TITLE: CARDIOVASCULAR DISEASE RISK IN LOW- AND MIDDLE-INCOME COUNTRIES: BETTER DATA FOR BETTER EVIDENCE

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To the Editor,

We thank Dr Martinez for their letter concerning our article “Risk of major adverse cardiovascular events with dolutegravir versus efavirenz-based antiretroviral therapy: emulated target trials using routine, de-identified data from South Africa”, and for their careful considerations regarding interpretation of our results.[1,2]

While our findings provide reassurance that in the short to medium term there is no large increased risk of major adverse cardiovascular events with dolutegravir, we agree that further data over longer follow up times and among older people living with HIV is required. These data are currently not available in low- and middle-income countries, where the majority of people taking dolutegravir live,[3] because dolutegravir has only been widely available for the past six years, and the average age of people living with HIV is generally younger than in high-income settings.[4] Over time, we plan to conduct these future analyses to determine cardiovascular risk over longer periods of dolutegravir exposure, and among older people, but comparing risk with other regimens will depend on whether there are subgroups of people living with HIV who remain on non-DTG regimens.

Accurately estimating risk of cardiovascular disease is challenging in many low- and middle-income country settings as there is a lack of large cohort studies with sufficient follow-up time, accurate and complete data on risk factors, and as Dr Martinez points out, difficulties in ascertaining outcomes. Leveraging programmatic HIV data systems, which have been historically better funded and developed for monitoring and evaluation, will be important. For analyses such as ours, which attempt to answer causal questions, more comprehensive data on a wider range of

potential confounders than typically recorded in HIV datasets are required to reduce the risk of bias.[5] Making the most of the rapid growth of electronic health records and/or administrative claims data in these settings will also be crucial. This will require investments and innovation to ensure datasets align with FAIR (Findable, Accessible, Interoperable and Reusable) principles,[6] maintain high standards of data security and ensure buy-in of people and communities whose data is being used for research. In particular, with the rapid growth of artificial intelligence in health, reassurances about data use with AI are imperative.[7]

To ensure generalisabiltiy and validity, studies using a range of data sources are likely to be needed, using a mix of public sector, private healthcare sector and research datasets. These data could then be used to provide important evidence that is difficult to ascertain through trials; for example, to monitor rare adverse events which require larger sample sizes than found in regulatory trials, to develop locally relevant cardiovascular risk prediction models to guide preventative treatment, and to ascertain outcomes from large scale, pragmatic trials of interventions to reduce cardiovascular disease. As Dr Martinez points out, preventing cardiovascular disease will require comprehensive assessment of cardiovascular risk beyond ART regimens, and development and evaluation of multiple interventions at scale. Better data systems will be fundamental to achieving these goals, and should be prioritized to help generate the evidence we need to reduce the impact of cardiovascular disease in people living with HIV.

DECLARATION OF INTERESTS

All other authors have no conflicts of interest to declare.

AUTHORSHIP CONTRIBUTIONS

JD wrote the first draft and all authors critically reviewed and edited the manuscript, and consented to final publication.

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