centers that have put roadblocks in the path of those wishing to serve need to rethink their priorities. They should be making it easier, not harder, for altruistic physicians, nurses, and other health care providers to help care for the sick and control the Ebola epidemic in West Africa. Our medical centers have immense resources and expertise; the countries wracked by Ebola have almost none. Something is wrong when some of the greatest health care centers in the world are not helping in the fight against this disastrously dangerous threat to human health. We ask the leaders of every medical center in the country to figure out how to make it possible for their staff, and even qualified trainees, to help on the ground in West Africa. And once the leaders have decided what to do, they need to tell their risk managers and their lawyers to make it work, rather than make decisions based on the worst-case scenarios and risks to their reputation, image, and market share painted by corporate advisors and legal staff. If in a year's time this epidemic has not been controlled, we will have only ourselves to blame.

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Preventing HIV in Women — Still Trying to Find Their VOICE

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The development and widespread use of potent antiretroviral therapy has transformed HIV infection from a near-certain death sentence to a chronic manageable condition, whereby patients who adhere fully to their medication regimen can have an almost normal life span.[1] Moreover, those who take their medications as prescribed generally do not transmit the virus to others.[2] If we could identify all persons infected with HIV, get them into care, successfully initiate antiretroviral therapy, and achieve and sustain suppression of the virus to undetectable levels, all patients would in theory have a near-normal life span and not transmit the virus to others — and the epidemic would end.[3] Despite the success of antiretroviral therapy in dramatically prolonging life expectancy, we have not seen much progress in preventing new infections. In most areas around the world, including the United States, the number of new persons infected last year was roughly the same as in years before.[4] Most experts indicate that "treatment as prevention" is an important approach, but we cannot treat our way out of the epidemic. Rather, multiple approaches to prevention are required.

One such approach is the use of preexposure prophylaxis, whereby antiretroviral agents are used, either through systemic administration or as topical microbicides such as vaginal gels. Well-conducted, randomized studies have had mixed results. In a study conducted in resource-rich countries, involving men who have sex with men, preexposure prophylaxis reduced transmission by 44% overall and by 92% among those who took their medications regularly.[5] In contrast, in a study conducted among women in sub-Saharan Africa (the Preexposure Prophylaxis Trial for HIV Prevention among African Women [FEM-PrEP]), the use of preexposure prophylaxis was ineffective, probably because of low levels of adherence to the medication regimen.[6] The use of vaginal gels as microbicides has also had mixed efficacy outcomes.

In this issue of the *Journal*, Marrazzo and colleagues report the findings of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial, a placebo-controlled, randomized study of preexposure prophylaxis that was provided as oral antiretroviral therapy or as a vaginal gel to women living in sub-Saharan Africa.[7] The study assessed five treatment groups (oral tenofovir alone, oral tenofovir with emtricitabine,

oral placebo, vaginal tenofovir gel, and vaginal placebo gel). Although it was planned for a 36-month maximum follow-up, the data and safety monitoring board recommended terminating treatment in the oral tenofovir and tenofovir gel study groups early, owing to futility. The oral tenofovir–emtricitabine group continued to completion, but the treatment showed no efficacy. Therefore, the study yielded results similar to those of the FEM-PrEP trial. The likely reason for the lack of efficacy can be gleaned from the pharmacokinetic data: approximately 30% of plasma samples in the VOICE study had detectable drug at the pharmacokinetic time points, which indicates that the majority of women in the trial were not taking their assigned medications regularly.

It is well established that medications don't work if they are not taken, which probably explains why no difference in efficacy was observed between the active-drug and placebo groups. On closer inspection, however, the striking finding in the VOICE trial is the disconnect between reported adherence and actual adherence to the regimen. Although approximately 30% of plasma samples collected from the women had detectable drug, 90% and 88% of the women indicated that they had not missed a dose when asked by either a study interviewer or a computerized questionnaire, respectively. More striking, the medication reconciliation, in which returned unused tablets were counted to determine missed doses, revealed that 86% of medication was "taken." This means that a large number of participants actively removed unused medications from their allotment before returning to the study site in order to create the appearance of compliance with the protocol.

The question that emerges is this: why did the participants go to such lengths to create the appearance that they were taking medications when they were not? To the study team's credit, they investigated this question through a series of qualitative interviews with VOICE participants after the study results became known.[8,9] In a recently published report, van der Straten and colleagues identified several factors associated with poor adherence to the protocol.[8] A common theme stemmed from fear of taking the medicine, because of concern either about adverse effects or about being falsely labeled as having HIV infection. The drugs used in the VOICE study are well known as anti-HIV agents. Despite detailed education provided by the study team, many of the participants feared that such potent treatment must have serious toxicity when used in uninfected people. In addition, because it is common knowledge within the community that antiretroviral therapy is associated with HIV infection, many women in the study were afraid that if they were seen taking HIV medications, they would be labeled as being infected. As a result, many of the women concealed their use of the products or hid the products out of a fear of stigma. The strong presence of stigma was identified among male partners and community members interviewed as part of the study, validating the concerns among the VOICE participants that their taking HIV pills would lead to gossip and rumor in the community, workplace, and household. In further work, the researchers specifically studied participants with low levels of drug in the blood versus those with high levels.[9] The group with low levels had significantly more fear of the drug side effects and had less trust in the clinic and its staff. In contrast, those with high drug levels developed strategies to overcome concerns about stigma, valued advice from nurses, and were more likely to believe that the products worked.[9]

At first glance, the VOICE study appears to indicate that preexposure prophylaxis doesn't work in women in Africa and that we should move on to explore other approaches to the prevention of HIV transmission in high-risk settings. On further review, the study indicates that much more work is needed, not so much in the realm of understanding the biologic basis of preexposure prophylaxis as a preventive treatment but rather in the realm of understanding behavioral barriers in the setting of strong social stigma.

The "Declaration of Sentiments," penned by Elizabeth Cady Stanton at the Women's Rights Convention in Seneca Falls, New York, in 1848, starts with the following statement: "When, in the course of human events, it becomes necessary for one portion of the family of man to assume among the people of the earth a position different from that which they have hitherto occupied . . . ."[10] This declaration represented the formal beginning of the women's rights movement in the United States. As in the fight for

women to find their voice in the United States against strong social stigma so long ago, victory in the battle to prevent HIV will require the women at risk for infection to find "a position different from that which they have hitherto occupied" in order for them to find their VOICE.

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Potential Relief for Refractory Angina

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Physicians who practice primarily in outpatient settings are faced with a large and growing population of patients with chronic, stable, but refractory angina,[1,2] as a consequence of an aging population and our ability to prolong the lives of patients with coronary disease. The mortality among patients with refractory angina is surprisingly low,[3] but the effect of persistent, recurrent, and frequent symptoms on quality of life is substantial and emphasizes the need for alternative therapeutic options.

The newest drug in this therapeutic area, ivabradine, which is approved in Europe, has been shown to reduce angina and improve exercise time in patients with chronic coronary disease. However, its role has been called into question on the basis of the results of the Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial.[4] SIGNIFY showed that ivabradine may be harmful for patients with activity-limiting angina with regard to cardiovascular death and myocardial infarction. This finding raises the question of whether and when new treatments for relieving angina should be evaluated in clinical trials with hard outcomes.

Although coronary-artery bypass grafting and percutaneous coronary intervention have been well established as therapies for patients with angina, there is also a long history of studies of other interventional procedures for such patients, including internal mammary-artery implants (Vineberg operation), intrapericardial talcum powder or asbestos, internal mammary-artery ligation, omentopexy, transmyocardial laser revascularization, gene therapy, and more recently, cell therapy.[1] For each of these, initial promising findings have not been confirmed in larger randomized, controlled trials. Another approach, manipulation of coronary venous return to improve perfusion of ischemic myocardium, has been studied with a variety of methods including partial or complete occlusion of the coronary sinus, in a fixed or dynamic fashion, with or without retroperfusion, and in a variety of preclinical and clinical settings. Although there is some experimental evidence to suggest that obstructing the coronary sinus may protect against myocardial ischemia,[5] this approach