The Fragility Index in HIV/AIDS Trials

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Dear Editor:

The recent report by Wayant and colleagues on the fragility index¹ did not include the African randomized clinical trials on HIV and adult male circumcision.^{2–4} Analysis of these trials may provide insight into the interaction between *p* values and fragility in overpowered studies. The three trials shared nearly identical methodologies, the same sources of differential bias (lead-time bias, attrition bias, selection bias, and confirmation bias), and nearly identical results. All three trials were powered to demonstrate an absolute risk reduction of 1%. All three were discontinued prematurely following interim analyses that satisfied pre-established early termination criteria.

Of interest, the fragility index for the three trials were 4, 5, and 6 for the Ugandan,² Kenyan,³ and South African⁴ trials, respectively. This suggests that 4 to 6 patients with an event changed to a nonevent would nullify the study's statistical significance. The fragility quotient for the trials were 0.0008, 0.0018, and 0.0018, respectively, suggesting that changes in between 1 and 2 patients per 1000 would likewise nullify the study's statistical significance. In the three trials, 205 participants seroconverted, while 700 were lost to follow-up. The men who seroconverted were assumed to have acquired their HIV infections through heterosexual transmission although the investigators made no attempt to confirm the source of infection. Applying the Cochran "risk of bias" tool 2.0, these trials are at "high risk" for bias.

The lack of robustness exhibited by these trials raises both statistical and policy concerns. Despite their fragility, these overpowered studies were able to generate small enough *p* values to trigger early termination using standard statistical criteria.

This highlights an important caveat when interpreting the results of trials powered to demonstrate small absolute differences: it is difficult to differentiate true signal from noise and

to differentiate any treatment effect from the influence of differential bias.

On the policy level, millions of dollars have been expended to roll out male circumcision as a primary preventive for HIV in African men. This policy was hastily adopted by the World Health Organization primarily based on these fragile trials.⁵ The impact of the rollout is unknown, with some countries showing an increase in HIV incidence following the rollout.⁶

The fragility index and quotient need to be applied to the results of all randomized clinical trials as they can help identify the weaknesses of overpowered trials.

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Compliance with ethical standards:

Conflict of Interest: The author declares that he has no conflict of interest.

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