clusion of women in the design of the DISCOVER trial and the gender-specific approval of F/TAF for HIV prevention rests on all of us. Clinical trial design requires diverse voices and intentional inclusion criteria. It is up to human-subjects committees to maintain vigilant oversight of study protocols with these FDA standards in mind, regardless of whether the studies in question are industry-sponsored. And when the FDA is presented with data that exclude half the world's population, it can use the tools at its disposal to address the violation.

The current approval of F/TAF that excludes "those who have receptive vaginal sex" establishes a two-tier system in which men may be prescribed the medication with insurance approval, whereas women may receive it only off-label, in the absence of data, and without insurance coverage. The path forward should be clear: a well-designed, rapidly enrolled, robust clinical trial of efficacy in cisgender women is urgently needed.

In granting approval for the drug's expanded indication, the FDA obligated the manufacturer to study the drug in cisgender women. In response, the company plans to undertake a limited study in 1500 women in sub-Saharan Africa focused on safety and noninferiority that is scheduled to begin enrollment by 2020. In short, a study involving women that was deemed infeasible in 2016 is finally being considered. The backlash from the scientific, global, and advocacy communities against the FDA's limited approval of F/TAF suggests that they expected and deserved better; they are all watching for remediation. The responsibility now lies with the FDA and the scientific community to enforce the rapid completion and reporting of this study in women and, in the process, to work to revise the current regulations and drug-approval process to truly require equity and inclusion.

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Female Genital Schistosomiasis

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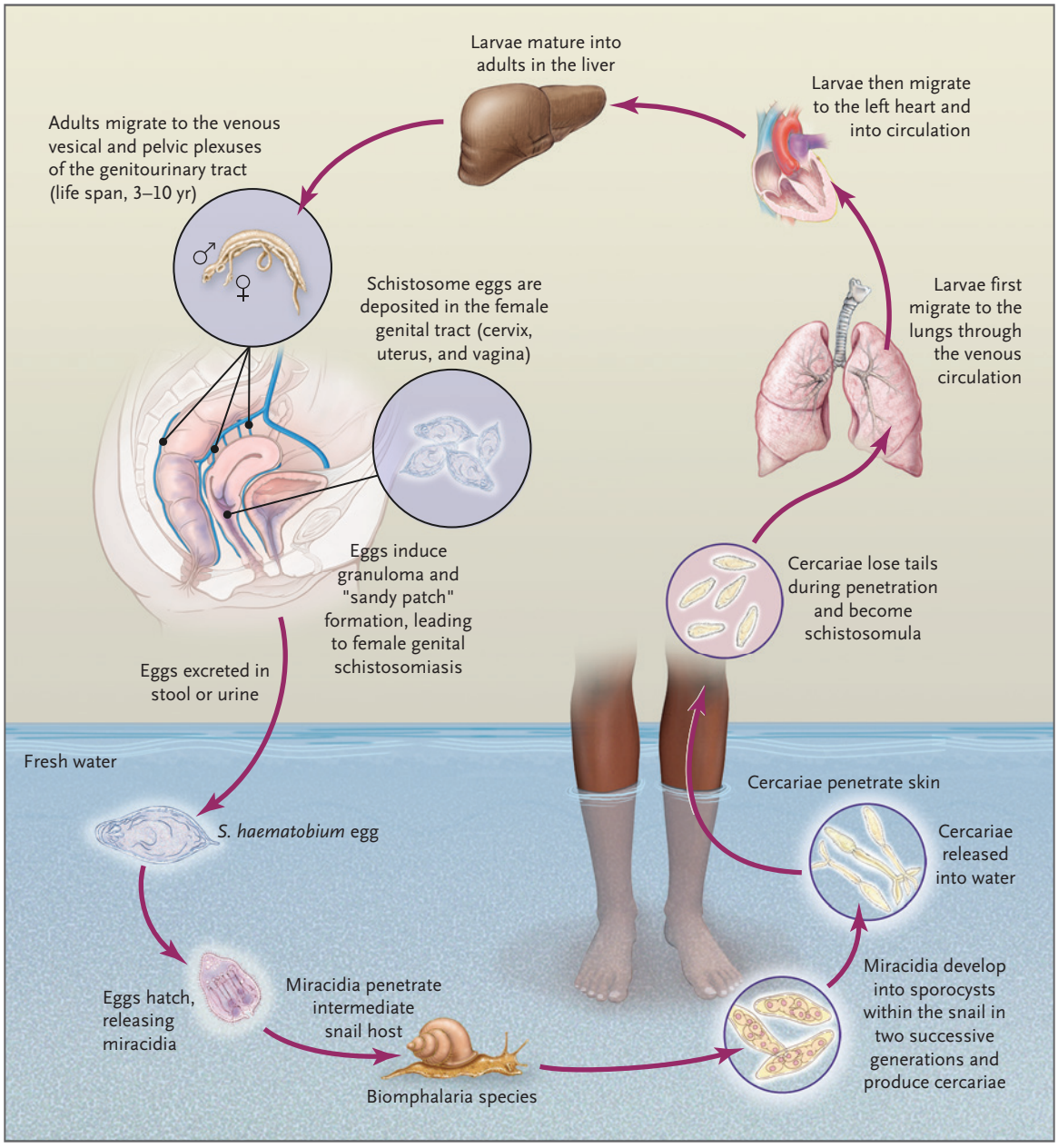
Promotion of universal health coverage, in line with the United Nations' Sustainable Development Goals, has focused global attention on sexual and reproductive health and rights and their impact on the overall health, safety, and equality of women, especially those who live in extreme poverty. Today, hundreds of millions of African women lack access to adequate sexual and reproductive health services, including HIV/AIDS prevention and cervical cancer prevention. But there are other important threats to sexual and reproductive health, such as female genital schistosomiasis (FGS).

Schistosomiasis affects at least 120 million people on the African continent, approximately two thirds of whom have the urinary tract form caused by *Schistosoma haematobium*. Schistosomiasis is acquired through contact with fresh water contaminated with larval helminths, known as cercariae, which are produced by intermediate snail hosts of the parasite. For centuries, chronic *S. haematobium* infection in Africa has caused hematuria and serious urinary tract sequelae, including hydronephrosis, renal failure, and bladder cancer due to the presence of schistosome eggs in the bladder and a vigorous inflammatory response in the human host. Beginning in the mid-20th century, clinical reports of schistosomiasis of the cervix began to emerge,[1] followed by full descriptions of FGS based on colposcopic examination and microscopy of geni-



Transmission Cycle of Female Genital Schistosomiasis.

tal biopsies that revealed *S. haematobium* eggs in the cervix, vagina, and vulva.[2] Girls and women with FGS present with genital sandy patches ("rubbery papules" or yellow sandy areas composed of schistosome eggs and host eosinophilic inflammatory tissue) that cause contact and postcoital bleeding, genital itch, abnormal discharge, stress incontinence, and dyspareunia, leading to infertility in the longer term.[2,3]

Today, FGS is recognized as a common complication of *S. haematobium* parasitism, occurring in approximately half (33 to 75%) of infected females,[3] or roughly 40 million girls and women. It is thus one of the most common gynecologic conditions in Africa. The problem is exacerbated by social stigma, both because community health workers often confuse FGS with sexually transmitted infections and because FGS can cause destruction of the hymen, lead-

ing to accusations of sexual promiscuity.[4] FGS also often leads to marital discord and depression.

Beyond having adverse gynecologic, mental health, and social consequences, FGS may also be a cofactor in the acquisition of HIV, with two large case–control studies conducted in Zimbabwe (527 participants) and Tanzania (345) finding odds ratios for HIV infection of 2.9 and 3.9, respectively, in women with schistosomiasis as compared with schistosomiasis-free women. A further analysis revealed that "each *S. haematobium* infection per 100 individuals was associated with a 2.9% (95% CI: 0.2–5.8%) increase in HIV prevalence."[3] There are also possible links between FGS and both human papillomavirus (HPV) infection and cervical cancer,[5] but additional study is required.

Praziquantel is a highly effective antiparasitic drug used for the treatment of schistosomiasis. Under the auspices of the World Health Organization (and assisted by drug donations from Merck), approximately 75 million school-aged children — representing approximately 60% of those at risk for this infection in Africa — received preventive treatment with praziquantel in 2018. Moreover, a new pediatric suspension formulation of praziquantel has become available for use in preschool-aged children. Administered early in the life of African girls and continued throughout adolescence, annual preventive treatment with praziquantel has the potential to prevent the onset of the genital lesions linked to FGS.

Many experts on neglected tropical diseases believe that praziquantel administration for the prevention of potentially infective FGS lesions should be added as a third major intervention to promote sexual and reproductive health among African women, alongside vaccination against HPV-associated cervical cancer and antiretroviral therapy or preexposure prophylaxis (PrEP) for HIV/AIDS. FGS represents a key component of sexual and reproductive health care over the life span of African women (see illustration).

We believe that priority should be placed on optimizing the incorporation of praziquantel preventive treatment into ongoing programs for HIV/AIDS and cervical cancer prevention. It is vital to create national pilot programs in a country where FGS is endemic — and which already receive support from the U.S. President's Emergency Plan for AIDS Relief or the Global Fund to Fight AIDS, Tuberculosis, and Malaria — such as Malawi, Mozambique, South Africa (KwaZulu-Natal), Tanzania, and Zimbabwe. Such programs would offer opportunities to address key operational research questions related to the field diagnosis of FGS and the use of rapid diagnostic tests, and ultimately the integration of both diagnostic and preventive treatment programs with those aimed at the prevention of HIV/AIDS and HPV and cervical cancer.

There are further opportunities to assess the use of praziquantel, including the use of suspension formulations in preschool-aged children and treatment programs for young women with FGS that simultaneously evaluate antiinflammatory agents. It is also essential to train health care personnel in order to destigmatize FGS, while strengthening community health systems to integrate preventive treatment programs with other sexual and reproductive health initiatives.

A package of sexual and reproductive health interventions would address the three overlapping health challenges. Lack of access to praziquantel, the social stigma associated with FGS, and the failure to consider FGS as a central element of sexual and reproductive health have emerged as important social justice issues for the girls and women of Africa. We now have the tools and technical ability to prevent FGS, HIV/AIDS, and cervical cancer simultaneously.

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