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Predictors of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Is There a Comprehensive Analysis?

To the Editor—We have read with interest by the article by Andrejko et al [1] on prediction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection following high-risk exposure. The authors found that nonpharmaceutical interventions (NPIs) and vaccine were useful in reducing individual risk of infection. While we applaud the authors making people aware of wearing a sanitary face mask and vaccination, there are several unmentioned factors that the authors should have considered before establishing the relevance.

Epidemiologic studies have confirmed that SARS-CoV-2 infection rates and genotype distributions vary between different regions and countries, and even among different regions of one country [2]. In the context of SARS-CoV-2 mutations since April 2020, the rapid spread of the D614G mutation is singular and has led to awareness that viruses with D614G have enhanced fitness [3]. As reported, P.1 and B.1.427/429 variants lead to increased transmissibility (2.2-fold and 1.2-fold increases, respectively) or to variants that evade prophylaxis [4, 5]. Unfortunately, the study by Andrejko et al does not consider this variable. To demonstrate the effectiveness of NPIs and vaccine, the authors would need to examine genotyping factors from these patients.

It was also surprising that the case group included in this study was selected from individuals who had received a positive molecular SARS-CoV-2 test result, not new cases. Different from incidence cases, features of prevalence cases may have changed [6], especially regarding behavior or life circumstances. This would imply that there might be a risk of Neyman bias arising from disease.

Furthermore, the authors considered that the diagnostic criteria were made based on the SARS-CoV-2 molecular test result. However, in fact, there may be false negatives associated with samples.

As previously reported, true coronavirus disease 2019 probably went undetected until several days into the disease course [7]. Inclusion criteria for this study should be stricter and should be combined with clinical, imaging, and pathological manifestations [8].

Although we contend that the evidence from Andrejko et al's study is insufficient to conclude predictors of SARS-CoV-2 infection of patients, we applaud the emphasis the authors place on the need to use NPIs in populations with limited vaccine access or ineligible to be vaccinated, and in response to changing epidemiologic conditions.

Notes

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Is Same-Day Antiretroviral Therapy Initiation Beneficial? Methodological Aspects when Comparing Observational and Randomized Studies

To the Editor—Labhardt et al have authored a timely article [1] that synthesizes evidence on the effectiveness of same-day antiretroviral therapy (ART) and emphasizes the importance of evaluating whether valid comparisons between studies are possible in light of the statistical analysis approaches employed. Furthermore, the article sheds light on the critical balance between using suitable methodology and reflecting on clinical practice and relevance, as recently discussed elsewhere [2].

We believe that the following considerations are important to contextualize their study:

1. Not all differences between observational studies and randomized trial results can be solely attributed to the methodological concerns raised by the authors.
2. In light of the first point, rigorously conducted observational studies should be considered as relevant evidence when drawing conclusions and giving recommendations.

The authors identified several potential issues that arose in observational studies

comparing patients offered ART on the same day of human immunodeficiency virus (HIV) diagnosis (or first healthcare contact) versus those who initiated treatment later ("rapid ART," "early ART," "late ART"). First, selection bias may occur if the study sample does not include all patients testing positive for HIV, but rather only those linked to HIV care or starting treatment. Second, the two comparison groups need to refer to the same patient population to avoid invalid comparisons. Third, immortal time bias can arise as those in the delayed treatment group have, by definition, to stay in care until treatment initiation.

As an example that those issues do not always apply or only partly apply, consider our observational study [3], which was included in Labhardt and colleagues' summary. First, while the primary analysis starts at the date of ART initiation (and the review correctly identifies that it excludes patients who were lost to follow-up between HIV diagnosis and ART initiation), a second analysis starts earlier, at the day of HIV care enrollment—with almost identical results. While one may argue that this is still not necessarily the day of the HIV-positive test, it is important to note that (1) for some patients enrolled, this is, in fact the first test; (2) the target population could be the group of patients who initiate contact with HIV care because it is only them in whom an intervention can be implemented and have an impact; (3) and even if the former point is debatable, it requires knowledge about the reasons why patients do not make contact with the healthcare system after receiving a HIV-positive test, to decide whether a selection bias exists, if it can be corrected or not, and in which direction it leads [4].

Second, our observational analyses mimic a randomized trial where treatment and control groups refer to the *same* patient population of *identical* sample size (that is, use the same denominators) and counterfactual risks under each treatment strategy, adjusted for measured confounders, are reported. This substantially reduces the risks of selection and confounding bias.

Last, immortal time bias may exist, but given that the comparison group comprises "early ART initiation" between 2 and 14 days after the respective time zero, this bias would likely be small, if it exists at all.

These examples demonstrate that additional reasons are needed to explain why observational studies report negative effects of same-day ART. These factors include the nature of trial settings where patients receive additional attention [5], psychological reasons related to treatment readiness [3], and the context of the study population [1], among others.

Moving forward, a systematic evaluation of healthcare behavior after a positive diagnosis could take the form of both qualitative and quantitative analyses, and results of trial and observational data can be synthesized with modern transportability and data fusion techniques [6].

Notes

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Is Higher Adherence Required for Women Using Oral Emtricitabine/Tenofovir Disoproxil Fumarate for Human Immunodeficiency Virus Preexposure Prophylaxis?

To the Editor—Anderson et al utilized tenofovir-diphosphate (TFV-DP) data from the oral preexposure prophylaxis (PrEP) arms in Human Immunodeficiency Virus (HIV) Prevention Trials Network (HPTN) 083 (men) and HPTN 084 (women) studies to estimate the adherence-response relationship for oral Emtricitabine/Tenofovir Disoproxil Fumarate (F-TDF) [1, 2, 3]. Their findings suggest that women may require higher adherence to oral PrEP to achieve the same level of protective efficacy as men, but these results should be interpreted with caution.

In their analyses, percentages of HIV risk reduction were calculated to estimate PrEP efficacy by using participants with the lowest rate of PrEP adherence, identified by drug concentrations below the limit of quantification (BLQ), as the reference group. However, women included in this reference group may not have had similar baseline HIV risks as the women who exhibited higher PrEP adherence. The HIV incidence in this reference group from HPTN 084 (2.9/100 person-years) was lower than women who were not receiving any PrEP in the VOICE (4.6/100 person-years) and the FEM-PrEP (5.0/100 person-years) studies [4, 5], indicating potential differences in