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Heart to heart: Progress in cardiovascular disease prevention for people living with HIV

Advances in the United States and in other high-resource settings have led to longer life expectancy for individuals living with human immunodeficiency virus (HIV) infection and more opportunities to investigate long-term complications of the infection and related treatments.[1] Globally, acquired immunodeficiency disease–related illnesses and bacterial infections remain the leading causes of hospital admissions for patients with HIV.[2] Yet in the United States and other resource-rich nations, simplified medication regimens, including combination pills and injectable therapies, have changed the landscape of inquiry to include cardiovascular diseases.[3]

See related article, page 159

HISTORICAL CONTEXT

The well-considered article on cardiovascular disease in patients living with HIV by Ghandakly and colleagues[4] in this issue of the *Journal* is reminiscent of a time when structured treatment interruptions were considered an acceptable alternative to patients consistently taking their daily medications. The era saw patients and clinicians eager to press pause on the administration of medications with considerable toxicity and wishing to lessen the burden of what was then referred to as "pill fatigue." Combination therapies formulated into a single tablet were rare, leading to complexity in daily medication administration. Many patients took matters into their own hands and stopped medications, earnestly believing that the cure was worse than the disease. This was before the widespread uptake of the integrase strand transfer inhibitor class of antiretrovirals (eg, raltegravir, bictegravir, dolutegravir), which were highly effective and well tolerated, and novel nucleoside reverse transcriptase inhibitors (eg, tenofovir disoproxil, tenofovir alafenamide, emtricitabine) and nonnucleoside reverse transcriptase inhibitors (eg, doravirine, rilpivirine), which were easier to take, had fewer toxic effects, and were more likely to be effective against circulating resistant strains of virus. At the time, a few medications with limited use were becoming available, including injectable enfuvirtide and the C-C chemokine receptor 5 antagonist maraviroc.

However, many patients were relegated to using the medications discussed in the authors' article,[4] including lopinavir, efavirenz, and ritonavir, with their known interactions with many of the then-commonly used statins (lovastatin, simvastatin), and the metabolically damaging nucleoside reverse transcriptase inhibitors zidovudine, didanosine, and stavudine. When patients approached clinicians informing them of their drug holiday, there was no evidence to guide discussions about the risks and benefits of that decision. It was extremely difficult to choose between the risks of treatment and the risks associated with uncontrolled viremia.

A CHANGING LANDSCAPE FOR HIV TREATMENT

The paradigm-shifting 2006 study on CD4-count–guided interruption of antiviral treatment fundamentally changed the landscape of HIV treatment.[5] Episodic use of antiretrovirals in 1 arm of the study allowed for treatment interruption until CD4 lymphocyte counts decreased to less than 250 cells/mm^3. Highly active antiretroviral therapy was then resumed and maintained until CD4 counts surpassed 350 cells/mm^3.

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Rationales at that time for treatment interruptions included reduction in pill fatigue, medication-related toxicity (significant at the time), and cost reduction. Results of this group were then compared with a group of patients continuing medications without interruption. The study found that, after approximately 16 months, there was an increase in death from opportunistic infection in the treatment-interruption group, as well as an increase in death from any cause, including major cardiovascular, renal, and hepatic disease, with death from cardiovascular disease being more common than renal or hepatic causes. These findings suggested that an increase in immunodeficiency and related inflammation was more harmful to patients than the effects of highly active retroviral therapy.[5]

Subsequent pivotal work included proof that starting antiretroviral therapy early was superior to delayed initiation.[6] In the following years, several studies, including those recounted by the authors, were developed to better understand the effects of inflammation on cardiovascular and other systems.

STATIN THERAPY AND HIV

Ongoing investigations have informed the guidelines from the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents with HIV,[7] which have been developed in collaboration with representatives from the American College of Cardiology, American Heart Association, and the HIV Medicine Association. The guidelines provide recommendations on the use of statin therapy in primary prevention of atherosclerotic cardiovascular disease in people with HIV receiving care in the United States.[7] Key among them are the following:

- For persons age 40 to 75, when 10-year atherosclerotic cardiovascular disease risk estimates exceed 5%, starting a statin is recommended, given that HIV is a risk intensifier and available risk calculators underestimate associated cardiovascular risk
- Treatment in this age group is recommended with pitavastatin, atorvastatin, or rosuvastatin
- For those under age 40, data are insufficient to recommend for or against statin therapy.

There are drug-drug interactions among some of the recommended statins (eg, atorvastatin) and integrase inhibitors and protease inhibitors, and in these instances, dose adjustments or substitutions are recommended.[7] While REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV)[8] showed statins like pitavastatin reduced the risk of major adverse cardiovascular events in people living with HIV without preexisting heart disease, not all individuals tolerate statin medications. In addition to dietary and lifestyle modifications, nonstatin options for lipid lowering include fibrates, ezetimibe, niacin, omega-3 fatty acids, and proprotein convertase subtilisin/kexin (PCSK) 9 inhibitors. However, with the exception of PCSK-9 inhibitors, nonstatin therapies have not been shown to reduce major clinical events.[9]

After starting antiretroviral therapy, many patients experience weight gain, which may increase cardiovascular disease risk. Integrase inhibitors, in particular, can increase body mass index.[10] Patients who already live with metabolic syndrome and obesity may see a further increase in cardiovascular disease risk with weight gain.[11]

SOCIAL DETERMINANTS OF HEALTH, HIV, AND HEART DISEASE

Social determinants of health play a crucial role in influencing heart disease outcomes among marginalized groups, including transgender, African American, and Black, Indigenous, and People of Color populations. These determinants, such as socioeconomic status, access to healthcare, and systemic discrimination, contribute to disparities in obesity, tobacco use, and HIV, all of which are risk factors for heart disease. Higher risk for heart disease has been described in studies on lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ+) youth,[12] African American sexual minority women,[13] and transgender beneficiaries of Medicare.[14] Higher rates of tobacco use have been found in communities with intersectional identities, such as those who are Puerto Rican and LGBTQ+.[15]

SUMMARY

Emerging research highlights the interconnectedness between HIV and heart disease risk, underscoring the role of changing science and social determinants of health. People living with HIV face higher rates of cardiovascular issues due to chronic inflammation and metabolic changes. However, social determinants of health, as noted above, exacerbate these risks, particularly in individuals from under-resourced communities. Factors like limited access to preventive care and the stress of social stigma can hinder even the most effective treatments available for both HIV and heart health. Successful interventions will be those based in medical science and equity, thereby improving outcomes and reducing the burden of heart disease in those living with HIV.

DISCLOSURES

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