The Next Frontier of U=U Science

Sony SalzmanMarch 26, 2019

Nneka Nwokolo, M.B.B.S., speaks at CROI 2019 in Seattle, Washington.Kenyon Farrow
The science is clear, the evidence overwhelming: HIV-positive people with an undetectable viral load cannot transmit the virus to sex partners. This message has gone a long way in combating HIV stigma, as Carrie Foote, Ph.D., a founder of the Undetectable Equals Untransmittable (U=U) campaign, can attest.

"Having tested positive myself in 1988, I lived in fear for nearly 25 years," said Foote, speaking at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI). "U=U takes away that fear."

At CROI 2019, the evidence of U=U was not up for debate. Rather, attendees gathered on March 6 to learn about the next frontiers of HIV transmission research at a symposium titled "The Story of U: Implications of Undetectable Viral Load on Transmission."

A Swiss History of U=U

In 2008, Switzerland's Pietro Vernazza, M.D., published a controversial statement in the *Bulletin of Swiss Medicine* that said people with an undetectable viral load for at least six months do not need to use condoms during sex to prevent HIV transmission.

That statement sparked a global debate on the validity of a premise that, at the time, ran counter to medical consensus about condom use.

By 2008, substantial evidence pointed to the fact that serodiscordant partners could have unprotected sex if the HIV-positive partner had sustained viral suppression and condoms weren't needed to prevent other sexually transmitted infections (STIs) or pregnancy. But, as Vernazza pointed out, there's an inherent problem in science, in that the absence of proof does not necessarily mean the chances are zero.

Still, Vernazza felt the situation was akin to the 1986 public-health messaging around kissing as an HIV transmission risk: Because transmission had never been documented, the risk was low enough for public health professionals to stand behind a zero-risk message.

In publishing the Swiss Statement in 2008, Vernazza aimed to "alleviate fears of people living with HIV" and allow them to have "a 'normal' sexual life."

Today, Switzerland's nearly decade-long headstart on U=U messaging has made a significant impact on the lives of people living with HIV in the country. Prior to Vernazza's publication, Switzerland had one of the highest rates of non-disclosure HIV criminal convictions. Since 2008, "we have had no further convictions," Vernazza said.

"If the Swiss Statement has done one thing, it motivated everybody in this room and in all the clinics to prove that we were wrong," Vernazza. So far, the opposite has happened, with U=U now firmly established science.

Transmission Conundrums

Instead of rehashing the well-worn evidence from the HPTN 052 and PARTNER studies, Nneka Nwokolo, M.B.B.S., with Chelsea and Westminster Hospital in London drew the audience's attention to current gaps in knowledge.

For example, she pointed out that the implications of poor treatment adherence are not fully understood when it comes to the risk of sexual transmission. "What we don't know is what number or pattern of missed doses will result in an increased risk of transmission," she said.

Meanwhile, while an undetectable viral load means the risk of sexual transmission is zero, it's not yet obvious whether the same premise is true for other transmission routes.

Nwokolo noted that clinical guidelines differ across countries for post-exposure prophylaxis (PEP) in the case of non-sexual HIV exposure. The U.S., for example, recommends PEP for accidental needlestick injuries even if the HIV-positive person has an undetectable viral load, while the U.K. does not.

Guidelines on needle-sharing among injection drug users follow the same pattern, with the U.S. recommending PEP even if the HIV-positive person has an undetectable viral load, while the U.K. does not. That's despite the fact that transmission risk data among needle-sharing partners are quite thin, Nwokolo pointed out.

Another grey area is breastfeeding, where guidelines can generally be split between high-resource and low-income countries. In the latter, guidelines tend to recommend breastfeeding among women with an undetectable viral load. Though there have been a few documented cases of transmission from virally suppressed mothers to their babies, the risk is thought to be low and is outweighed by the greater risk of malnutrition and other dangers to a newborn infant.

In wealthy countries where mothers can easily access formula, guidelines tend to dissuade breastfeeding. However, Nwokolo said the risk of transmission is low enough that mothers who choose to breastfeed should be supported in their decision.

Inching Closer to 90-90-90

Not only is U=U a "human rights issue," said Foote, but it is also now seen as a key pillar in achieving the UNAIDS 90-90-90 target -- 90% of all HIV-positive people diagnosed, 90% of those diagnosed on treatment, and viral suppression for 90% of those in treatment.

In particular, the treatment-as-prevention concept is thought to have contributed to declines in new HIV infections, said Andrew E. Grulich, Ph.D., with the University of New South Wales in Sydney, Australia.

In particular, this decline has been observed in sub-Saharan African heterosexual populations, although there are other factors, such as a higher rate of male circumcision, that may have contributed to that decline.

Meanwhile, among gay and bisexual men in the U.K., new HIV diagnoses have been declining since 2016, likely as a result of pre-exposure prophylaxis (PrEP) use and treatment as prevention. An almost identical trend can be observed in U.S. cities like New York and San Francisco, Grulich noted.

Overall, it's difficult to separate PrEP from treatment as prevention in terms of their relative impacts on declines in new HIV diagnoses. Regardless, both should be critical components of any public-health strategy to achieving the UNAIDS 90-90-90 goals, Grulich said.