

## PrEP & drug resistance

*Gus Cairns, Published January 2019*

**A lot of concern has been expressed that taking PrEP might cause HIV to become drug resistant, and that both PrEP and HIV treatment might fail more often in the future as a result.**

In 2016 and 2017, two confirmed cases of PrEP failure, in [Toronto](#) and in [New York](#), featured HIV resistant to PrEP drugs, though one puzzling case in [Amsterdam](#) did not.

Concerns were raised again in 2018 by [a fourth case of apparent PrEP failure featuring resistant HIV](#). However poor monitoring in this case means that we are not so certain that this was definitely PrEP failure and, if so, whether the infection was caused by resistant HIV, or happened because the patient kept taking PrEP while already infected.

HIV drug resistance is undeniably a major concern in HIV treatment, especially in countries that cannot afford regular viral load tests.

[One study](#) found that 20% of people in low- and middle-income countries whose first-line HIV therapy had failed had resistance to all three commonly-used drug classes, and [another](#) found that one in eight people starting HIV therapy had been infected with drug-resistant HIV, prompting recommendations that first-line therapies need to change.

This guide, however, is mainly about resistance and PrEP. People still suspicious of PrEP may believe that the threat of drug resistance is a major reason to be cautious about its use. And PrEP users may be even more likely than people with HIV to lack basic information about what HIV drug resistance is, how it happens, and whether PrEP could cause it.

In this case, the news is largely good, and concerns about resistance may be exaggerated. For reasons spelt out below, PrEP use is less likely to give rise to HIV drug resistance than HIV treatment does. And the amount of HIV circulating in communities that is sufficiently resistant to PrEP to make it fail is probably very small.

However these figures are very dependent on how adherent people are to PrEP, and we don't know whether the risk of resistance and PrEP failure is higher among groups other than men who have sex with men.

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- Key points**
- > HIV drug resistance can only arise in PrEP users if they take PrEP when they already have HIV.
  - > This is why you should get tested or HIV before you start PrEP, and keep testing regularly.
  - > If you take PrEP as directed, you won't catch HIV, you won't develop drug resistance, and PrEP will continue to work.
  - > A study has found that, in a largely gay HIV+ population with adequate treatment levels, at most one in 500 cases of HIV infection featured a virus that might possibly be resistant to PrEP.
  - > There are differing views on how much PrEP use will add to the burden of HIV drug resistance. But its contribution will be small, compared to the impact of lack of support for adherence and for regular viral load testing.

## **How drug resistance happens in HIV infection**

**HIV doesn't copy its own genetic material very accurately, so genetic mutations do surface spontaneously. Most of the time these either have no effect on HIV's ability to cause disease, or actually impair it.**

Some mutations, by chance, also confer resistance to one drug or a class of drugs. This does not mean your HIV will be untreatable. It means that specific drugs will work less well, or not at all, against HIV with those mutations.

This means that if you do take that specific HIV drug and already have HIV with the drug resistance mutation, then the resistant HIV is able to keep reproducing, even as the non-resistant viruses are stopped. The resistant strain soon becomes the predominant strain of virus in your body and the drug won't work.

In addition, even if you don't already have resistance but are not taking a sufficiently strong combination of drugs, or aren't taking them consistently, then HIV can still reproduce – and this means it can spontaneously develop drug resistance mutations. If this happens, then the resistant virus will be the only strain that can reproduce and will soon come to dominate the viral population, causing treatment failure.

HIV finds it easy to develop new resistance to some drugs (such as emtricitabine, one of the components of PrEP) and very hard to do with others.

Scientists discovered this in the early years of HIV treatment research. The earliest HIV drugs like AZT (zidovudine), if taken singly, were only effective for a few months at most, because HIV drug resistance soon appeared. Two drugs worked for somewhat longer but were still not effective in the long run.

This was partly because the early HIV drugs all had the same mode of action – and PrEP consists of two drugs, tenofovir and emtricitabine, that belong to the same class. (This is why, while PrEP is sufficient to prevent HIV, it is not strong enough to treat it.)

The scientists then discovered that if you gave people three or more HIV drugs, especially if they had different mechanisms of action, then it became almost impossible for the virus to develop the exact combination of resistance mutations that would mean that the drugs fail. This is why HIV is treated with combination therapy, which should keep on working as long as people keep taking it consistently.

### **To summarise:**

- > If you have HIV and take no treatment, then HIV will continue to spread through your system and cause damage, but it won't develop resistance.**
  - > If you take all your treatment consistently, it will work, and your HIV won't develop resistance.**
  - > But if you take drugs inconsistently – some drugs, but not enough - then you provide an ideal environment for drug-resistant strains to prevail.**
  - > Nearly all drug-resistant HIV develops this way - in HIV-positive people who are taking inconsistent or inadequate treatment.**
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**How drug resistance arises in people taking PrEP**

**When it comes to PrEP, however, drug resistance is much less likely to happen - because people taking PrEP, by definition, generally don't have HIV.**

The only way you could develop resistance due to PrEP is if you unwittingly take PrEP while you already have HIV. This could be because you didn't take an HIV test before you started PrEP, or because you did take a test but caught HIV so recently (within the last 2-3 weeks) that the test didn't detect it.

This doesn't happen often, but it has happened, and in some cases those people have developed HIV resistant to one or both PrEP drugs. We have many other HIV drugs to choose from and in all those cases, once diagnosed as HIV positive, they went on to be successfully treated with other drugs.

If someone in this situation were to have condomless sex with another person during the period they thought they were HIV negative, then they could conceivably transmit drug-resistant HIV.

So drug resistance might become more common if lots of people were to start PrEP without an HIV test first, or unwittingly caught it due to inconsistent PrEP use.

This is why it is so important to get an HIV test before you start PrEP and to keep testing regularly.

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**How common is HIV that is already resistant to PrEP?**

**So some HIV that has resistance mutations to PrEP is infectious and can be successfully transmitted. It would obviously be a worry if were lots of HIV resistant to PrEP drugs out there.**

However [one study](#) found that HIV with the kind of drug resistance that might stop PrEP working was quite rare – or at least was in an urban US population, where most people with HIV were gay men, and there were adequate levels of HIV treatment and viral undetectability.

This study estimates that within the area it looked at - King County in Washington State, which includes the city of Seattle - only twelve out of 3381 people tested for HIV drug resistance in the last two years (one in 323 people) had resistance mutations that might mean PrEP would not work and, at the same time, had a detectable viral load and were therefore infectious.

Taking into account that not everyone was tested for drug resistance, the researchers calculated that, at any one time, there were a maximum of 20 people in the community with potentially PrEP-resistant HIV and unsuppressed viral loads.

Not all these people would pass on their HIV, even if they were infectious. This is partly because not all of them would be having risky sex, and partly because resistant viruses tend to be weaker and appear to be less often successfully transmitted.

So the study also looked at actual cases of HIV being transmitted that was probably PrEP-resistant.

It found that, in King County, just three people in the last ten years – maybe four, if you allow for people untested for resistance – were probably infected by HIV with the resistance mutations that might make it resistant to PrEP. That's roughly one per 500 cases of HIV infection.

Resistance is not always absolute. In particular, the mutations that confer resistance to tenofovir [may only impair the drug's activity by 50%](#). This means that PrEP might have stopped infection even in some of these cases, because the drug levels in their bodies might still be enough to stop it.

**Does resistance cause PrEP failure? And could PrEP increase global HIV drug resistance?**

**The two cases we have where it looks likely that drug-resistant virus led to a failure of PrEP are pretty certain precisely because they were unusually well documented. It's hard to prove that people caught HIV while absolutely, definitely, taking PrEP as prescribed. There could be more undocumented PrEP failures out there.**

We also know less about whether PrEP-resistant HIV might cause failure more often in heterosexual women and men, and in people with other risks; a study in a non-gay male population needs to be done.

There is one study – [Partners PrEP](#) – in heterosexual couples that documented PrEP resistance. In that study, of 121 people who caught HIV, 26 were in the arm who were allocated to PrEP rather than placebo, and of them, [five developed PrEP resistance mutations](#). However this does not mean they caught HIV because it was drug-resistant, and so their PrEP didn't work: they almost certainly caught HIV due to inconsistent PrEP use, and then developed resistance.

We are not certain about whether PrEP use could cause more HIV to be drug-resistant generally. But [one review of studies](#) did find that it was much less likely to arise than it did in HIV treatment. The studies estimated that, ten years after the introduction of a PrEP programme in a population, between 0.6% and 1% of HIV-infected persons would have HIV resistance due to PrEP if PrEP adherence was 100%, and 3.5% to 6% would have HIV resistance due to PrEP if adherence was 50%. This is a considerably lower proportion than resistance arising during HIV treatment.

The Seattle study, if replicated elsewhere, shows that if you contrast the number of potential PrEP infections with the number of people on PrEP, then HIV infection due to PrEP drug resistance is very rare, though it could conceivably be higher in a population with poorer PrEP adherence, or who don't test regularly for HIV.

The important thing, therefore, is to take PrEP correctly – either daily, or, if intermittently, in accordance with IPERGAY, the study that showed that one type of intermittent PrEP use worked.

And it's vital to get tested for HIV before you start, and regularly thereafter.

