Jetsons-Era HIV Care and Prevention

Futuristic highlights from the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

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The Conference on Retroviruses and Opportunistic Infections (CROI) is one of a handful of yearly medical meetings in which HIV experts trot out their latest and greatest research findings, jostling to outdo one another in the race for the most headline-grabbing advancements in science about the virus. This year's CROI, which took place in Boston from March 3 to 6, boasted a world's fair air of excitement and intrigue as many of the marquee presentations opened a window into how the next generation of HIV care and prevention techniques may revolutionize the pandemic.

Below are some of the biggest newsmakers from the conference. To read in greater detail about the studies, click the hyperlinks imbedded in the text or visit the CROI highlight web page here.

Risk of Transmitting With Undetectable Virus: Possibly "Close to Zero"

Perhaps the biggest buzz of the conference came from the ongoing PARTNER study, which has researchers following 1,110 heterosexual and gay serodiscordant couples in which the HIV-positive partner is taking antiretrovirals (ARVs) and has a fully suppressed viral load. A total of 767 couples were included in an analysis conducted at the study's two-year mark (final results are expected in 2017), providing an average of 1.16 years of follow-up per couple. Despite the fact that inclusion in the study required that the couples were having intercourse without condoms at least some of the time, there have been no HIV transmissions during the study so far.

The PARTNER study team estimated at CROI that the chance of transmitting HIV in the absence of a detectable viral load may be close to zero, or even zero itself.

However, the PARTNER study has not yet proved that a figure very close to zero is indeed the transmission risk for undetectable people with HIV. Even with no transmissions over the course of the first couple of years of the study, the researchers must still estimate a margin of error.

Under the PARTNER researchers' current estimates, the largest margin of error, also known as a confidence interval, accounts for receptive anal intercourse with ejaculation: having an undetectable viral load in that case cuts the risk of transmission somewhere in the range between 96 percent to a figure approaching 100 percent. (It is not scientifically possible to prove a 100

percent risk reduction beyond all shadow of a doubt.) Another way of looking at this statistically is that, over a 10-year period, there is up to a 32 percent likelihood of HIV acquisition through receptive anal intercourse without a condom when the virus is fully suppressed—although the actual likelihood is probably closer to zero.

For other sex acts, the estimated risk reduction range is narrower, thanks to relatively large sample sizes in the study of couples engaging in vaginal sex, receptive anal sex without ejaculation and insertive anal sex.

The longer the study runs and the more years of follow-up the researchers have to include in their calculations, the more this margin of error will likely shrink.

The Benefits of Very Early Treatment

Following on the heels of last year's heady CROI announcement that a baby born to an untreated HIV-positive mother in Mississippi had apparently been functionally cured of HIV, a baby born in similar circumstances in Long Beach, California, and then treated with a similarly aggressive ARV cocktail shows no signs of the virus now that she is a year old.

According to Deborah Persaud, MD, a pediatric infectious disease researcher at Johns Hopkins Children's Center who has been involved in both cases, the Long Beach baby's medical team will follow the child closely with the intention of discussing the possibility of interrupting her treatment in another year.

Meanwhile, the National Institutes of Health is sponsoring a global study through the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network in which researchers will search for babies being born to HIV-positive mothers who have not undergone treatment to prevent mother-to-child transmission. Upon finding such cases, the investigators will attempt to prescribe treatment protocols similar to those used with the Mississippi and Long Beach babies in order to prove they can lead to a functional cure. Persaud emphasizes, however, that HIV prevention as opposed to cure is the primary goal of such treatment.

In a parallel case, a man who contracted HIV about five days before starting a pre-exposure prophylaxis (PrEP) regimen and who then started a full HIV treatment cocktail an estimated 12 days after infection does not appear to have any virus in his body several months down the line. Researchers intend to interrupt his treatment after a year has passed since he was infected.

Another study found that the earliest days of infection with SIV, HIV's simian cousin, represent a crucial window during which even a few days' delay in beginning treatment can make a tremendous difference in the establishment of the viral reservoir in monkeys. Researchers infected 22 macaque monkeys by injection with a virulent version of SIV and then started them on ARVs after varying lengths of time: seven days, 10 days and 42 days. After 32 weeks, there was an exponential difference in the size of the reservoir in the respective groups of monkeys.

Genetic Therapies

Researchers reported results from a promising Phase II safety trial of a method in which the immune cells of people with HIV were genetically modified to resist the virus. While such a treatment revolution is hardly around the corner in terms of the technique's availability outside of a research setting, a successful clinical trials process could one day open the door for an alternative to ARV therapy.

Investigators drew immune cells from a dozen study participants who were on stable ARVs. Then they used Sangamo BioSciences' zinc-finger nuclease (ZFN) technology to edit the genetic code for the CD4 cell's CCR5 coreceptor, creating a mutation that blocks the ability for most variants of HIV to latch onto and then enter the immune cell. The researchers then re-infused huge numbers of genetically altered cells into the participants.

Four weeks later, six of the study participants stopped taking their ARVs in a treatment interruption planned to last 12 weeks. Two of them restarted therapy after just eight weeks because of rapidly rising viral loads.

The good news is that on average the peak viral loads of the four participants who did complete the full treatment interruption were more than 90 percent lower than their peak levels from before they started ARVs. Perhaps the most important finding was that one of the participants, who turned out to have been born with one of the two genes necessary to create the beneficial CCR5 mutation, saw a peak viral load of 6,247 at week six, after which it dropped to an undetectable level.

Long-Term Injectable ARVs

In two different studies, researchers gave monthly injections of the long-acting integrase inhibitor GSK1265744 (GSK744 LA) to monkeys in order to test the drug's use as a form of PrEP. The drug was successful at preventing both rectal and vaginal exposures to SIV among the primates. The findings are particularly promising for the future of PrEP as a means of HIV prevention, considering that research of daily Truvada (tenofovir/emtricitabine) has shown that adherence to the drug tends to be poor and that the drug's efficacy drops off when it is not taken as prescribed. Replacing daily pills with a PrEP injection given every one to three months could address this problem.

A Phase II trial of GSK744 LA, in which the drug will be given to men at low risk for HIV, will begin in the next few months. If that goes well, researchers will move on to a Phase III study among high-risk individuals.

The daily oral version of GSK744, coupled with the non-nucleoside reverse transcriptase inhibitor Edurant (rilpivirine), has also shown promise in a Phase IIb tolerability and efficacy study of the pair as a treatment for HIV. The drugs were measured against a traditional three-drug ARV cocktail and ultimately proved comparable in efficacy. Future research will look at injections of long-acting

versions of GSK744 and Edurant given every four to eight weeks.

A New Drug Class

Bristol-Myers Squibb's investigational BMS-663068 is poised to establish a new ARV drug class: the attachment inhibitor. A Phase IIb trial of the drug showed that it was similar in efficacy to other standard ARVs. Its introduction into the pool of available HIV medications could be especially beneficial to those with multidrug resistance.

BMS-663068, which is a pro-drug that the body metabolizes into an active drug known as BMS-626529, attaches to the gp120 protein on HIV's surface. This impedes the virus's ability to bind to the two CD4 cell coreceptors, CCR5 and CXCR4, and begin the process of infecting the immune cell. In contrast to the CCR5 coreceptor antagonist Selzentry (maraviroc), which only combats HIV that is inclined to attach to the CCR5 coreceptor, BMS-626529 fights CXCR4-favoring viruses as well.
