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EDITORIAL COMMENTARY

Cardiovascular diseases and exposure to integrase inhibitors: causal interpretation of treatment effect in observational studies

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In 2019, the publication of 2 randomized clinical trials conducted in sub-Saharan Africa (SSA) sent a potential safety signal by reporting greater weight gain with dolutegravir than with efavirenz, especially when used with tenofovir alafenamide and emtricitabine (TAF/FTC) [1,2]. The weight gain observed was likely exacerbated by the large proportion of people presenting with advanced HIV disease in those 2 trials [3], but results were confirmed in other settings and for other integrase strand transfer inhibitors (INSTI) [4]. The obvious concern raised by these results was relative to the potential consequences of the observed differences on the risk of metabolic disorders, hypertension and cardiovascular diseases.

The results of a large collaboration of HIV cohorts in Europe and Australia (RESPOND) came as a surprise, because if an association was reported between cumulative exposure to INSTI, whether naïve or preexposed to other antiretroviral treatment (ART), and the risk of cardiovascular diseases (myocardial infarction, stroke or invasive cardiovascular procedures), the largest increase was observed in the first 2 years of exposure, mainly in the first 6 months, with similar rates afterwards, in contradiction with the long process of atherosclerosis development [5]. Compared with those with no INSTI exposure, the adjusted incidence rate ratio of

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cardiovascular disease (CVD) was estimated as 1·85 [1·44–2·39] for >0 to 6 months of exposure; 1·19 [0·84–1·68] for >6 to 12 months of exposure; 1·46 [1·13–1·88] for >12 to 24 months of exposure and non-significant thereafter.

In this issue of Clinical Infectious Diseases, Surial et al reports the results of an emulated trial in the Swiss HIV cohort study trying to answer the clinical question of a potential increased risk of CVD in people with HIV infection (PWH) initiating with an INSTI-based regimen versus another antiretroviral regimen. They report an adjusted hazard ratio of 0.80 (95% confidence intervals 0.46– 1.39).

Can we reconcile the two studies? Were the differences associated with differences in the question asked in the two studies? The role of exposure to hormonal replacement therapy (HRT) on coronary heart disease (CHD) offers a paradigm to illustrate the issue of causal inference on the treatment effect in observational studies. Analyses in the Nurse Health Study (NHS) highlighted a potential protective effect of HRT on the risk of cardiovascular disease [6]. Later on, the WHI trial showed a deleterious effect of exposure to HRT on the risk of CHD [7]. However, Hernan et al [8], elegantly showed that the question asked in the NHS analysis was not clinically relevant to assess whether or not a woman should start or stop HRT. The analysis compared the risk between prevalent users and nonusers of HRT (current users vs. never users). However, when the analysis of the NHS study was emulating as closely as possible the WHI trial, comparing the CHD risk in women who initiate hormone therapy compared with women who do not, the results were no longer discordant [8]. The issue here was to compare risk between incident users and non-users of HRT [9].

In light of this example, can we understand the question that was answered in the two studies assessing the impact of INSTI exposure on the risk of CVD? In the Swiss study, it was whether initiating ART with an INSTI based regimen was associated with a higher risk of CVD than initiating ART with another regimen. They explicitly used the framework of the emulated trial [10]. The design was dependent of the date of availability of the first INSTI in Switzerland, limiting the risk of initial selection bias. Immortal time bias, associated with not correctly defining a time zero in both compared groups was clearly limited. In addition, the authors took into account potential selection bias associated with loss to follow-up. One may question some of the decisions, such as censoring INSTI initiator when stopping INSTI, as the impact of exposure may continue after cessation of exposure. It is still possible that there are remaining bias and confounders in the analysis, but their impact is likely small. Overall, the analyses, including the sensitivity analyses, are appropriately conceived to lead to a causal interpretation.

In the RESPOND analyses, the question answered was more complex, on the impact of cumulative exposure to INSTI, with less clear direct clinical interpretation, as it combined INSTI users in three different typical clinical situations in HIV care, that is treatment naïve participants, treatment experienced participants switching to an INSTI based regimen after virological failure and treatment experienced participants switching to an INSTI based regimen with controlled

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viral load. The inclusion criteria differed for the INSTI users, as PWH exposed to INSTI prior to 2012 were excluded from the analysis, while no such criterion was used for PWH unexposed to INSTI and this may be associated with selection bias. The analyses did not try to reproduce a clinical trial aiming to assess the risk of CVD when using INSTI versus not using it in the 3 clinical situations described above. Because of the various clinical situations, the control of selection and immortal time bias are uncertain. The role of the potential confounders may also differ in the 3 clinical situations and controlling then in a single analysis may be an unreachable goal. The fact that the study was combining cohorts of different countries, although useful because of the power it provides, makes it difficult to control for when was INSTI available and for which clinical situations, which may also lead to some selection bias. Finally, potential selection bias associated with loss to follow-up was not accounted for.

Similar ascertainment and validation procedures were used in the two studies. None of the 2 studies had enough power to differentiate the risk between INSTIs, while weight gain was smaller with elvitegravir than other INSTIs [4] or relative to protease inhibitors versus non-nucleoside reverse transcriptase inhibitors.

Observational studies are critical to analyze the potential risks associated with treatment exposure because of their size and duration, while clinical trials have usually shorter duration and smaller size. Their analyses must be built on recent methodological developments aiming at improving causal inference for observational data [11]. To gain additional insight on the risk of CVD in PWH using INSTI, it would be very important that RESPOND as well as other cohorts or collaborations of cohort analyze this issue using the emulated trial framework in well-defined HIV clinical care situations such as the SWISS HIV cohort investigators did for naïve PWH.

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