

## Factsheet

# CAPRISA 004 and HIV Drug Resistance

### Summary

- No tenofovir-related drug resistance was found in the women who acquired HIV infection during study follow-up.
- The absence of tenofovir resistance is reassuring.
- Drug resistance testing methods conventionally used to identify drug resistance in patients on antiretroviral therapy were used in CAPRISA 004.
- We are currently using new highly sensitive DNA technologies to test for rare drug resistant strains; these results are expected in a few months.

### Tenofovir: an antiretroviral drug

The CAPRISA 004 trial tested the safety and effectiveness of the gel formulation of tenofovir, a well-known antiretroviral (ARV) drug that prevents HIV from replicating inside human cells. The oral (tablet) form of tenofovir has been used to treat HIV in hundreds of thousands of HIV-infected individuals in more than 50 countries, and it has been approved for HIV treatment by a number of regulatory agencies.

Animal studies show that tenofovir gel can prevent the vaginal (and rectal) transmission of a virus that is similar to HIV, but scientists do not know whether it has the same effect in humans. The CAPRISA 004 trial tested whether tenofovir gel can prevent vaginal acquisition of HIV in women.

Although the use of tenofovir gel for HIV prevention is promising, the use of an ARV-based drug always raises the question of whether *drug resistance* is taking place.

### Drug resistance

Drug resistance refers to the reduced effectiveness of a drug against an infectious organism, in this case a virus. HIV is said to be resistant to an ARV if the virus keeps reproducing even while a person is taking that drug. The resistant virus is known as a *drug-resistant strain*—it resists the drug and continues to multiply and spread. If a person does develop a type of HIV that is resistant to the drug being tested, it may limit which ARVs the person can take for their future treatment of AIDS.

### Possible mechanisms of drug resistance

Drug resistance may occur through different mechanisms:

1. Drug resistance may be acquired by a woman (whether or not she is taking the drug) through transmission of an already resistant virus from the man who is the source of her infection.

2. Drug resistant viruses may occur spontaneously, even in people who are not taking the drug. HIV reproduces at a very high rate, often mutating with each replication cycle. This rapid rate of mutation can lead to the formation of a drug-resistant virus. Hence many HIV-infected people carry very low levels of drug resistant viral strains. In these people, the growth of the drug-resistant virus is enhanced when the drug selectively suppresses the drug-sensitive viruses. This allows the drug-resistant strain to become the dominant virus.
3. Drug resistance may be acquired when the virus is exposed to low levels of the drug. Sub-optimal levels of drug, with concomitant failure of viral suppression, may lead to the virus developing resistance to the drug.

### **Viral mutations investigated to assess tenofovir-related resistance**

It is estimated that the women were exposed to gel episodically for about 3 to 4 weeks after becoming infected with HIV. The resistance assays were performed on 35 women in the tenofovir gel arm, on average 20 weeks after the estimated date of infection. No tenofovir-related resistance mutations (K65R, K70E) were detected and none of the women had thymidine analogue mutations (M41L, L210W, T215Y/F, D67N, K70R, and K219Q/E) or mutations that confer resistance to the class of drugs known as nucleoside reverse transcriptase inhibitors (multi-NRTI resistance). Combinations of thymidine analogue mutations can confer resistance to antiretroviral drugs that work inside cells by mimicking thymidine, including drugs like tenofovir.

### **Health impact of drug resistance**

When a drug-resistant virus becomes the dominant type of HIV in a woman, she may no longer respond well to treatment with that particular ARV. When most of the virus in her body is drug-resistant and her response to treatment with the drug is sub-optimal, a woman is said to have developed *clinical resistance* to that ARV. However, she would have the option to take other ARV drugs that are effective against HIV.

### **Risk of drug resistance in the trial**

A woman who remained HIV negative while using tenofovir gel was not at risk for drug resistance. Because she had no HIV in her body, a drug-resistant virus could not have emerged. However, drug resistance is a hypothetical concern for women who became infected with HIV while using tenofovir gel. The CAPRISA 004 finding of no tenofovir-related resistance is reassuring. However, further research is needed to correlate the lack of resistance to tenofovir drug levels and to determine whether low levels of drug resistant viruses are present.

### **Reducing drug resistance during the CAPRISA 004 trial**

The scientists tried to minimize a participant's exposure to the ARV (tenofovir) if she became infected with HIV. Each participant was tested monthly for HIV, and if she tested positive, she was immediately withdrawn from further use of the study gel. If she had been using a gel containing tenofovir (rather than the placebo), she would have been exposed to the drug for only a short period of time, estimated to be on average about 3 to 4 weeks. This would reduce the risk of a drug-resistant virus becoming the dominant virus. Nevertheless, the scientists followed these women closely to see whether a drug-resistant virus appeared in their blood.

**Monitoring drug resistance in women who became infected during the CAPRISA 004 trial**

Assessing the development of drug resistance was one of the five safety-related secondary objectives of the CAPRISA 004 trial. Blood was taken from each participant to look for resistant viruses at the earliest time point after an HIV infection and at subsequent time points to assess whether the resistant virus persisted or continued to evolve. Most women who acquired HIV infection during the follow up of the CAPRISA 004 trial were subsequently enrolled into the CAPRISA's Acute HIV Infection Study (CAPRISA 002) for continued care and to monitor the impact of resistance on their responses to antiretroviral treatment. At present, conventional and new highly sensitive DNA-based drug resistance assays are being conducted on viruses from the blood and vagina at the earliest time after HIV infection; these results are expected in a few months.