Tenofovir Resistance Is Common in Those Failing HIV Meds

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Among people who fail HIV treatment regimens, resistance to tenofovir is common, ranging between 20 and 57 percent among populations studied, and the incidence of such acquired resistance is likely increasing. Publishing their findings in The Lancet, researchers examined data on 1,926 HIV-positive people from 36 countries who experienced treatment failure between 1998 and 2015. The data was drawn from randomized controlled trials and a meta-analysis.

“Tenofovir is a critical part of our armamentarium against HIV, so it is extremely concerning to see such a high level of resistance to this drug,” the study’s lead author, Dr. Ravindra Gupta, an immunologist at the University College London, said in a press release. “It is a very potent drug with few side effects, and there aren’t any good alternatives that can be deployed using a public health approach. Tenofovir is used not only to treat HIV but also to prevent it in high-risk groups, so we urgently need to do more to combat the problem of emerging resistance.”

According to another of the study’s authors, Robert W. Shafer, MD, an infectious disease specialist at the Stanford University School of Medicine, “It’s likely that tenofovir resistance is increasing simply because an expanding proportion of the world’s infected population is being treated [for the virus], and because tenofovir is replacing older, more toxic drugs such as d4T [Zerit (stavudine)] and AZT [Retrovir (zidovudine)].”

Tenofovir is one of the two drugs in the tablet Truvada (tenofovir disoproxil fumarate/emtricitabine), which is used as pre-exposure prophylaxis (PrEP) against HIV among HIV-negative people and which is on course to worldwide approval. (For information on the relevance of the new study’s findings to the effectiveness of PrEP, see the latter half of the article.)

Tenofovir now comes in two forms: tenofovir disoproxil fumarate (TDF), and the updated version of the drug that is safer to the bones and kidneys, tenofovir alafenamide (TAF). In addition to Truvada, tenofovir is included in the combination tablets Atripla (efavirenz/TDF/emtricitabine), Complera (rilpivirine/TDF/emtricitabine), Stribild (elvitegravir/cobicistat/emtricitabine/TDF) and Genvoya (elvitegravir/cobicistat/emtricitabine/TAF). According to Shafer, TAF does not offer benefits over TDF when it comes to tenofovir resistance.

There are two types of drug resistance: acquired, in which someone develops resistance while on ARVs; and transmitted, in which drug-resistant HIV is passed from one person to another. Because

this new study looked only at individuals who failed an antiretroviral (ARV) regimen, its findings do not provide an estimate of how common acquired tenofovir resistance is overall, nor does the paper estimate the proportion of transmitted HIV that is resistant to tenofovir. Additionally, the groups of people included in the analysis are not necessarily representative of regional populations of those who fail treatment.

The researchers did, however, estimate that 7.5 to 17.5 percent of sub-Saharan Africans taking tenofovir along with Emtriva (emtricitabine) or Epivir (lamivudine, or 3TC) plus Sustiva (efavirenz) will develop tenofovir resistance within one year of starting treatment under present conditions. They reached this conclusion by considering an estimate that 15 percent to 35 percent of people in sub-Saharan Africa who start ARVs fail treatment within 12 months, and then multiplying those figures by a 50 percent rate of acquired tenofovir resistance (a conservative estimate).

The researchers found that the prevalence of tenofovir resistance among the populations studied was the highest in sub-Saharan Africa, at 57 percent, compared with 22 percent in North America and 20 percent in Western Europe.

Those who started antiretroviral (ARV) treatment with fewer than 100 CD4 cells were 50 percent more likely to have tenofovir resistance than those who began treatment with at least 100 CD4s. Also, pairing tenofovir with Epivir rather than Emtriva was associated with a 48 percent greater likelihood of developing tenofovir resistance. Those who took Viramune (nevirapine) were also more likely to develop tenofovir resistance.

Of the 700 people in the study who had tenofovir resistance, 578 (83 percent) had cytosine analogue resistance (an M184V/I mutation), 543 people (78 percent) had major non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance, and 457 (65 percent) had both.

The study authors found that, in contrast to previous research findings, tenofovir-resistant HIV replicates as well as virus that is not resistant to the drug, indicating that the resistant virus is transmissible. The average viral load when individuals failed treatment was similar among those who did and did not have tenofovir resistance.

Regional differences in tenofovir resistance rates, the study authors theorized, are due to differences in the frequency of viral load monitoring.

“Improvements in the quality of HIV care and viral load monitoring,” the study authors write, “could mitigate the emergence and spread of tenofovir resistance, thereby prolonging the lifetime of tenofovir-containing regimens for both treatment and prophylaxis [PrEP]. Surveillance of tenofovir and NNRTI resistance should be a priority both in untreated and treated populations.”

What does this news mean for the effectiveness of PrEP?

“In the next few years, PrEP is likely to remain highly effective,” Shafer says, given that about 99 percent of transmitted virus strains are susceptible (or not resistant) to tenofovir. In other words,

in an estimated 1 percent of new HIV cases, individuals acquire a strain that is resistant to tenofovir.

Shafer says that the prevalence of transmitted tenofovir resistance needs to be monitored, considering that the transmission rates of tenofovir-resistant HIV are likely to rise.

“PrEP alone has never been considered foolproof,” he cautions. “Using condoms will increase protection against non-resistant strains [of HIV] and could be the key protection against resistant strains.”

Responding to the new study’s findings, Susan Buchbinder, MD, an assistant clinical professor at the University of California, San Francisco (UCSF), who was one of the investigators of the iPrEX trial that first proved the efficacy of PrEP in 2010, says she doesn’t “yet have major concerns about PrEP” when it comes to the threat of transmissible HIV that is resistant to tenofovir. “This is something that we’ll need to watch.”

Given that there are two ARVs in Truvada, tenofovir and emtricitabine, people on PrEP may have a safety net if they are exposed to tenofovir-resistant virus, considering that it is unlikely that they will be exposed to virus that is resistant to both drugs. Additionally, a virus that is in fact resistant to both drugs might not be as “fit,” or able to transmit.

There have, however, been two reports of individuals taking tenofovir alone as hepatitis B virus (HBV) treatment who have contracted HIV. So one ARV may not be enough to protect against HIV infection.

To read a press release about the study, click here.

To read the study abstract, click here.
