EDITORIAL COMMENTARY

Weighing the Risk of Drug Resistance With the Benefits of HIV Preexposure Prophylaxis

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(See the major article by Lehman et al on pages 1211–8.)

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The threat of drug resistance deserves careful attention from clinicians and public health officials advocating antiretroviral use as a way to control the human immunodeficiency virus (HIV) epidemic. Such antiretroviral use includes early treatment and preexposure prophylaxis (PrEP) and postexposure prophylaxis (PEP). Concerns about drug resistance were raised before rolling out widespread antiretroviral therapy in Africa, based on the assumption that adherence to therapy would be poor and drug resistance would become prevalent. Defying expectations, the benefits of antiretroviral therapy for improving health, averting death, and preventing transmission were subsequently proven to outweigh the risks of drug resistance, and adherence to therapy in African populations is often outstanding [1].

Fear of drug resistance is now raised as we consider rolling out PrEP. Daily oral PrEP using emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or TDF alone is safe and effective for preventing HIV acquisition [2–5] in sexually active adults. Adherence is essential for effectiveness [2, 6, 7]. Such regimens do not fully suppress systemic HIV infection, so starting PrEP in people already infected with HIV may lead to drug resistance [2–4]. Recommendations for PrEP emphasize the importance of HIV testing prior to starting or restarting PrEP.

In this issue of *The Journal of Infectious Diseases*, Lehman et al report new information about the risk of antiretroviral resistance from the Partners PrEP Study of men and women in Africa who are partnered with a person living with HIV [8]. (The usual term, "discordant couple," obscures their commitment, courage, and cooperation.) The Partners PrEP Study is exceptional among randomized trials in that the levels of adherence were very high, with 71% of people randomly assigned to the active arm of the study having drug concentrations in plasma indicating consistent use [9]. Such higher adherence yielded higher PrEP effectiveness and makes this study ideal for evaluating the risk of drug resistance when PrEP fails to prevent HIV infection.

The article confirms that drug resistance primarily occurs if systemic HIV infection is present when PrEP is started. This occurred in trials if people were enrolled during the HIV RNA–positive/HIV antibody–negative period of acute infection. Furthermore, drug resistance was primarily to FTC, which leaves multiple options for successful combination antiretroviral therapy. Importantly, the risk of drug resistance tended to be higher among people receiving FTC/TDF, compared with those receiving TDF alone (20% vs 5%; $P = .1$); this finding is consistent with nonhuman primate research on PrEP [10] and demonstrates how HIV develops resistance to the drug in the regimen with the lowest barrier to resistance. In HIV treatment, virological failure with resistance to only 1 drug in the multidrug regimen is the usual pattern, although resistance to other drugs appears later if a failing regimen is continued. This can occur with PrEP as well, as demonstrated by a trial participant who received FTC/TDF PrEP for 7 months before infection was detected by an oral fluid assay (seroconversion was detected after 1 month of PrEP, using a blood test conducted retrospectively) [4]. The lesson for PrEP drug development is that increasing the number of drugs in the regimen may increase, rather than decrease, the risk of drug resistance, especially if the added drug strongly selects for a single mutation having minimal effects on viral replication capacity.

However, the risk of FTC resistance must be weighed with any added efficacy afforded by adding FTC to TDF for PrEP. In the Partners PrEP Study, the relative

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protection of receiving TDF alone vs FTC/TDF was 0.67 (95% confidence interval, .39–1.17) [11], a difference that would be clinically important and is consistent with findings from nonhuman primate studies. Additional evidence that TDF may fail more frequently when used without FTC is the higher rate of drug detection among TDF PrEP seroconverters (19 of 39 [49%]), compared with FTC/TDF PrEP seroconverters (7 of 25 [28%]). These rates of drug detection among heterosexual men and women seroconverting while receiving PrEP are higher than were observed among rectally exposed men who have sex with men and transgender women who seroconverted after receiving FTC/TDF PrEP (9%) [12], which helps explain why drug resistance during emergent infection while receiving PrEP was not observed in these groups [13]; rectally exposed people were not infected if substantial drug concentrations were present [14], leaving little opportunity for drug resistance to emerge. FTC may be particularly important for blocking infection after viral exposure to vaginal or penile tissues, because of its higher bioavailability and penetration beyond the intestinal tract compared with TDF [15].

Drug resistance due to PrEP in 5 persons in the Partners PrEP Study should be weighed against the prevention of an estimated 123 infections over the entire course of the study. As such, there were 25 HIV infections prevented for every drug-resistant infection caused. Such infections, had they occurred, could have caused secondary infections and substantial morbidity and mortality and would require lifelong therapy. Treatment of HIV infection has improved dramatically over the past 27 years, with increasingly safe and convenient regimens [16], although virological failure still occurs among 5%–24% of treated people per year [17]. The cumulative risk of drug resistance from PrEP services could be much lower than that associated with treating infections that would otherwise occur, as was predicted by mathematical models [18]: preventing HIV infection also prevents drug resistance.

Other benefits of PrEP are important. Coupled with regular monitoring, PrEP affords detection of breakthrough HIV-1 infection in a few weeks to months after infection, while diagnosis is frequently delayed for years among people who are not receiving prevention services. Access to PrEP and PEP may motivate people recently or frequently exposed to HIV to seek services. As such, population engagement motivated by PrEP access also creates opportunities for earlier diagnosis and treatment, preventing transmission and disease while minimizing viral reservoir size and enabling more timely services for partners, which should include PEP, PrEP, and early treatment.

Findings from trials may not necessarily apply to less controlled and monitored settings such as clinical practice. The Partners PrEP Study, like other trials, conducted monthly HIV testing, which minimized the duration of PrEP exposure after infection. Such frequent monitoring is not feasible in practice, and recommendations are to test for HIV every 3 months [19]. Nondaily use of PrEP or restarting PrEP after a lapse in use may occur in clinical practice, although this was not recommended in oral PrEP trials published so far. New information about the effectiveness and drug resistance risk associated with nondaily PrEP is expected from the ongoing ANRS-sponsored IPERGAY trial.

Lehman et al also provide evidence that more-sensitive assays for HIV drug resistance are warranted. Standard genotypic and phenotypic assays miss low-frequency mutations within a viral population that may affect virological response to therapy. Deep sequencing can detect such variants, although the clinical utility of this technology awaits clearly defined cutoff frequencies for individual drug resistance mutations. Lehman et al report that viral mutations were associated with the treatment arms when they occurred in >1% of the virus population, providing additional support for this being a clinically significant cutoff associated with drug selection, rather than naturally occurring polymorphism. Treatment responses were not evaluated, although they are expected to be excellent if therapy is guided by resistance testing.

There are ways to minimize the risk of drug resistance during PrEP use. Highly sensitive viral tests that detect RNA or antigen can rule out acute infection prior to starting PrEP. Point-of-care rapid RNA tests are available for research use, and feasible regulatory pathways leading to routine clinical use are urgently needed. If testing for HIV RNA or antigen is not available or not affordable, deferring PrEP in people with an acute viral syndrome will help, as the majority of acute HIV infections are symptomatic. Inviting PrEP users to inform providers about their stopping and starting of PrEP is important and provides an opportunity to arrange timely HIV testing. Home testing may make test access easier.

Some practices used to minimize the risk of HIV resistance are ill advised: attempting to restrict access to PrEP is expected to foster intermittent dosing, hoarding of medications, sharing among friends and partners, and other unsupervised use. Fomenting fear of drug resistance is also misguided if it distracts us from fear of HIV itself, by far the greater threat to human health.

Notes

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