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CORRESPONDENCE

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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