FOTO24/GALLO IMAGES/GETTY

People wait to be seen at an HIV clinic in Johannesburg, South Africa.

HIV-PREVENTION DRUG HAS AN ACHILLES HEEL

In rare cases, cabotegravir hides infections and fuels resistance.

By Amy Maxmen

An injectable drug that was lauded last year for being able to prevent HIV infection looks less perfect today, in light of a new analysis.

Researchers revisited a 4,570-person clinical trial of the drug, examining blood samples collected during the study. They found that four people who contracted HIV despite receiving injections of cabotegravir — which is used to treat HIV as well as to prevent it — had been infected for more than a month before standard HIV tests detected the virus. During this time, they developed resistance to cabotegravir and closely related HIV treatments. Although alternatives to these common drugs can be used to treat HIV infection, they are expensive or difficult to obtain in some countries.

The team thinks that cabotegravir suppressed the virus enough to prevent the HIV tests from detecting it during early stages of infection.

The news comes as several other potent drugs used to prevent HIV — a type of therapy known as pre-exposure prophylaxis, or PrEP — are entering clinical trials. Raphael Landovitz, an HIV-prevention researcher at the University of California, Los Angeles, who presented the cabotegravir results at the online Conference on Retroviruses and Opportunistic Infections on 9 March, suggests that scientists leading those studies should monitor their participants with more sensitive HIV tests than usual, to avoid a similar situation.

Still, Landovitz and other scientists say that PrEP remains one of the most hopeful tools for curbing a virus that infects approximately 1.7 million people each year. Despite the findings from the cabotegravir study, Quarraisha Abdool Karim, associate scientific director at the Centre for the AIDS Programme of Research in South Africa, based in Durban, remains positive about the drug's potential. She wasn't involved with the trial but is part of the same network developing these therapies. "When people are on PrEP, perhaps we should up the game in what tests we use," she adds, noting that this will cost more.

Improving compliance

In 2012, the US Food and Drug Administration gave the green light to the use of daily pills of an HIV medication called Truvada (emtricitabine/tenofovir), developed by Gilead Sciences in Foster City, California, to prevent infection. It proved more than 85% effective when taken on schedule. However, studies revealed that many people who don't have HIV won't take a protective pill every day. For example, a clinical trial of women in Kenya, Tanzania and South Africa stopped early because the pills didn't seem to be working. Analyses of drug levels in the blood revealed that many participants weren't taking them (L. Van Damme *et al*. *N. Engl. J. Med*. **367**, 411–422; 2012).

As a result, researchers have developed longer-lasting treatments, such as the cabotegravir injection, to improve compliance. These remain in a person's system for weeks or months and so require less frequent doses. Last year, there was excitement when Landovitz reported that, in a clinical trial, a shot of cabotegravir administered every other month proved three times more effective at preventing HIV infection than did daily Truvada pills. The trial compared Truvada with cabotegravir in cisgender men who have sex with men and transgender women who have sex with men across seven countries, including the United States, South Africa and Brazil. Cabotegravir proved so successful that an independent monitoring board recommended 'unblinding' the trial, so that participants could learn if they were being given Truvada (and a placebo injection), or cabotegravir (and placebo pills) and switch to the more effective drug.

A trial revisited

But the research team wanted to understand why some people still got infected. The researchers found that some individuals didn't stick to their daily Truvada regimen, and others picked up the virus after the treatments stopped.

They were surprised, however, when they analysed blood samples from four people who had become infected while receiving cabotegravir. Sensitive tests that detect RNA from HIV revealed that the participants had been infected for 6–16 weeks before standard HIV tests, given monthly as part of the trial, spotted the infection. Landovitz suggests that cabotegravir is so potent that it kept the level of virus in these individuals too low to be detected by the standard tests. But that changed when the virus evolved resistance to the drug — then replicated, causing levels to surge.

"The take-home message here is that we need better diagnostics, and we need to be ready to get people into suppressive treatment as soon as you diagnose the infection," says Landovitz. He notes that the participants responded well to HIV therapies that are alternatives to cabotegravir and similar drugs.

Michael Robertson, executive director of Merck Research Laboratories in West Point, Pennsylvania, says that scientists plan to assess blood samples for signs of drug-resistant HIV in two clinical trials of long-acting PrEP treatments launched by Merck in the past few months. One study will test how well a monthly

pill of a new HIV drug, islatravir, prevents HIV. Another is examining the performance of a matchstick-sized implant – to be embedded in a person's upper arm – filled with islatravir. He remains enthusiastic about the treatments, despite the cabotegravir results, saying that a monthly pill or an implant might appeal to people who feel a stigma in taking a drug every day to prevent HIV.

Landovitz agrees. "I take a step back and remember that we've seen remarkable results," he says. "This could be incredible, so let's just figure out how to minimize the risk to individuals."

But some of the communities that these researchers are trying hardest to reach because they have high rates of HIV might not react to the news so optimistically. Levi Maxwell, a Black transgender community activist in San Francisco, California, warns that the news on cabotegravir could cause a backlash. "The answer is not to tell people this is better than nothing," they say. Maxwell explains that many Black and transgender people are wary of government officials and scientists because of a history of harm and discrimination. That mistrust might be exacerbated by a negative effect – even a rare one – caused by a drug meant to prevent HIV.

Maxwell recommends that HIV scientists concentrate on developing new forms of PrEP that don't cause drug resistance. And they suggest that HIV-prevention researchers push for policy changes to improve the conditions that put Black and transgender people at risk of HIV infection in the first place, such as unaffordable housing and mass incarceration. "Scientists may be well intentioned, but they need to understand that they can't have tunnel vision if they want to succeed in their goals," says Maxwell. "This isn't just a medical issue."

RECORD NUMBER OF NEAR-EARTH ASTEROIDS DISCOVERED IN 2020

Despite pandemic disruption, astronomers detected thousands of these small rocky worlds last year.

By Alexandra Witze

A 340-metre-wide space rock named Apophis whizzed safely past Earth on 6 March. The next time it returns, in 2029, won't be so uneventful: Apophis will come within 40,000 kilometres of the planet, skimming just above the region where some high-flying satellites orbit. Never before will astronomers have been able to watch such a big asteroid pass so close to us.

The 6 March fly-by gave scientists an opportunity to test the worldwide planetary defence system, in which astronomers quickly assess the chances of an asteroid hitting Earth as they follow its path across the night sky. "It's a fire drill with a real asteroid," says Vishnu Reddy, a planetary scientist at the University of Arizona in Tucson who coordinated the observing campaign.

The Apophis fly-by highlights how much astronomers have learnt about near-Earth asteroids – and how much they still have to learn. Since 1998, when NASA kicked off the biggest search for near-Earth asteroids, scientists have detected more than 25,000 of them. And 2020 turned out to be a record year for discoveries. Despite the COVID-19 pandemic interrupting many of the surveys, astronomers catalogued 2,958 previously unknown near-Earth asteroids over the course of the year (see 'Space rocks').

A large number came from the Catalina Sky Survey, which uses three telescopes in Arizona to hunt for threatening space rocks. Operations closed briefly last spring because of the pandemic, and a wildfire in June caused a longer closure, yet the Catalina survey still discovered 1,548 near-Earth objects. These included a rare 'minimoon' named 2020 CD3, a tiny asteroid less than 3 metres in diameter that had been temporarily captured by Earth's gravity. The minimoon broke away from Earth's pull last April.

A further batch of 1,152 discoveries last year came from the Pan-STARRS survey telescopes in Hawaii. The finds included an object named 2020 SO, which turned out to be not an asteroid, but a leftover rocket booster that had been looping around in space since it helped to launch a NASA mission to the Moon in 1966.

Close calls

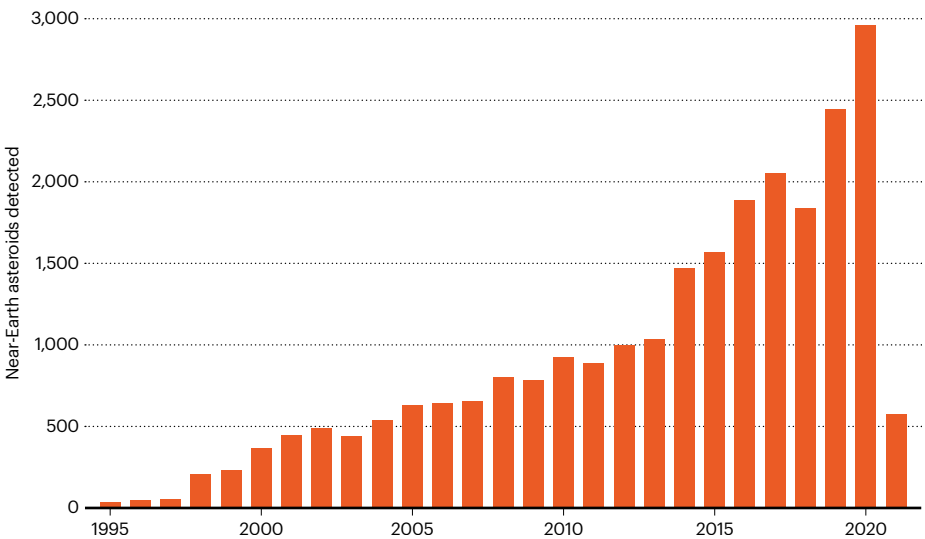
Some of the asteroids discovered last year came close to Earth – at least 107 of them passed the planet at a distance less than that of the Moon. Last year's close shaves included the tiny asteroid 2020 QG, which skimmed just 2,950 kilometres above the Indian Ocean in August. That made it the closest known approach – a record broken just three months later by another small object, 2020 VT4. That one passed less than 400 kilometres from the planet, and wasn't spotted until 15 hours after it had whizzed by. Had it hit, it would probably have broken apart in Earth's atmosphere.

All of these discoveries are making astronomers more aware of the billiard-ball nature of the Solar System, where plenty of asteroids ping around in the space near Earth. The recent push to observe Apophis highlights how astronomers around the world can work together to assess the threat posed by asteroids, says Reddy.

"It's been a huge international effort," he says, "and a lot of fun." By the time Apophis comes around again, in eight years' time, scientists will have an even more detailed census of threatening space rocks.

SPACE ROCKS

Astronomers catalogued almost 3,000 near-Earth asteroids in 2020.



SOURCE: NASA CENTER FOR NEAR EARTH OBJECT STUDIES