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INVITED COMMENTARY

From Evidence to Effectiveness: Implications of the Randomized Trial to Prevent Vascular Events in HIV Study for People With HIV in Low- and Middle-Income Settings

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The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study found a 35% reduction in major adverse cardiovascular events for people with human immunodeficiency virus who received daily pitavastatin. However, how this evidence will change practice is far from certain. Here, we outline evidence gaps and political and healthcare delivery challenges that will need to be addressed for REPRIEVE to offer public health benefits in low- and middle-income countries.

Keywords. HIV; cardiovascular disease; integrated care.

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study observed a 35% reduction in major adverse cardiovascular events for low-risk people with human immunodeficiency virus (HIV, PWH) who were randomized to receive daily pitavastatin versus placebo [1]. This remarkable trial raises both exciting and challenging questions for national and international policymakers, authors of clinical guidelines, donors, and implementers. However, how this evidence will change practice is far from certain. REPRIEVE draws attention to a much-overlooked issue: that use of well-proven preventive interventions for cardiovascular disease (CVD), such as statins, remains startlingly scarce in low- and middle-income countries (LMICs). For example, an analysis of data from 41 LMICs showed that fewer than 1 in 10 people at high risk of CVD were receiving statins for primary prevention, and only about 1 in 5 of those eligible were receiving them for secondary prevention [2].

For REPRIEVE to be transformed from an important scientific finding to public health benefit, it will be necessary to fill several HIV-specific evidence gaps and address key political and healthcare delivery challenges [3]. Without attention to these obstacles, the study may remain an impressive scientific undertaking whose potential benefits for PWH are unable to be fully realized.

First, we need greater clarity around which regions and individuals will benefit most from primary prevention. Though the trial was not powered to assess regional differences, event rates were lower in the control groups in both sub-Saharan Africa and Southeast Asia, making the absolute risk reduction relatively small in those areas. It will be important to learn whether such heterogeneity was driven by differences in baseline risk, ascertainment bias, or other factors. For example, fewer than 1 in 4 participants (22%) from sub-Saharan Africa in the REPRIEVE trial were obese, whereas approximately 40% of women in the dolutegravir arms of the ADVANCE study were obese by 96 weeks. Increasing obesity among PWH in LMICs may impact CVD risk and result in greater need for statins [4]. Consequently, data from both REPRIEVE and other studies in LMICs are needed to update regionally validated CVD risk equations specific to PWH. Previous efforts to create such risk equations for global populations not specific to PWH, such as the World Health Organization (WHO) 2019 CVD risk equations, have been pursued with moderate success but have been generally limited by insufficient data from the diverse populations for which the equations were intended [5]. However, the REPRIEVE study provides a uniquely large cohort of PWH across a diverse range of sites with ample follow-up to calibrate and validate these equations for regional use. It will be critical to incorporate both the benefits and well-described increased risk of diabetes found in REPRIEVE and other statin trials into these risk prediction models to determine

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who will most benefit from long-term statin use [6]. Systems of care for diagnosis and management of diabetes remain very weak in many LMICs. This may favor a higher CVD risk threshold for statin initiation and will increase the urgency of strengthening diabetes screening for PWH in these settings [7].

Even with these data, political barriers to widespread implementation of statins in the public sector persist. Major donors to HIV care programs, including the US President's Emergency Plan for AIDS Relief and the Global Fund to Fight HIV, TB, and Malaria, have historically been hesitant to become involved in the purchasing of medications for noncommunicable comorbidities. This hesitancy has been due, in part, to capped resources, funding unpredictability due to political infighting, and an already sizable mandate to provide HIV-specific prevention and treatment support. Furthermore, there have been concerns that a departure from the targeted focus on PWH may bleed into an unrealistic scope that includes reproductive health, CVD, cancer, undernutrition, and mental health services, among others. However, that door has cracked open, and the results of the REPRIEVE trial may force it to open even further. The 2023–2025 Global Fund application cycle established a mechanism for applying to fund the integration of services for comorbidities within HIV programs. This Prioritization Framework for Supporting Health and Longevity in PLHIV (people living with HIV) outlines the specific diagnostic and treatment services that the Global Fund considers eligible. Based on this, countries are asked to prioritize specific actions and build an "investment case" for those funding requests [8, 9]. Until now, statins have not been among the listed priorities. However, with these new data from REPRIEVE and their possible addition to HIV management guidelines, the clinical impact and cost-effectiveness of statins can be measured against potential interventions for other common comorbidities, including antihypertensive use or diabetes treatment. With such analyses, the investment case for statins may be clearer. Furthermore, if pitavastatin or other specific statins are recommended in future HIV care guidelines, it may motivate generic manufacturers to produce them at lower cost, a change that would also likely affect this investment case.

Finally, healthcare delivery for CVD prevention has often been stymied by the perceived need for wraparound services, such as lipid panels, and the use of complex CVD risk calculator assessments that are often considered cumbersome even in well-resourced primary care systems [10]. By contrast, data from REPRIEVE suggest that many populations will benefit irrespective of these panels. HIV care programs have relied heavily and to great success on task-shifted, guideline-focused care for a chronic incurable disease. Therefore, the human resource pieces are in place to convert this finding into practice if statins are made available and HIV care guidelines by the WHO and others are updated to recommend them for at-risk populations.

REPRIEVE stands to be a catalyst for CVD care optimization for PWH in LMICs, building on decades of both effective HIV advocacy and some of the world's best donor-supported global health programs. However, the question remains as to whether we will seize the opportunity that REPRIEVE offers to examine integrated HIV and CVD care in LMICs with the highest burden of HIV or whether we will look back 10 years from now on REPRIEVE as a call to action that ultimately went unanswered.

Notes

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