Does HIV status confer a higher risk of acquiring COVID-19? Using Clinical Decision Science to combat patients' anxiety

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ABSTRACT   A clinical decision report using:

del Amo J, Polo R, Moreno S, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy. *Annals of Internal Medicine*. 2020;173(7):536-541. https://doi.org/10.7326/m20-3689

for a patient with HIV and concerns about COVID-19 for immunocompromised individuals.

Keywords: *HIV, COVID-19, tenofovir, Clinical Decision Science*

Clinical-Social Context

Mr. Lopez (pseudonym) is a 57-year-old Hispanic man with a past medical history of generalized anxiety disorder and hyperlipidemia who presented in August 2020 for his biannual chronic Human Immunodeficiency Virus (HIV) visit. During the visit, Mr. Lopez reported full adherence to Biktarvy® (bictegravir, emtricitabine, and tenofovir alafenamide) without any issues obtaining the medication or any noticeable side effects. A basic metabolic panel and lipid panel revealed no abnormalities, and his HIV viral load was at the lower limit (<20 HIV1 copies/mL) with a total helper CD4 count of 653 cells/uL. Thus, Mr. Lopez was encouraged to continue the same regimen.

Though Mr. Lopez was encouraged to hear that there were no new health concerns, he expressed concerns surrounding the ongoing COVID-19 pandemic. While he was grateful to keep his job and therefore his medical insurance, he was struggling with 'work from home.' He worked as a social worker and felt he could not communicate effectively with clients through virtual interactions. Additionally, he was concerned that the immunocompromise associated with HIV diagnosis could increase susceptibility to COVID-19, not only for his own sake but also for the sake of his partner, who had both HIV and early-stage Parkinson's Disease. They had both been proactive and diligent in achieving control of their illness and were fearful at the prospect of infection with another potentially lethal virus. Furthermore, if one of them did become ill, it would introduce multiple uncertainties into their household, as standard 'isolate at home' protocols might not suffice for someone with an immunocompromised partner.

More broadly, Mr. Lopez was also heavily involved in the HIV community, both through his employment and social life, as he had lived with the virus for over 30 years. He had been a participant in the earliest HIV drug trials and

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knew all too well what it was like to watch a virus devastate his loved ones and his community. Due to these additional stressors, Mr. Lopez had increased his consumption of alprazolam from once to twice per week.

At the time of the appointment, the scientific community was struggling to understand a virus that was equally confusing as it was devastating. Just one month prior, the World Health Organization had finally announced that COVID-19 can be airborne, while simultaneously, the total cases in the United States (US) surpassed three million. As such, we asked Mr. Lopez for some time to investigate this question that carried such crucial implications for him.

Clinical Question

For a 57-year-old male person living with HIV (PLWH) receiving Biktarvy® and living in an urban center in the Midwestern US, is the risk of acquiring COVID-19 infection different from a seronegative person of the general population?

Research Article

del Amo J, Polo R, Moreno S, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy. *Annals of Internal Medicine*. 2020;173(7):536-541. https://doi.org/10.7326/m20-3689 [1]

Description of Related Literature

On August 30, 2020, the search engines Google Scholar and PubMed were used for the search terms "Incidence of COVID-19 in HIV" and "Prevalence of COVID-19 in HIV." Though the research question is primarily concerned with COVID-19 incidence (i.e. likelihood of acquiring the virus), the virus was first discovered just eight months before the clinical encounter, making these two terms virtually synonymous. PubMed yielded 184 and 185 results for these terms, respectively, while Google Scholar yielded 30,800 and 34,500 results. Only the first 100 results from these four searches were examined further with respect to the inclusion criteria, as results past this mark became irrelevant for the question.

The inclusion criteria were any cohort, cross-sectional or case-control studies that compared the incidence or prevalence of COVID-19 infection between HIV-negative and HIV-positive individuals. In total, seven studies met these criteria, and they are examined below in order of increasing relevance for the clinical question.

Various studies were discarded due to their relatively small PLWH sample sizes (i.e. 200[2], 116[3], 2873[4], 5683[5] and 6001[6]). These studies had wildly conflicting results, perhaps due to their small samples, varying definitions (e.g. symptom-based characterizations of COVID-19[2] vs. positive PCR[3-6] with additional radiologic evidence of pneumonia[3]) and different geographic locations (i.e. Iran[2], South Africa[3], Spain[4-5] and China[6]). To summarize, one study found a higher prevalence of COVID-19 in PLWHs[3], two found a lower prevalence[2, 5], one found no difference[6] and to further complicate matters, one had opposite results when comparing suspected COVID-19 cases with confirmed cases.[4] Three of these studies examined the role of demographic factors and ART regimen on COVID-19 prevalence. [4-6] Of these, two found no significant association with demographic factors[4,5] while one found a higher prevalence in older participants[6], though it only described two categories of age (<50 and ≥50). Only one study found an association with ART regimen[4], as tenofovir-based regimens were more prevalent in PLWHs who acquired COVID-19. However, other studies also accounted for all these variables while involving a much greater sample, thus increasing our confidence in the validity of their results.

For example, Boulle et al.[7] used public sector data in Western Cape, South Africa, to derive a cohort of over 500,000 PLWHs. The study focused on predictors of mortality from COVID-19 rather than incidence rate of the infection. However, the data can be used to derive risk ratios for the variables of interest as they pertain to COVID-19 incidence. As such, HIV status has a risk ratio of 1.17 (P <0.0001), male sex has 0.56 (P <0.0001) and the age group 50-59 has 1.05 (P = 0.36) when compared to all other age groups cumulatively. However, the data provided is not sufficient to perform this calculation for ART regimens.

The study ultimately selected for critical appraisal was del Amo et al.[1], a prospective cohort study in Spain that followed a cohort of PLWHs to calculate the incidence of COVID-19 and examined how epidemiological and therapeutic factors influenced this outcome variable. By addressing these factors, the study accounted for various of Mr. Lopez's social factors. Furthermore, its PLWH cohort of 77,590 encompassed 65% of all PWLHs in Spain, and it was the second-largest PLWH cohort of all studies that met the inclusion criteria.

Though Boulle et al. had a larger PLWH cohort, it did not describe the effect of ART on COVID-19 incidence. This was an essential aspect of the research question because there is speculation that ART can protect against COVID-19 infection, as it was previously suggested to protect against SARS.[8] Additionally, previous *in-vitro* studies showed that ARTs could inhibit RNA-dependent RNA polymerase[9,10], and current clinical trials are examining the efficacy of ARTs against COVID-19 e.g. RECOVERY (ClinicalTrials.gov: NCT04381936) and SOLIDARITY (ISRCTN83971151).

As the virus struck the Americas after Asia and Europe, no studies involved a Hispanic sample, and no studies were located in the US. Seeing as how COVID-19 incidence is highly dependent on spatial[11] and socioeconomic[12] factors, comparing an urban Hispanic male in the US with nation-wide Spanish participants carries significant limitations. On the other hand, of all the study locations above (i.e. Iran, South Africa, China, Spain), Spain is the most similar to the US. For instance, it ranks 25th in Human Development Index, compared with 17th for the US and 114th for South Africa.[13] As such, luxuries like avoiding public transit and having access to infectious disease specialists are most applicable in a country like Spain. Similarly, being a service-driven economy, Spanish participants were most likely able to 'work from home,' as Mr. Lopez could. Furthermore, the COVID-19 incidence was similar when comparing Spain during the study period (~1/16,000 per day) with the local incidence surrounding Mr. Lopez in August.[14] Lastly, many Hispanics have ancestries that can be partly traced back to Spain, which indeed manifests as high concordance at a genetic level.[15] Thus, though by no means an exact comparison, the external validity was greatest with the Spanish sample.

No studies matched Mr. Lopez's timeline adequately. The studies occurred from February to June, whereas Mr. Lopez posed his question in August. Notably, del Amo was the earliest of the studies, taking place from February to April. Though COVID-19 has a relatively low mutation rate[16], multiple variants have emerged with different infectivity, and extrapolating data from six months in the past is therefore a significant limitation. On the other hand, improving the match by 1-2 months was not sufficient rationale for altering the study of choice in light of the multiple advantages mentioned above.

Overall, by accounting for most of the variables in the research question while involving a large sample from a comparable population, del Amo was chosen for critical appraisal.

Critical Appraisal

Del Amo et al. examined all HIV-positive individuals receiving ART across 60 Spanish hospitals, which totaled 77,590 PLWHs. For each PLWH, it ascertained age, sex and ART regimen. It then followed this cohort of PLWHs for 75 days (February 1 to April 15) to calculate the risk of COVID-19 diagnosis, which it defined solely as PCR-confirmed cases.

In total, there were 236 COVID-19 diagnoses among the PLWHs, which represented a lower incidence of COVID-19 infection compared to the general Spanish population (risk per 10,000 = 29.8-30.2 vs. 41.7). Regarding the effect of epidemiological factors, it found a higher risk of COVID-19 acquisition in PLWHs who were male (risk per 10,000 = 30.4-40.3 in men vs. 11.2-23.2 in females) or elderly (risk per 10,000 = 52.4-126.7 in 70-79 year-olds; 26.9-54.2 in 60-69; 21.0-32.5 in 50-59; 20.9-36.4 in 40-49; 20.3-38.3 in 20-39). Regarding the role of ART, it found a lower risk of COVID-19 acquisition in people receiving tenofovir disoproxil fumarate/emtricitabine (risk per 10,000 = 10.5-25.9; 31.8-47.6 for tenofovir alafenamide/emtricitabine; 21.5-36.7 for abacavir/lamivudine; 22.6-38.4 for "other regimens"). Evidently, by addressing the role of HIV status, epidemiological factors and therapeutic factors, the study addressed most aspects of the research question.

If instead of calculating risk per 10,000 people, the data from del Amo et al. is used to calculate risk ratios for each of the four variables, one could derive a cumulative risk ratio that accounts for all of the variables. As such, the COVID-19 risk ratio calculation gives 0.72 for HIV-positive status, 2.14 for male sex, 0.78 for age 50-59 (compared to all other age groups cumulatively) and 1.50 for tenofovir alafenamide/emtricitabine (compared to all other regimens cumulatively). Age, sex, and HIV-status are not amenable to change, and this information was shared with Mr. Lopez.

According to the Strength of Recommendation Taxonomy (SORT) criteria[17], this is a level 2 study, as it is a cohort study. A higher level of evidence, such as a randomized clinical trial, was not feasible for the research question as the independent variable was HIV status. Thus, the findings have to be interpreted as correlational rather than causal. For example, PLWHs may have lower COVID-19 incidence because they take more aggressive precautions rather than because HIV is protective per se.

Another limitation of this study was that it could not account for any COVID-19 infections that were not confirmed by RT-PCR. Presumably, asymptomatic and mild infections were underrepresented in this study, as they would be less likely to pursue an RT-PCR test. However, this limitation likely had less impact on PWLHs, as they tend to receive more medical attention and likely received more RT-PCR tests.

There are also various confounders underlying the association between ART regimen and COVID-19 incidence. ART regimens are not selected at random, and there could be confounding variables that influenced both ART regimen and COVID-19 incidence. For example, older patients tend to take more aggressive precautions against COVID-19 and are also more likely to be on older ART regimens. Furthermore, the study claimed to have ascertained ART regimen at the time of COVID-19 diagnosis, but it was only able to verify this information with the pharmacy for 36 out of 60 hospitals. Perhaps more importantly, it only verified the information for the PLWHs who acquired COVID-19. While the distribution was similar for the ART regimens that they verified, it still raises the concern that a significant portion of the ART data may not have been current, especially since the authors used data from 2019 and ART regimen changes are not uncommon.

Furthermore, the authors did not provide an explanation or supposition about why male sex was associated with a higher COVID-19 incidence in PLWHs. They did say that "the observed age and sex patterns are consistent with those reported for HIV-negative persons," but this is technically incorrect. The rate of COVID-19 infection in Spain is actually higher in females than males (risk per 10,000 = 96.8 in females vs. 84.6 in males as of August 27)[18]. Thus, the authors' findings in PLWHs with regard to sex are in stark contrast with the general Spanish population.

Also, as mentioned in the related literature section, a study in Madrid[4] found that suspected COVID-19 cases in PLWHs were >4-fold higher than suspected cases in the general population due to local restrictions on confirmatory testing. A similar bias could have affected the del Amo study as both studies were in Spain. However, this bias most likely reduced the effect size, as PLWHs could be expected to have less restrictions on testing. Accordingly, while Mr. Lopez had not developed symptoms and had thus not sought a test, he had access to an infectious disease specialist who could have obtained one if needed.

The authors also did not provide a rationale for how they selected the 60 hospitals, which could be a source of selection bias if the hospitals were not selected randomly. However, by including all PWLHs within these hospitals, the authors were able to avoid participation bias.

Lastly, according to the study, "the funding sources had no role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication."

Clinical Application

Overall, Mr. Lopez was relieved by the results of the study. His anxiety was primarily tied to the uncertainty surrounding the role of HIV status and what it meant for himself, his partner and the greater HIV community. Accordingly, the study provided concrete evidence that HIV was not associated with increased COVID-19 incidence.

On the other hand, I cautioned Mr. Lopez against assuming his HIV status would protect him from COVID-19, explaining that this type of study could not rule out other differences in PLWHs that could account for the findings (e.g. increased protective measures). Mr. Lopez understood this perfectly well, as he and his partner had been diligent about their protective precautions in part due to their HIV status.

Because Mr. Lopez was a trained social worker, he realized that one of his risk factors was modifiable in nature. Mr. Lopez inquired about the possibility of switching to a different ART regimen, based on the observation that his ART regimen was associated with the highest risk in the study. However, Mr. Lopez understood that confounders could be influencing this association, as his own ART regimen was influenced by insurance coverage. He joked that

if tenofovir disoproxil fumarate/emtricitabine was truly as protective as the study suggested, soon the entire world might be taking it prophylactically. He agreed that altering his ART regimen for the sake of COVID-19 protection was premature at the moment, especially since his current regimen had worked well for him.

Mr. Lopez rightfully questioned why we did not select a study with a Hispanic dataset to answer his question. We explained that there appeared to be no such studies at the moment as COVID-19 struck Latin America after it struck Asia and Europe. However, he agreed that Spain provided the most relatable context, agreeing with the reasons we provided, and jokingly adding that "well we both speak Spanish." We agreed to contact Mr. Lopez if a study with a Hispanic dataset was published or if further evidence arose to support a protective role for switching ART regimens.

In the meantime, Mr. Lopez intended on continuing his diligent precautions as being cautious gave him peace of mind during an otherwise uncertain period. He marveled at the rate of scientific progress pertaining to his question and appreciated that we had shared this information with him in real-time.

New Knowledge Related to Clinical Decision Science

Clinical Decision Science involves using intimate knowledge of our patients to improve the patient care experience and deliver better care. Patients are more than their problem lists or their medications. They each exist in a unique milieu of social, psychological, spiritual, and of course, medical factors. The more factors we can account for, the more we can individualize, and thus optimize, the care we deliver. In this case, Mr. Lopez's social circumstances were intricately tied to his anxiety and were thus put at the center of the medical decision-making process.

During the early months of the pandemic, physicians were expected to take poor quality evidence and use it to solve life-or-death scenarios.[19] Though the study selected for this report is of high quality and the study population was comparable to Mr. Lopez, comparing across continents and timeframes is not ideal. However, as the body of literature continues to evolve, so does the process of clinical decision science. As of July 2021, the search results have grown from 184 to 952 on PubMed, and indeed, some of these new studies have high external validity for Mr. Lopez. For example, a study in San Francisco, California, with a large subset of Hispanic participants found a higher COVID-19 positivity rate in PLWHs.[20] However, this difference was attributed to higher rates of homelessness within PLWHs, whereas Mr. Lopez is middle class. And so begins a new clinical decision process to find the best "up-to-date" evidence for Mr. Lopez.

Conflict Of Interest Statement

The author declares no conflicts of interest.

Acknowledgements

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