Risk estimation in HIV reveals our usual blind spots

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In *The Lancet HIV*, Steven K Grinspoon and colleagues[1] examine the performance of cardiovascular risk estimators in people living with HIV, leveraging data from the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE).[2] Grinspoon and colleagues[1] compare the observed rate of major adverse cardiovascular events in the placebo group of REPRIEVE with the predicted rate of events according to baseline cardiovascular risk, calculated using the pooled cohort equations for atherosclerotic cardiovascular disease (ASCVD) and the data-collection on adverse effects of anti-HIV drugs (D:A:D) risk scores. Perhaps unsurprisingly, the authors find that risk calculators perform best in White men from high-income countries. But how exactly do those findings matter in the post-REPRIEVE era?

The REPRIEVE study showed that, in people living with HIV over the age of 40 years and with no existing indication for lipid-lowering therapy, treatment with a moderate-intensity statin reduced the incidence of cardiovascular events.[2] Although the increased risk of cardiovascular disease associated with HIV has been known and studied for decades,[3,4] REPRIEVE is the first study to show that a pharmacological intervention can reduce the incidence of cardiovascular events in people living with HIV.

Cardiovascular risk calculation was not used to guide treatment in REPRIEVE (other than to exclude ineligible participants whose calculated risk made statin therapy recommended regardless of their HIV status). However, as included in the supplementary material of the original REPRIEVE publication,[2] the 5-year number needed to treat with a statin to prevent one event varied widely according to baseline risk. In people with a 10-year calculated baseline risk of 10% or more, the number needed to treat was estimated at 35, but increased to 199 for those with a baseline risk of less than 2·5%. Therefore, although the absolute benefit expected from statin therapy varies with baseline risk, pill burden, medication costs, and side-effects are expected to remain constant. This finding makes baseline risk estimation the main determinant of the risk–benefit ratio and a crucial piece of information for shared decision making.

Recognising this dynamic, all major HIV clinical care guidelines integrated the REPRIEVE results with statements that differ in strength according to calculated baseline risk, recommending statin therapy more strongly for people with a 10-year calculated risk greater than 5%.[5–7] In keeping with these recommendations, as a health-care provider, I routinely discuss with patients their calculated risk, and I tend to be much less persuasive for statin therapy with patients at low risk. In other words, I do rely on risk calculation to guide my practice, even if I know this was not the tested strategy in the clinical trial.

However, as Grinspoon and colleagues describe, risk calculators are biased. In high-income countries (the setting where I work), calculated risks underestimate the incidence of major cardiovascular events for women and for Black people. For other important subgroups such as Asian or Latino people, data were not available in this study because of the paucity of observed events—yet previous studies showed a similar underestimation of risk for south Asian people living in the USA.[8] Therefore, guiding my decision making process on risk calculation will result in undertreatment for groups that already notably experience underdiagnosis, undertreatment, and overburden of cardiovascular disease.[9,10]

In low-income and middle-income countries, which account for most of the burden of HIV-associated cardiovascular disease,[3] Grinspoon and colleagues report that risk calculators overpredicted the incidence of cardiovascular events. Unfortunately, data were too sparse to obtain estimates of calibration by regions or in subgroups. Here, risk-based treatment could unnecessarily burden already strained health-care systems and cause harm.

In essence, more than 40 years into the HIV pandemic, the REPRIEVE trial has finally delivered on an intervention to curb the increased cardiovascular risk for people living with HIV—and this breakthrough gives cause to celebrate. However, for those most affected by this pandemic, we lack the tools needed to implement the recommended risk-based shared decision making—ie, unbiased risk calculators. Meanwhile, implementing REPRIEVE for what it is—a positive randomised controlled trial—rather than relying on biased risk estimators, might be what needs to be done. Crucially, shared decision making will always rely on appropriate risk prediction for every person, and investigating the

performance of our risk calculators with an equity lens is essential if we are to, one day, cure our blind spots.

I declare no competing interests.

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