Researchers have for the first time documented a case of an individual contracting HIV, a multi-drug resistant strain, while apparently adhering well to the daily regimen of Truvada (tenofovir/emtricitabine) as pre-exposure prophylaxis (PrEP). The scientists concluded that it is indeed possible for individuals who are adherent to PrEP to contract HIV when they are exposed to a virus that is resistant to both drugs included in Truvada.

While this case is concerning, experts in the PrEP field believe that such failures of PrEP will likely remain rare.

David Knox, MD, an HIV specialist at the Maple Leaf Medical Clinic and the lead author of the case study, presented findings at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

Evidence suggests that the individual in question, a 43-year-old Canadian man who has sex with men, adhered well to PrEP over the long-term. Nevertheless, after 24 months on Truvada he tested positive for HIV. Initial tests indicated that he was acutely (very recently) infected: He tested positive for the p24 antigen, which appears within about three weeks of HIV infection and disappears a few weeks afterward; and at that time he tested negative for HIV antibodies, which typically appear two to eight weeks after infection.

Researchers estimate that men who have sex with men (MSM) who take Truvada at least four times a week are more than 99 percent protected against HIV. (CDC guidelines advise taking Truvada daily for maximum protection, but the drug apparently has a good amount of dosing "forgiveness.") Real-world use of Truvada as HIV prevention has suggested it is indeed highly effective. For example, none of the more than 1,400 generally high-risk individuals taking PrEP through the Kaiser Permanente San Francisco PrEP program have contracted HIV to date, despite their very high rate of other sexually transmitted infections, including two cases of hepatitis C virus (HCV).

All of PrEP’s power to curb HIV notwithstanding, this new case study underlines the fact that in science there is, unfortunately, no 100 percent guarantee.

"After 32 years of experience with HIV research, I have learned never to say ‘never’,” said Robert
M. Grant, MD, MPH, a professor at the University of California, San Francisco, who was the head of the iPrEx trial that first proved PrEP’s effectiveness among MSM and transgender women in 2010. “Yet I also think that gay men benefit from feeling safer during sex, and I am grateful that PrEP affords that feeling.”

The man in the case study reported multiple acts of receptive anal intercourse without a condom during the two-to-six week period before testing positive for HIV. He has no reported history of injection drug use.

Pharmacy records indicated that the man had consistently filled his Truvada prescription on schedule. Dried blood-spot testing on a sample taken 20 days after he tested positive for HIV indicated that he had adhered well to Truvada during the previous one to two months, a period that overlapped with the estimated time when he contracted the virus. Additionally, a recent analysis of the blood sample the man gave for the test that first indicated he was HIV positive showed that he had high blood levels of both drugs included in Truvada at that time.

“This person claims he was taking PrEP every day and I believe him,” said Grant.

Tests for antiretroviral (ARV) resistance that were conducted on a sample taken a week after the man tested positive for HIV indicated that his virus was clade B HIV-1 and CCR5 tropic (meaning it attached to the CCR5 coreceptor on the surface of CD4 cells, as opposed to the CXCR4 coreceptor). Tests also indicated that his drug resistance had been transmitted from another person, rather than acquired post-transmission, and that he had contracted the virus from a single person. Evidence suggests that this single person was failing the HIV single-tablet combination regimen Strivil (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate), which includes the components of Truvada.

The man’s virus was resistant to multiple drugs. It had numerous nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations, including those known as 41L, 67G, 69D, 70R, 184V and 215E, which in the resistance tests reduced the response to Ziagen (abacavir) by 1.9 fold, raised the resistance to Epivir (lamivudine) by 61 fold, raised the resistance to Emtriva (emtricitabine, which is one of the two drugs in Truvada) by 38 fold, and reduced the response to Viread (tenofovir, the other drug in Truvada) by 1.3 fold. (In other words, this virus was highly resistant to emtricitabine, but only somewhat so to tenofovir.) The virus also had the non-nucleoside reverse transcriptase (NNRTI) resistance mutation 181C, raising the resistance to Viramune (nevirapine) 43 fold. Lastly, the virus had mutations conferring reduced response to all integrase strand-transfer inhibitors (INSTIs), including 51Y and 92Q, which reduced the response to Isentress (raltegravir) 2.7 fold, increased resistance to Vitekta (elvitegravir) by greater than 100 fold, and reduced the response to Tivicay (dolutegravir) 9.6 fold.
Despite all these resistance mutations, the man in the case study is currently on successful HIV treatment, with a fully suppressed viral load. He is taking Tivicay (dolutegravir), Prezcobix (darunavir/cobicistat), and Edurant (rilpivirine).

Recent research suggested that, among HIV-positive individuals failing treatment regimens, resistance to tenofovir, which is the most commonly prescribed ARV in the world, is increasing. Perhaps as much as 1 percent of all individuals who contract HIV today inherit virus that has mutations conferring resistance to tenofovir. Resistance to emtricitabine is more common, likely because only a single resistance mutation is required to confer resistance to that drug, while for tenofovir more than one mutation is usually required.

What is more rare is a virus that is highly resistant to both tenofovir and emtricitabine, as in this new case report. Indeed, according to Grant, among more than 9,200 participants in the clinical trials of PrEP, such a virus that was highly resistant to both components of Truvada was never seen.

According to Richard Harrigan, PhD, director of the lab program at the British Columbia Center for Excellence in HIV/AIDS in Vancouver, Canada, who was one of the researchers on this case study, “I think we would assume that the efficacy of PrEP would be lower if there is exposure to virus which is resistant to either drug, and lowered further if there is exposure to virus resistant to both drugs.”

There have been two documented cases of men contracting HIV while taking tenofovir alone for hepatitis B virus (HBV) treatment. One of these individuals did not have a tenofovir-resistant strain of the virus, while researchers could not determine if the other person had such resistance. These cases apparently stress the importance of using two drugs for PrEP rather than one, even in the absence of resistant virus—at least when using the components of Truvada. (Another study presented at CROI compared the single drug Selzentry (maraviroc) to Truvada as PrEP.)

Reflecting on the new case study, Harrigan said, “I certainly don’t think that this is a situation which calls for panic. It is an example that demonstrates that PrEP can sometimes be ineffective in the face of drug resistant virus, in the same way that treatment itself can sometimes be ineffective in the face of drug resistant virus.”

Harrigan added, “This case demonstrates that while PrEP is beneficial, we can’t rely on it to be an infallible magic bullet.”

To read the conference abstract, click here, and to view the conference presentation webcast, click here.

For a POZ exclusive interview with the anonymous man from this case study, read "Meet the Man Who Got HIV While on Daily PrEP."

Editor’s note: There has been concern among some readers about the statement in this article asserting that researchers estimate that taking four or more tablets of Truvada per week reduces
the risk of HIV among MSM by more than 99 percent. This figure comes from the 2014 iPrEx open-label extension study, which used mathematical modeling to reach this estimate. No participant in a PrEP clinical trial has contracted HIV while apparently taking Truvada at least four days per week.

Older estimates of PrEP’s effectiveness come from two papers. The 2010 iPrEx study estimated that among those who had any detectable drug in their systems, Truvada reduced the risk of infection by 92 percent among MSM. A 2012 analysis of that paper used mathematical modeling to estimate that taking seven tablets of Truvada per week reduced the risk of HIV by 99 percent.

Today, many research papers that examine adherence to PrEP use four-plus tablets per week as the threshold for maximum adherence; they do not even differentiate between taking seven tablets per week and taking four to six tablets per week.

For a more detailed description of these figures, please refer to the end of this article.

To visit POZ’s PrEP reporting page, click here.