"CURE" RESEACH HIGHLIGHTS FROM THE CROI 2014

The 21st annual Conference on Retroviruses and Opportunistic Infections (CROI) was held in Boston from March 3-6, 2014. This article will address HIV "cure" research at CROI. It is important to note that a cure for HIV is defined in two ways, a "functional cure", currently described as disease free HIV remission without the need for antiretroviral (ARV) use and total HIV eradication from the body which is even more of a challenge. We are now working toward a "functional cure" which is much like remission in cancer cases. Even a "functional cure" will be a long time coming. But we have to start somewhere. AIDS Action Baltimore is right in the middle of "cure" research, working with government and industry as well as national and international researchers.

Last year we learned about the Mississippi Baby, the first toddler cured of HIV. The Mississippi Baby remains "cured" of HIV. The initial results were reported by our own Deborah Persaud of Johns Hopkins at CROI 2013. This year Dr. Persuad reported on another baby from Long Beach, California who is also being treated in the same manner as the Mississippi Baby. In the California case, the baby was treated four hours after birth and remains on treatment. We will not know if this very early treatment case will be successful until the child has a treatment interruption, the only way we have at this juncture to ascertain whether the baby will experience a viral load rebound while not taking ARV treatment.

This year we confirmed that the earlier you treat with ARVs, the better outcome patients will have. Research efforts to treat HIV infected babies soon after birth is underway. Results from a number of these internationally conducted trials were presented at CROI, including results from Katherine Luzuriaga of the University of Massachusetts Medical School, confirming that treating as early as possible, at least within three months of birth and even before, is better than delayed treatment.

We also know that inflammation drives HIV disease, but we don't know the actual cause of inflammation and CD4 depletion. Michaela Muller-Trutwin from the Pasteur Institute in Paris gave a presentation that suggests caspace-3 inhibitors may have the potential to limit inflammation and CD4 depletion by activating cells that counteract the strong inflammatory responses caused by HIV.

We also learned from a presentation from Alexandra Schuetz of the Armed Forces Research Institute that treatment very soon after infection may prevent damage to the gut which causes bacteria to leak from the gut to other areas of the body, resulting in inflammation and immune activation that fuels the HIV spread of HIV throughout the body. Research efforts are ongoing to identify adults very soon after HIV infection known as the acute infection stage. Collaborations with centers conducting HIV prevention research are beginning in an effort to immediately refer acutely infected patients to research and treatment centers.

This year we learned that two Boston patients reported on at CROI 2013 that we hoped were "cured" experienced viral rebound and needed to restart ARVs. These patients had cancer like the Berlin patient, the only known adult to be "cured" of HIV. The Boston patients were given bone marrow transplants (BMTs), but their BMT donors did not carry the delta 32 genetic mutation like the Berlin patient's donor. The delta 32 mutation is very rare and is thought to make one immune to HIV. Although this is bad news, we are in very early stages of cure research. We have much to learn. But every experiment adds to our knowledge.

HIV latency research was also a big topic of discussion at CROI. This type of research was fueled by the discovery of persisting latent pools of HIV even when people have undetectable viral loads. Latent HIV infection was discovered by our own Bob Siliciano also from Hopkins. Because latent HIV exists in the body of infected people, we are not able to "cure" HIV with only ARV use. The current research trend is to attempt to jump start latent virus, then kill it with ARVs in what is known as a "kick and kill" strategy. A number of latency studies have been undertaken with a class of drugs known as HDAC inhibitors. Like all drug research, latency questions are driven by whether a drug is safe and effective.

Regarding safety, a presentation by Thor Wagner from the University of Washington has caused some controversy. Wagner apparently believes that the "kick and kill" strategy to purge the viral reservoir will cause a proliferation of cells that may cause cancer. Many say that this is a great leap given the current data.

Sharon Lewin from Monash University in Australia showed results on nine patients treated with the HDAC inhibitor vorinistat for 14 days. She believes that the major effects of vorinistat occur very early in treatment and that thereafter mechanisms in the body take over to compensate for any such proliferation response.

A presentation from Greg Laird local rising star Johns Hopkins covered the effectiveness of a number of drugs to reverse HIV latency, including disulfiram, JQ1, bryostatin, and HDAC inhibitors, panobinostat, romidepsin, and vorinostat in resting CD4 cells taken from patients on suppressive ARV therapy. None of these drugs were able to reverse latency in any of the patient cells. In another experiment, only bryostatin was able to cause viral outgrowth, but only in certain patient cells. Many researchers believe that combinations of the drugs will be necessary to "kick" the virus out of latency and that it will also be necessary for immunomodulators like therapeutic vaccines to boost the immune system of people infected for long periods of time, the chronically infected, so that they can produce the immune system function that will be necessary to kill HIV even when ARVs are also on board.

Joe Wong from University of California San Francisco described how HIV infected DNA and RNA in the blood and in various tissue compartments acts differently, complicating matters even more. Drugs may work differently in these various compartments, requiring the use of different drugs and maybe even different doses, depending on the compartment in the body being targeted.

All the CROI "cure" research presentations demonstrate that we have a lot to learn. I am reminded of the early days of the epidemic when we first began studying AZT. We didn't know if it was safe and effective. It took us many years to get to where we are now. There is no reason to think it won't take many years to actually get to the point where people can control HIV replication without the need for ARVs. But the effort to cure HIV has begun and we are well on our way. Stay tuned for the latest in "cure" research.