

HIGHLIGHTS FROM THE MELBOURNE IAS TOWARDS A CURE WORKSHOP

The International AIDS Society's (IAS) Towards a Cure Workshop was held in Melbourne, Australia on July 19-20, 2014, immediately before the 20th International AIDS Conference (IAC). This article will provide highlights of the "Cure" Symposium. I have included numerous presentations from Martin Delaney CARE Collaboratory researchers. I am the co-coordinator of the CARE Collaboratory's Community Advisory Board. As a member of CARE, I am more familiar with their "kick and kill" virology work that I will be discussing in this article. There were also a number of immunology and genetic research presentations at this meeting which I have not addressed.

There was a palpable pall over both meetings as a result of the horrible Malaysian Airlines MH 17 crash that killed six IAC delegates en route to Melbourne. Work in the HIV field requires an inordinate amount of flying which is anything but glamorous. While planes do crash, who starts a trip wondering if they will be shot out of the sky by a surface to air missile! This is a horrific blow to the members of the HIV community who have not experienced such a devastating crash since Jonathan Mann and his wife Hopkins researcher Mary Lou Clements were killed in a plane crash on the way to the 1998 IAC.

Flight MH 17 was shot down over the Ukraine, apparently by Ukraine separatists. It was originally thought that 108 delegates were killed in the crash. Eventually, we learned that six conference delegates were lost on the flight, including former IAS President, Joep Lange, a long-time Dutch AIDS researcher and giant in the HIV field. We were all very proud of our own Chris Beyrer from Hopkins who is the incoming IAS President. What a trial by fire for his first IAC! Chris did a wonderful job of keeping his powder dry, not announcing the number of delegates lost until the exact number was confirmed.

The IAS did a fabulous job of honoring the dead, but also of making sure the meeting accomplished its vital purpose in the wake of this unbelievable tragedy. I must admit that most conference attendees are all too familiar with death and dying. As a result, most of us were able to continue with our important work albeit sadly and surreally.

The "Cure" Symposium did not disappoint, although there was some very discouraging news. The most anticipated news of the meeting was a follow-up report on the "Mississippi Baby" who is now a toddler. Last year I reported on the "Mississippi Baby" who we had hoped would be the second person who was cured of HIV. One of my favorite "cure" researchers Debbie Persaud from Hopkins has lead the research aspect of this case. The baby's mother did not receive prenatal care. As a result, the baby was born HIV infected, and started antiretroviral therapy (ARV) hours after birth which was continued for about 12 months. Thereafter ARVs were stopped and the baby was lost to follow-up. The child re-entered care at about 23 months after birth. There was no detectable viral load at this juncture, and it was believed that giving the baby ARVs so soon after birth may have prevented HIV reservoirs from being seeded throughout its body, and may have actually allowed the baby's own immune system to combat HIV. The child's viral load was still undetectable at 24 months. We all hoped that this would prove to be a case of HIV "remission" which is the probably the most accurate way to describe this type of possible HIV "cure". Unfortunately, there was a viral rebound at 27 months.

While we are all disheartened and feel much remorse for the child and its family, Deb Persaud stressed that these are early days and that we all learned much from this case. We know the child was not what

is called an elite controller whose immune systems are able to control HIV without ARVs. Giving the baby ARVs so early apparently resulted in HIV being controlled without drugs for over one year. Research is ongoing to ascertain if there were signals that might describe when it is time to again start ARVs after a treatment interruption. Maybe the duration of treatment was not long enough before ARVs were stopped. Maybe a different ARV regimen might be more effective. Studies of this very early treatment approach are ongoing in babies and adults.

Jeff Lifson, a non-human primate (NHP) CARE researcher from the NCI gave the keynote speech of the meeting. He stressed what we know from Hopkins researcher Bob Siliciano's work. HIV appears to be more and more like cancer. If one hidden HIV cell remains, including dormant HIV cells, the HIV virus can rebound or become active and infectious. Lifson reported on work from his lab on a "kick and kill" strategy that would attempt to awaken HIV dormant cells with HDAC inhibitors, SAHA and vorinostat used in cancer, which were given to NHPs that were previously on ARVs. Lifson believes that drug combinations will be necessary to awaken dormant HIV cells to kick these resting cells into an active state, and that combinations will also be necessary to kill these dormant cells once they are awakened, including ARV combinations as well as immune stimulating vaccines that Lifson believes will be a key part of controlling HIV.

Ole Sogaard who is a Danish researcher from Aarhus University Hospital presented the most promising "kick and kill" research at this meeting. He presented data on his work with romidepsin, another HDAC inhibitor used in cancer. Sogaard studied romidepsin in five men and one woman for 14 days without toxicity. All participants were HIV undetectable and were all on ARVs for an average of nine years. This long duration of ARV use reasonably ensures that all participants had only small HIV reservoirs. Romidepsin use resulted in the creation of active HIV particles that were detectable with ordinary viral load tests. This data demonstrates that we can find hidden HIV and shock it out of hiding.

Melanie Ott from the Gladstone Institute who is another CARE researcher gave an overview of Bromodomain (BRD) inhibitors that have also been used in cancer treatment. It appears that BRD inhibitors might be capable of inducing or inhibiting HIV expression in cell models. Apparently, BRD inhibitor JQ-1 may be able to turn on HIV in resting cells with minimal cell toxicity. It is important to note that many current studies are conducted with cell lines, not in human cells or people. We have a lot more to learn before these compounds are used in people. Much of this early work will be done in human cells once we overcome a number of important scientific hurdles like being able to accurately measure HIV reservoirs. Thereafter studies will be conducted in animals so that we can avoid unknown toxicity in people, including turning on latent pools of HIV hiding in reservoirs throughout the body and causing opportunistic type diseases in people.

Vincente Planelles from Utah, also a CARE researcher, is trying to identify signals that would prevent toxicity like the development of dangerous cytokine storms that might be awakened when latency reversing drugs are administered to people whose dormant HIV has subsequently become active as a result of the kick strategy. Planelles is studying drugs that he hopes will reactivate latent HIV without causing a cytokine storm. He is looking at C7 which apparently does not induce cell/cytokine activation or toxicity in cell models. This will also need to be confirmed in animal studies.

Victor Garcia, also from CARE, presented his work on a mouse model that will hopefully allow us to conduct experiments in mice that will have the same results in people because Garcia's mouse model has been designed to have human immune characteristics. Garcia's model has been tested in a variety

of cells, including brain cells. If Garcia's mouse model is successful, people may be spared from the very real risk of serious toxicities that may be related to participation in "kick and kill" "cure" research.

Dave Margolis, Principal Investigator of CARE, presented data from members of his lab who are trying to develop a human cell model. They hope to create a system wherein experiments are only conducted with human cells, not other cell models. The belief is that experiments in non-human cell models may not have the same results in human cells. The goal here is to develop a human cell model that can be used to study the efficacy of single and combinations drugs as well as to describe impact on the immune system and possible toxicities.

As you can see, we are in the infancy stages of HIV "cure" research. We are still studying strategies and research methods in cell lines and animal models. Although a few drugs and strategies have been studied in humans, we have a very long way to go before this research is ready for prime time. We are in the AZT phase of "cure" research and have a very long way to go before we have more answers than questions. But every year we make more progress. I haven't seen this much excitement and creativity since the early days of HIV research. Mercifully, people aren't dropping like flies while we are waiting for new developments. We need to ensure that nothing we do during in these early days does more harm than good in people who now have every chance of living a fairly normal life with HIV. Thus, we need to proceed with caution and do our best to quell unreasonable community expectations on the way.