specific groups.

Whether HIV-infected individuals also fall into this “susceptible” group remains a matter for debate. This is a non-trivial issue as some people living with HIV (PLWH) have seen their freedoms curtailed “for their own good”, but guidance has varied widely between countries. Are such restrictions necessary or helpful? Early in the pandemic, in the absence of epidemiological evidence, advice followed theoretical reasoning: ‘PLWH have impaired immunity so are likely to be more susceptible to COVID-19’. However, in situations where most PLWH are taking antiretroviral treatment (ART) - which we know repletes lymphocyte subsets, restores clinical immunocompetence and endues normal life expectancy – a counter-argument might be made: ‘PWHL on effective treatment may be considered no more “susceptible” than the general population’. Some guidelines, distinguished between those on effective treatment and those not; this was the approach taken by BHIVA who advised a more cautious approach for those with CD4 counts <50 cells/µl. (3) Basing advice on theoretical considerations is however fraught with
difficulty in this setting. Firstly, PLWH are very heterogenous; secondly, even those on long-term ART still have a degree of immune dysfunction; thirdly, it might be argued that since most COVID-19 pathology is immunopathology, HIV infection may attenuate rather than exaggerate disease severity; finally, some anti-retroviral drugs taken by PLWH may have direct anti-viral effects on SARS-CoV2. Such theoretical complexity underlines the need for good observational data. In the absence of such data, many international guidelines followed a cautious approach in order to protect PLWH from COVID-related morbidity and mortality. (3,4)

The object of this paper is to summarise the currently available published or pre-published data on the susceptibility of PLWH to COVID-19. In order to evaluate published data, we utilise a model that separates the two risks that contribute to the probability of having an adverse clinical outcome from COVID-19 (Figure 1). If we denote ‘risk of exposure to COVID-19’ by $\alpha$, ‘risk of becoming infected’ by $\beta$, and ‘risk of adverse clinical outcome’ by $\gamma$, the probability of developing an adverse outcome from COVID-19 infection can be expressed as $\alpha \times \beta \times \gamma$ (Figure 1). Here $\alpha$, $\beta$ and $\gamma$ are probability coefficients which range between 0 and 1. Shielding seeks to reduce $\alpha$ and is beyond the scope of this review. We will focus on evidence that informs us whether $\beta$ and/or $\gamma$ are higher for PLWH than for the general population. Firstly, we will consider whether HIV increases susceptibility to SARS-CoV-2 infection; in terms of our model, ‘Is $\beta_{\text{HIV}} > \beta_0$?’ (using the suffix to denote the population, HIV being PLWH and 0 being the background population). Secondly, we will ask, does HIV increase the risk of COVID-19 infection developing into severe infection with adverse outcomes? In our model, ‘Is $\gamma_{\text{HIV}} > \gamma_0$?’ Thirdly, we will ask whether the literature supports risk stratification between PLWH according to CD4 counts and viral load. Such data are important because they provide the evidence base to inform national and regional guidance.
Methods.

A review of relevant literature published between December 2019 and a final census date at the end of November 2020 was undertaken. We identified studies using keywords, ‘COVID-19’, ‘coronavirus disease-19’, ‘SARS-CoV-2’, ‘novel coronavirus’, ‘new coronavirus’, ‘severe acute respiratory syndrome coronavirus 2’, ‘people living with HIV’, ‘HIV/ AIDS’, ‘co-infection’, ‘immunosuppression’ in electronic databases: PubMed, Google Scholar and ScienceDirect, as well as direct searches in specific journals: The Lancet, JAMA, The BMJ, NEJM, Clinical Infectious Diseases, The Journal of Infectious Diseases. Since COVID-19 is a new disease, first identified in December 2019, some recent studies are not yet published. Therefore, the same search terms were used to search for literature on the preprint servers, Medrxiv and Biorxiv. For both published and pre-published studies the selection criteria included primary studies on HIV/ COVID-19 co-infection cases and secondary review studies. For the purposes of this analysis, we present only studies published in English. In total, we identified 68 studies, of which 54 were peer-reviewed, while 11 were preprints and 2 are conference abstracts.
Results.

**Does HIV increase the susceptibility to SARS-CoV-2 infection?**

In order to answer this question, is $\beta_{\text{HIV}} > \beta_0$, we have to rely on the “natural experiment” of pandemic exposure. Since many SARS-CoV-2 infections are asymptomatic, one would ideally compare the prevalence of swab PCR-positivity in PLWH versus the background population regardless of symptoms, assuming similar levels of exposure and assuming a similar magnitude and duration of PCR-positivity (both of which may be untrue). To date, although many community prevalence studies have been performed, to our knowledge, none have yet reported prevalence or incidence of swab-test positivity against HIV status except where prompted by symptoms.

The next-best “natural experiment” is to see if PLWH are over-represented in patients being diagnosed with COVID-19? Of course, this is not completely independent of the severity question (is $\gamma_{\text{HIV}} > \gamma_0$?) since swabbing is usually prompted by the individual accessing healthcare, usually because of symptoms; this will introduce bias if thresholds for testing differ between PLWH and controls. Several studies have reported such data; a summary of HIV/ COVID-19 co-infection studies with prevalence data is shown in Table 1. Most are small and do not specifically focus on the relationship between HIV infection and COVID-19 susceptibility. Richardson et al published a study early in the epidemic that reported the clinical characteristics of 5,700 sequential patients hospitalized with COVID-19. (5) Of these, 43 were HIV seropositive, an HIV prevalence rate of 0.8%, similar to that in the community (~0.9% from other sources). (6) More recent studies, conducted mainly in USA and Spain, report similar results. (7-11) These observations tally with our own experience (albeit biased by need for hospitalisation); of 1,584 admissions to our tertiary centre with COVID-19 during the first wave of the pandemic, 11 were seropositive (0.7%), a similar proportion to the HIV prevalence of our locality (0.54%).

A much larger, more-recent population-based study in New York state captured information on COVID diagnoses from across the state (over 19M people), so should not be biased by need for hospitalisation, but may be influenced by reason for swabbing. (12) Strikingly, although rates of
COVID diagnosis were higher overall in PLWH (2.8% versus 1.9%), when adjusted for other risk factors (age, region of residence, race and ethnicity), the relative risk (RR) was virtually the same as non-HIV infected members of the same community (RR=0.94, 0.91-0.97). (12)

The converse approach is to investigate the incidence of COVID-19 in PLWH versus the general population (rather than the prevalence of HIV in COVID-19 incident cases as above). One Spanish study for example reported 51 co-infections from an HIV clinic population of 2,873 patients. (13) Including all suspected cases, gave a lower incidence rate in PLWH, 1.8% versus 4.0% in the community. However, rates were similar when only ‘confirmed case’ were considered (1.2% versus 0.9%), although confirmatory testing rates differed between PLWH (69%) and others (22%). Other studies have taken a similar approach reaching similar conclusions. (7, 14-17) Taken together, both prevalence (of HIV) and incidence (of COVID-19) studies seem to point to a rate of infection in PLWH similar to the background population.

Does HIV increase the risk of severe infection with adverse outcomes in COVID-19 infection?

The second question we sought to address from current literature is whether, once infected, PLWH suffer more adverse outcomes than a comparable population without HIV. In our model this is represented by: ‘Is $\gamma_{HIV} > \gamma_0$’? Detailed clinical outcomes are difficult to define and compare; hence most studies focus on mortality data. A summary of HIV/ COVID-19 co-infection studies with mortality data is shown in Table 2.

The literature broadly splits into two camps. On one hand, there are a large number of small studies, many of which emerged early in the pandemic. Most cite comparisons of crude mortality rates in PLWH versus the background population; generally, they are not powered to control for other comorbidities. However, in the absence of better data, these papers contributed to a general consensus that HIV does not predispose to more severe disease or higher mortality; as one author put it, there is an “… under-representation of people living with HIV (PLWH) among severe
COVID-19 cases”. (18) More recently, four studies have been published with much larger numbers of cases that appear to overturn this relatively benign paradigm, the papers by Boulle et al, (19) Bhaskaran et al, (20) Geretti et al, (21) and Tesoriero et al, (12) which we will consider in more detail.

Boulle et al (19) studied 22,308 public-sector patients with laboratory-confirmed COVID-19 in Western Cape Province, South Africa where the background HIV prevalence is ~7%. Of these 3,978 (18%) were PLWH. 625 patients died, including 115 PLWH (18%). Although crude mortality rates are almost identical, age at death was lower in PLWH. Hence, when mortality risk was adjusted for risk factors, including age and gender, it became apparent that, in this cohort, HIV doubled COVID-19 mortality rates (aHR 2.14; 95%CI 1.70-2.70), although the authors acknowledge that the risk might be overestimated due to residual confounding. (Current or past TB also increased COVID-19 mortality.) Interestingly, the effect appeared greater in non-hospitalised patients being “… progressively attenuated when restricting to cases (people with sufficiently severe symptoms to be tested) and hospitalised patients”. (19)

Another population-based study reviewed primary care data from ~17M people in the UK, of whom 0.16% were HIV-infected (a relatively low proportion as London, where HIV-positivity rates are highest, was under-represented). (20) Of 14,882 people who died from COVID-19-related causes (according to cause of death records) in the first wave of the pandemic, 25 were HIV-positive (0.17%). The strength of this study is the wealth of co-morbidity data captured. Adjusting just for age and gender gave a hazard ratio of death of 2.9 for PLWH; when all comorbidities were considered the HR was 2.3. Strikingly, the mortality risk from HIV was greater among people of black ethnicity (HR = 3.8). CD4 and viral load data were not available but, in the study setting, ~94% of PLWH would be expected to be on effective ART.

Considering only hospitalised patients, Geretti et al (21) compared 122 HIV/COVID-19 co-infected patients with 47,470 HIV-negative controls in a large UK-based study (the ISARIC
WHO CCP study). PLWH were relatively younger with fewer comorbidities than the HIV-negative cohort. Although the crude cumulative 28-day mortality was similar between PLWH and HIV-negative patients (26.7% vs. 32.1%, p=0.16), after adjusting for age, PLWH had a 47% higher mortality rate. After adjusting for further variables (sex, ethnicity, age, baseline date, indeterminate/probable acquisition of COVID-19, ten comorbidities, hypoxia/receiving oxygen at presentation) HIV was associated with a 69% higher mortality. The authors could not assess the impact of HIV-related parameters on COVID-19 outcomes as they did not have details of HIV viral load, CD4 count or ART history but they did observe that documented ART was associated with lower mortality.

The Tesoreiro et al. study, (12) summarised above also reported mortality risk. Interestingly, in their study, the mortality risk once patients were hospitalised was similar to non-HIV infected individuals, but taking increased diagnosis and admission rates into account, the standardized mortality ratio for PLWH was higher than the general population (1.23; 95% CI: 1.13-1.48). As in Geretti et al. (21) hospitalized and fatal COVID-19 cases were younger among PLWH.

Do viral load and CD4 status influence COVID-19 risk?

In many of the studies reviewed, HIV infection is conflated to a single entity. It is clear however that there is a great disparity between someone with suppressed disease (undetectable viral load, high CD4 count) and someone with advanced disease (low CD4 count) and/or an uncontrolled viral load. Many studies have either had insufficient numbers to draw conclusions or been unable to address this issue because of their data collection approach. In terms of data, if we consider CD4 count during the episode as more reflective of COVID-induced lymphopenia than the underlying HIV-related immune deficit, we are left with a relatively small number of studies with CD4 count data preceding the COVID-19 diagnosis. Examples include the Spanish COVID-19 incidence study cited above, (13) which reported a trend linking lower CD4 counts with more severe disease (422 vs 668 cells/uL) but was not significant (p=0.115). In the NYC study, COVID-19 diagnosis rates were higher in those with viral suppression (perhaps reflecting greater
engagement with healthcare) as were PLWH with low CD4 counts. In terms of hospitalisation, those with unsuppressed viral loads and low CD4 counts were more likely to be admitted, but CD4 count was not significantly associated with in-hospital death. (12) In the South African study, those in the \( \{ \text{VL} \geq 1000 \text{ copies/ml (last 15 months)} \text{ or } \text{CD4} <200 \text{ cells/µl (last 18 months)} \} \) category appeared to have a higher mortality rate, (19) although many patients did not have recent CD4 or viral load measurements, limiting the power of this observation.
Discussion

In this paper we summarise the extant literature on the interaction of HIV with COVID-19. We used an analytic model separating risk of infection from risk of severe disease. In terms of risk of infection, the definitive answer would come from asymptomatic screening, but HIV status is unlikely to be collected as part of such exercises. Hence, diagnosis rates are the next-best surrogate marker, even though they are profoundly influenced by the occurrence of symptoms or hospitalization. We identified 27 studies to date which address infection risk as a function of HIV status. Most studies assessed HIV prevalence in COVID-19 diagnosed individuals, although some followed COVID-19 incidence in HIV clinic cohorts. (7, 13-17) The consensus that has emerged provides reassurance that PLWH appear no more likely to become infected than their non-infected counterparts; in our model, $\beta_{HIV} = \beta_0$. The caveat to this conclusion is that PLWH may have been shielding or otherwise reducing their exposure (reducing the factor, $\alpha$) during the pandemic, in which case, true infection risk may be higher than estimated.

In terms of severity, early studies were reassuring. PLWH did not appear over-represented among those experiencing complications with COVID-19. However, it is now apparent that, when adjusted for other risk factors, even well-controlled HIV infection does appear associated with increased mortality risk. Indeed, much of the disparity between the findings of different studies can be accounted for by the way in which authors have accounted (or not) for co-factors and confounders in their models. Almost all studies that have considered comorbidities have found that the same factors operate within HIV-positive COVID-19-infected cohorts as have been identified in the general population (age, cardiovascular disease, obesity etc), as might be expected. Taking co-factors into account is not possible in small studies, but larger studies allow adjustment which may be crucial for interpretation. So, for example, in Geretti et al (21) and Bhaskaran et al, (20) unadjusted mortality rates in PLWH are no higher than background mortality rates. However, in both studies, once data are adjusted for age etc, the independent adverse impact of HIV infection is evident. This increased mortality risk with HIV infection manifests itself in different parts of the patient pathway in different settings. Thus in the South African study cited above, the increased
mortality risk was most apparent in non-hospitalised individuals; (19) in the NYC study, the big difference was in diagnosis and hospitalisation rates - once admitted mortality was similar to non-HIV-infected individuals; (12) in the UK study, in which hospitalisation was an entry criterion, mortality rates were found to be significantly higher in PLWH after admission. (21)

It does therefore appear reasonable to take HIV status into account in developing policies and practice, but do we treat all PLWH the same? What about the impact of CD4 count and viral load? Here, the data is far less clear-cut. We can postulate with some confidence that the additional risk of HIV infection for mortality seems to apply even to those with well-controlled HIV. Several studies observe an independent effect of HIV infection across all strata; for example Tesoriero et al found an increased hospitalisation risk in individuals with CD4≥500 and viral suppression. (12) Furthermore, the two UK studies discussed above were performed in settings where 94% of subjects would be expected to be well-controlled. Whether those with low CD4 counts and/or viraemia are at higher risk remains unclear. Several studies show a relationship between lower CD4 counts and worse outcomes, (12-13,19), but some studies suggest low CD4 counts are protective. (7, 22) Although it might appear counter-intuitive that “immunosuppression” would worsen “immunopathology”, it should be remembered that advanced HIV is characterised by immune dysfunction with heightened levels of immune activation as much as “immunosuppression”.

Recommendations based upon CD4 and/or viral load status thus appear to have a weak evidence-base, but may be justified in a pragmatic risk-stratified model. Current UK guidelines differentiate those with a CD4 count <50 cells/μL for special consideration, (3) but there is little evidence supporting where to make this cut-off. In the NYC study, the authors separated out a cohort with a CD4 count <200 cells/μL or <14% (“Stage 3”) and found they had a higher HIV-attributable mortality risk, (12) but they did not explore lower cut-offs. At the other end of the scale, it does not appear possible to define a “safe” level of CD4 count from the studies published to date; indeed, one can argue from the mortality impact of HIV even in settings where almost everyone is on
effective treatment, (20-21) that no such “safe” level exists. One might however pragmatically define a level where recommendations for PLWH match those for the general population. Such stratified advice is likely to vary on a regional basis. Currently, the countries with most COVID-19 cases are relatively low HIV seroprevalence countries. Conversely, countries with high HIV seroprevalence may have limited COVID-19 testing resources and incidence rates may be underestimated. This is why studies such as Boulle et al (19) are particularly valuable as they address COVID-19 risks in a high HIV burden setting (as well as making intriguing observations about TB/COVID interactions). Although their conclusions may not be generalisable to other settings, the consistency in message, if not magnitude, of the effect of HIV on COVID-19 mortality across all the larger studies cited is notable.

This overview has attempted to be comprehensive, but we may have missed publications and have not captured those in languages other than English. Of course, in such a rapidly-changing situation new studies are being published every month but this study summarises the current state-of-play and constitutes a comprehensive basis for future literature reviews. We have deliberately chosen not to focus on whether some antiretroviral drugs impact COVID-19 outcomes directly as the data are conflicting and such questions are best addressed in prospective clinical trials. We considered a meta-analysis, but after reviewing the disparate nature of studies with their different data collection strategies, and estimating the number of studies that would need to be excluded, felt that a comprehensive descriptive analysis was more helpful.

Understanding the impact of HIV on COVID-19 is important in order to inform guidance and policy. “Shielding” has costs in terms of emotional and psychological wellbeing, finances and quality of life. If PLWH are to be asked to take extra precautions, this guidance needs to be based on good data. Additionally, as vaccines become available, prioritisation for vaccination is likely, in which case we need data to establish where PLWH stand in any risk-stratification. Despite an extensive body of literature, more research is needed to clarify risk in different settings and particularly to clarify how guidance should be shaped by measures such as CD4 count and viral load, but the
new data from large studies is consistent: even well-controlled HIV appears associated with an increased COVID-19 mortality risk.

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Table 1. HIV/ COVID-19 co-infection studies with prevalence data

| # | Authors                  | Setting               | Number of participants | Readout                                                                 | Comments / Conclusions                                                                 |
|---|--------------------------|-----------------------|------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| 1 | Tesoriero et al (12)     | New York State, USA   | 2,988 HIV/ COVID-19, vs 375,260 non-HIV COVID-19 from a population of 19.4M | 1.43-fold higher risk of COVID-19 in PLWH vs non-HIV, but difference disappears with adjustment for other factors. | PLWH have a similar adjusted risk of infection as non-HIV individuals (RR=0.94, 0.91-0.97) |
| 2 | Toombs et al (23)        | UK                    | 3 HIV/ COVID-19 from a population of 500,000 | HIV prevalence in the catchment area and COVID-19 patients (0.34% vs 0.43%) | HIV does not appear to increase the risk of contracting COVID-19                        |
| 3 | Molina-Iturritza et al (7)| Basque Country, Spain | 8 HIV/ COVID-19 out of 902 PLWH from a population of 331,549 | Similar prevalence to the general population, 0.89% vs 0.93% | HIV does not appear to increase the risk of contracting COVID-19                        |
| 4 | Sachdev et al (8)        | San Francisco, USA    | 193 HIV/ COVID-19 vs 9,626 non-HIV COVID-19 from a population of 276,807 | Similar prevalence to HIV-negative people tested for COVID-19, 4.5% vs 3.5% | “In San Francisco, susceptibility to COVID-19 was increased among PLWH over the first 6 months of the pandemic” |
| 5 | Braunstein et al (9)     | NYC                   | 2,410 HIV/ COVID-19 out of 204,583 COVID-19 and 113,907 PLWH without COVID-19 | Similar prevalence to the general population, 1.2% vs 1.5% | HIV does not appear to increase the risk of contracting COVID-19                        |
| 6 | Park et al (24)          | USA                   | 189 HIV/ COVID-19 and 380 HIV-negative COVID-19 from a population of 107,636 | Similar prevalence between the 2 groups, 12.7% vs 13.9% of whom tested for COVID-19 | HIV does not appear to increase the risk of contracting COVID-19                        |
| 7 | Del Amo et al (14)       | Spain                 | 77,590 PLWH of whom 236 HIV/ COVID-19 | Risk of incidence (30.0 per 10 000) lower than the general population (41.7 per 10 000) | Risk of COVID-19 diagnosis lower among PLWH receiving TDF/FTC than other ART          |
| 8 | Cabello et al (10)       | Madrid, Spain         | 66,860 COVID-19 pts, of whom 63 were HIV+ | Similar prevalence rate to the community, 0.86% (confirmed cases) -1.68% (confirmed + suspected) vs | HIV severity or type of ART do not influence COVID-19 outcome                         |
| Study         | Location          | Number of Participants | Details |
|--------------|-------------------|------------------------|---------|
| Gudipati et al (25) | Detroit, Michigan, USA | 14 HIV/ COVID-19 out of 7,372 | 1% (confirmed cases in the community) |
| Marcello et al (11) | NYC, USA | 159 HIV/ COVID-19 out of 13,442 | Similar incidence to the general population, 1.6% vs 1.7% |
| Charre et al (26) | Rhone, Lyon, France | 12 HIV/ COVID-19: 4 PrEP user/ COVID-19 and 3,632 HIV-negative COVID-19 from a tested population of 19,113 | Similar prevalence between PLWH, PrEP users and HIV-negative cohort, 15.6% vs 14.8% vs 19.1% |
| Miyashita and Kuno (27) | NYC, USA | 8,912 COVID-19 of whom 161 PLWH | Similar HIV prevalence to community 1.8% vs 1.3% |
| Huang et al (15) | Wuhan, China | 6001 PLWH of whom 35 HIV/ COVID-19 | Similar incidence to the general population, 0.58% vs 0.46% |
| Richardson et al (5) | NYC, USA | 5,700 COVID-19 of whom 43 HIV/ COVID-19 | 0.8% HIV prevalence in hospitalised patients with COVID-19 versus 0.9% in community |
| Inciarte et al (16) | Barcelona, Spain | 5,683 PLWH of whom 53 HIV/ COVID-19 | Lower incidence (62%) than the population in Barcelona |
| D’Souza et al (28) | USA | 2,078 PLWH out of 3,411 survey participants | Among participants tested for COVID-19 PLWH had higher positive results, (11.2% vs 6.1%, P=0.08) |
| Vizcarra P et al (13) | Madrid, Spain | 51 HIV/ COVID-19 vs 1,288 non-COVID-19 HIV pts from 2,873 PLWH | Slightly higher prevalence than the general population: 1.2% vs 0.96% |
| Shalev et al (29) | NYC, USA | 2,159 COVID-19 of whom 31 HIV/ COVID-19 | HIV prevalence in the catchment area and COVID-19 patients (1.4% vs 1.5%) |

HIV does not appear to increase the risk of contracting COVID-19.
| Study | Location | Participants | Findings | Notes |
|-------|----------|--------------|----------|-------|
| Jimenez et al (30) | Madrid, Spain | 9 HIV/ COVID-19 out of 1,542 COVID-19 | Low HIV prevalence (0.6%) | No clinical details for HIV+ presented. |
| Mondi et al (31) | Rome, Italy | 604 COVID-19 of whom 5 HIV/ COVID-19 | PLWH represent less than 1% of all COVID-19 cases admitted to the hospital; Not compared to the general population | PLWH do not appear at increased risk of contracting COVID-19 |
| Blanco et al (32) | Spain | 543 COVID-19 of whom 5 HIV/ COVID-19 | 1% HIV prevalence in patients with COVID-19 | 4 discharged, 1 in ICU; Community prevalence not cited |
| Goyal et al (33) | NYC, USA | 393 COVID-19 of whom 7 HIV/ COVID-19 | 1.8% HIV prevalence in patients with COVID-19 | Clinical details not presented |
| Sasset et al (34) | Padua, Italy | 2 HIV/ COVID-19 (1,745 PLWH in the community) out of 383 hospitalized COVID-19 | 1 discharged, 1 in ICU | Low prevalence (0.5%) of PLWH among hospitalized patients |
| Fernandez-Fuertes et al (17) | Southern Spain | 4 HIV/ COVID-19 out of 326 PLWH | Similar incidence to the general population, 1.22% vs 0.417% | HIV does not appear to increase the risk of contracting COVID-19 |
| Karim et al (35) | KwaZulu-Natal, South Africa | 55 HIV/ COVID-19 out of 124 COVID-19 | Higher prevalence than the general population, 44% vs 18% | HIV does not appear to increase the risk of contracting COVID-19 (considering age and gender distribution of participants) |
| Parker et al (36) | Cape Town, South Africa | 24 HIV/ COVID-19 out of 116 COVID-19 pts | Higher prevalence than the general population, 21% vs 12.6% | “PLWH may have a high probability of hospital admission...” |
| Härter et al (37) | Germany | 32 HIV/ COVID-19 | Higher hospitalization than the general population (42% vs 17%) | Measured only symptomatic hospitalization rate |

*Studies ranked by number of participants. Note studies may also appear in Table 2. All papers are 2020 publication date. Abbreviations: PrEP, pre-exposure prophylaxis (HIV); NYC, New York City; ICU, Intensive Care Unit. Studies # 1; 4; 10; 24; 25 are pre-published at the time of writing.
| #  | Authors                  | Setting                  | Number of participants                                                                 | Readout                                                                 | Conclusion                                                                 |
|----|--------------------------|--------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1  | Tesoriero et al (12)     | New York State, USA      | 2,988 HIV/COVID-19, vs 375,260 non-HIV COVID-19 from a population of 19.4M            | 2.55-fold higher mortality than the general population                  | PLWH had poorer COVID-19 outcomes than HIV-negative people                |
| 2  | Bhaskaran et al (20)     | UK                      | 27,480 HIV/COVID-19 from a population of 17.3M                                         | 25 died; PLWH had 2.3-fold higher mortality risk after adjusting for age, gender, ethnicity, deprivation and comorbidities | “PLWH may be a high-risk group for COVID-19 death”                          |
| 3  | Boule et al (19)         | South Africa             | 22,308 COVID-19 pts, (from population number of 3.5M) of whom 3,978 HIV+             | HIV associated with higher risk of death: aHR 2.14 (1.70-2.70)          | PLWH should be considered more susceptible to COVID-19 mortality            |
| 4  | Byrd et al (38)          | RI, USA                  | 27 HIV/COVID-19 from a population of 1.06M (2800 PLWH)                                  | 1 died                                                                  | Similar clinical outcomes to the general population                       |
| 5  | Toombs et al (23)        | UK                      | 3 HIV/COVID-19 from a population of 500 000                                            | 1 died; 2 were discharged                                               | HIV does not increase the risk of mortality from COVID-19 – but only n=3 |
| 6  | Molina-Iturritza et al (7)| Basque Country, Spain    | 8 HIV/COVID-19 out of 902 PLWH from a population of 331,549                            | 1 died                                                                  | 3 patients with the worst clinical course had a CD4> 400 cells/µl          |
| 7  | Sachdev et al (8)        | San Francisco, USA       | 193 HIV/COVID-19 vs 9,626 non-HIV COVID-19 from a population of 276,807                |                                                                         | Risk of severe COVID-19 was not increased among PLWH                      |
| 8  | Braunstein et al (9)     | NYC                     | 2,410 HIV/COVID-19 out of 204,583 COVID-19 and 113,907 PLWH without COVID-19          | 312 died                                                                | Higher mortality rate than the general population, 13% vs 8%             |
|   | Study Reference | Country | Description | Findings |
|---|-----------------|---------|-------------|---------|
| 9 | Park LS (24)    | USA     | 189 HIV/COVID-19 and 380 HIV-negative COVID-19 from a population of 107,636 | Risk of severe COVID-19 was similar between the 2 groups |
| 10| Del Amo et al (14) | Spain | 77,590 PLWH of whom 236 HIV/COVID-19 | Higher risk of mortality than the general population 3.7 per 10,000 vs 2.1 per 10,000 |
| 11| Cabello et al (10) | Madrid, Spain | 66,860 COVID-19 pts, of whom 63 were HIV+ | Lower mortality rate than the community, 3.2% vs 13.3% |
| 12| Gudipati et al (25) | Michigan, USA | 14 HIV/COVID-19 out of 7372 COVID-19 pts at the local clinic from a population of 65,549 COVID-19 (278 HIV/COVID-19) | PLWH are not at higher risk of severe COVID-19 |
| 13| Etienne et al (39) | Paris, France | 54 HIV/COVID-19 from a population of 51,000 PLWH | Not compared to the general population |
| 14| Hadi et al (40) | Massachussets, USA | 404 HIV/COVID-19 and 49,763 HIV-negative pts (404 propensity-matched) | PLWH are at higher risk of adverse outcomes from COVID-19 (due to higher burden of comorbidities) |
| 15| Geretti et al (21) | UK | 122 HIV/COVID-19 and 47,470 HIV-negative controls | HIV may be associated with higher mortality rate from COVID-19 |
| 16| Wang et al (41) | NYC | 52 HIV/COVID-19 out of 3,273 hospitalized COVID-19 (from 28,336 patients tested for COVID-19) | No significant association between HIV and hospitalization |
| 17| Marcello et al (11) | NYC | 159 HIV/COVID-19 out of 13,442 COVID-19 from a population of 22,176 (277 PLWH) | Could not be compared to mortality rates in the general population; low CD4 can be associated with severe COVID-19 |
| 18| Di Biagio et al (42) | Italy | 69 HIV/COVID-19 (38 hospitalised) out of 22,000 COVID-19 cases | Mortality rate was lower in states with higher HIV prevalence; "HIV prevalence had a protective effect" |
| 19| Hassan et al (43) | Nigeria | 15,742 (303 deaths) COVID-19 in high burden states and 9,952 (287 deaths) COVID-19 in other 30 states | HIV prevalence 3.7 in high burden; 2.9 in other 30 states |
| No. | Authors (Reference) | Location | Description | Results/Notes |
|-----|---------------------|----------|-------------|---------------|
| 20  | Bastos et al (44)   | Lisbon, Portugal | 14 HIV/COVID-19 (132 PLWH tested) out of 815 COVID-19 (12,192 HIV-negative tested) | All survived | “Evolution of COVID-19 was similar between PLWH and non-HIV patients” |
| 21  | Miyashita and Kuno (27) | NYC | 8,912 COVID-19 of whom 161 PLWH | Death rate: 23 (14%) in PLWH and 1,235 (14%) in HIV-negative cohort | Higher mortality rate in PLWH younger than 50 years; no significant difference in other age groups |
| 22  | Huang et al (15)    | Wuhan, China | 6,001 PLWH of whom 35 HIV/COVID-19 | Similar mortality rate to the general population, 5.7% vs 7.7% | Delayed viral clearance, HIV-related immunosuppression might result in SARS-CoV-2 persistence |
| 23  | Gervasoni et al (45) | Milan, Italy | 47 HIV/COVID-19 out of 6,000 PLWH | Lower mortality rates than HIV-negative cohort (4% vs 17%) | Numbers small: 2 died; one overweight, one with comorbidities |
| 24  | Inciarte et al (16) | Barcelona, Spain | 5,683 PLWH of whom 53 HIV/COVID-19 | 2 died | HIV was not associated with severe COVID-19 |
| 25  | Isernia et al (46)  | Paris, France | 30 HIV/COVID-19 out of 5,327 PLWH | Not compared to the general population | 2 died; HIV is probably not an independent risk factor for COVID-19 |
| 26  | Patel et al (47)    | Bronx, NY, USA | 4,662 COVID-19 pts, of whom 77 HIV+ | 14 (18%) PLWH died compared to 1037 (23%) HIV-negative pts | No significant difference in mortality between PLWH and HIV-negative cohort |
| 27  | Sigel et al (48)    | NYC | 88 HIV/COVID-19 and 405 HIV-negative matched controls from 4,402 COVID-19 pts | Similar disease course and mortality rates to HIV-negative controls | No differences in adverse outcomes between the cohorts matched by age, gender, ethnicity and calendar week of infection |
| 28  | Palmieri et al (49) | Italy | 3,032 deaths with COVID-19 of whom 6 PLWH | HIV was more common (4 cases) in younger adults (< 65 years) |
| 29  | Maggiolo et al (50) | Italy | 55 HIV/COVID-19 and 69 non-COVID-19 PLWH from a population of 2,898 PLWH | Mortality rate 7.2%; Not compared to the general population | HIV does not appear to be a risk factor for a severe COVID-19 disease |
| 30  | Vizcarra et al (13) | Madrid, Spain | 51 HIV/COVID-19 vs 1,288 non-COVID-19 HIV pts out of 2,873 PLWH | Lower mortality rates than the general population (4% vs 20%) | PLWH “should receive the same treatment as the general population” |
| 31  | Karmen-Tuohy et al (51) | NYC, USA | 21 PLWH and 42 matched HIV-negative controls out of 2,617 HIV-neg COVID-19 | Similar mortality rate to HIV-negative controls (28.6% vs 23.8%) | HIV does not significantly impact clinical outcomes |
| Study          | Location         | Patients Description                                      | Mortality                           | Notes                                                                 |
|---------------|------------------|-----------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------|
| Shalev et al  | NYC, USA         | 2,159 COVID-19 of whom 31 HIV/COVID-19                    | 8 died                              | Not compared to the general population                               |
| Jimenez et al | Madrid, Spain    | 9 HIV/COVID-19 out of 1,542 COVID-19                      | 8 survived                          |                                                                      |
| Altuntas Aydin| Istanbul, Turkey | 4 HIV/COVID-19 out of 1,224 PLWH                          | 1 died                              | Comorbidities are important risk factor in mortality in HIV/COVID-19 patients |
| Guo et al     | Wuhan, China     | 1,178 PLWH                                                | 8 / 1178 were co-infected; 1 died   | Authors suggest HIV might reduce COVID-19 symptoms by reducing immunopathology |
| Argenziano et | NYC              | 21 HIV/COVID-19 out of 1000 consecutive patients with COVID-19 | 6 required ICU                     | HIV was significantly associated with mortality                       |
| Calza et al   | Italy            | 26 HIV/COVID-19 out of 756 COVID-19                       | All survived                        | Comparable or milder clinical presentation than the general population |
| Mondi et al   | Rome, Italy      | 604 COVID-19 of whom 5 HIV/COVID-19                       | All survived                        | PLWH are not at increased risk of severe COVID-19                     |
| Collins et al | Atlanta, Georgia, USA | 20 HIV/COVID-19 out of 530 COVID-19                     | Not compared to the general population | 3 died; high prevalence of severe COVID-19 was not observed among PLWH |
| Fernandez-     | Southern Spain   | 4 HIV/COVID-19 out of 326 PLWH                            | 1 died; 3 mild disease              |                                                                      |
| Fuertes et al |                 |                                                           |                                     |                                                                      |
| Dandachi et   | USA              | 286 HIV/COVID-19                                          | 27 died; similar mortality rate to the general population | Low CD4 (<200 cells/µl) associated with poor outcomes                  |
| Nagarakanti et| New Jersey, USA  | 23 HIV/COVID-19 and 23 HIV-negative controls out of 254 HIV-negative COVID-19 pts | Lower mortality than unmatched (254 pts) (13% vs 60%, p=0.001) and matched cohorts (13% vs 26%, p=0.261) | CD4 lymphopenia can be protective against severe COVID-19; 3 patients with AIDS survived |
| Shekhar et al | New Mexico, USA  | 125 vs 5 HIV/COVID-19                                     | Not compared to the general population | All survived; PLWH may have a milder COVID-19 disease; but only n=5 |
| Parker et al  | Cape Town, South Africa | 24 HIV/COVID-19 out of 116 COVID-19 pts                  | Similar death rate, 6 (25%) vs 22 (25%) | PLWH did not have higher mortality                                      |
| Ho et al      | NYC              | 72 hospitalised HIV/COVID-19 from 93 HIV/COVID-19         | Higher mortality rate (26.3%) than the general population (10.2%-24.5%) | PLWH are at higher risk of a severe COVID-19 disease, but not directly |
| #  | Authors                  | Location            | HIV/COVID-19 Details                                                                 | PLWH Details                                                                 |
|----|--------------------------|---------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| 46 | Stoeckle et al (60)      | NYC                 | 30 HIV/ COVID-19 and 90 HIV-negative pts matched by age, gender and ethnicity          | Death rate: 2 (7%) in PLWH and 14 (16%) in HIV-negative pts No significant difference in mortality rate between PLWH and HIV-negative cohort |
| 47 | Yamamoto et al (61)      | Tokyo, Japan        | 83 COVID-19 vs 5 HIV/ COVID-19 All survived                                           | Not compared to the general population                                        |
| 48 | Meyerowitz et al (62)    | Massachussetts, USA | 36 confirmed HIV/ COVID-19 2 died                                                   | Not compared to the general population                                        |
| 49 | Kase et al (63)          | 12 countries in Central and Eastern Europe | 34 HIV/ COVID-19 2 died                                                           | Mild disease in majority of PLWH                                              |
| 50 | Härter et al (37)        | Germany             | 32 HIV/ COVID-19 Higher mortality rates than the general population (9% vs 3.7%)      | Numbers small: 3 died, 2 of whom had undetectable viral load                   |
| 51 | Calza et al (64)         | Bologna, Italy      | 9 PLWH with uncontrolled HIV out of 31 HIV/ COVID-19 All (9) survived, 4 had AIDS.   | Uncontrolled HIV infection did not seem to be associated with severe COVID-19 |
| 52 | Okoh et al (65)          | NJ, USA             | 27 HIV/ COVID-19 2 died                                                            | Similar presentation to the general population                                 |
| 53 | Childs et al (66)        | London, UK          | 18 HIV/ COVID-19 5 died                                                            | Not compared to the general population                                        |
| 54 | Madge et al (67)         | London, UK          | 18 HIV/ COVID-19 3 died; no patients required ventilation or had a prolonged COVID-19 hospital stay 9 days (PLWH) vs 7 days (general hospital population) | Not compared to the general population                                        |
| 55 | Jewsbury et al (68)      | Manchester, UK      | 16 HIV/ COVID-19 4 died                                                            | PLWH with well controlled HIV may have similar outcomes to the general population |
| 56 | Hu et al (69)            | Wuhan, China        | 12 HIV/ COVID-19 1 died                                                            | Not compared to the general population                                        |
| 57 | Suwanwongse et al (70)   | NY, USA             | 9 HIV/ COVID-19 7 died; PLWH with low CD4 count may have higher mortality; high mortality – suggest T cell lymphopenia does not protect against severe COVID-19 | Not compared to the general population                                        |
| 58 | Marimuthu et al          | South India         | 6 HIV/ COVID-19 Not compared to the general                                       | All survived; HIV does not increase                                            |
| Studies ranked by number of participants. Note studies may also appear in Table 1. aHR, adjusted hazard ratio with 95% confidence intervals. Studies # 1; 2; 7; 17; 35; 40; 47; 49; 51; 54 are pre-published at the time of writing. |
|---|---|---|---|
| 59 | Swaminathan et al (72) Philadelphia, USA | 6 HIV/COVID-19 | 2 (33%) died; death rate of the general population, 60% | Numbers too small for comparison |
| 60 | Ridgway et al (73) Chicago, USA | 5 HIV/COVID-19 | Similar ICU admission rate to the general population (20%) | All survived |
| 61 | Benkovic et al (74) Long Island, USA | 4 HIV/COVID-19 | All survived | “uncomplicated COVID-19 in PLWH can be managed with self-isolation at home” |
Figures

Figure 1. A model describing the probability of developing an adverse outcome from COVID-19.

$\alpha$, risk of exposure to COVID-19; $\beta$, risk of contracting COVID-19; $\gamma$, risk of developing a severe infection resulting in an adverse outcome.
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