Eliminating Viral Reservoirs Key to Curing HIV

BY SUSAN LONDON
Contributing Writer

MEXICO CITY — A cure for HIV infection will require identifying and eliminating reservoirs of silent HIV in the body, in addition to using highly active antiretroviral therapy to stop viral replication.

"It's 11 years since the introduction of HAART. The dramatic reductions in viremia seen in patients on HAART initially [fueled] hopes that the infection could be cured with 2-3 years of continuous treatment. But to date, not a single patient has been cured," Dr. Robert F. Siliciano said in a plenary session at the International AIDS Conference.

Typically, when patients begin antiretroviral therapy, they experience a sharp drop in plasma HIV viral load, below the limits of detection of clinical assays, because the infected cells that produce most of the virus are short lived and the therapy stops new cells from becoming infected, Dr. Siciliano explained.

However, more sensitive assays show that instead of continued reduction of viral load with eventual cure, patients still have a very low level of viremia because of "the unique mechanism of viral persistence that exploits the fundamental physiology of CD4-positive T cells," he said.

In particular, HIV occasionally infects and replicates in activated T cells that revert to a resting state in which they can survive for decades. "This gives you a stably integrated form of the viral genome in a long-lived memory T cell," and in addition, the cells undergo molecular changes during the reversion that turn off HIV viral gene expression, said Dr. Siliciano, professor of medicine at Johns Hopkins University, Baltimore.

"This is almost a perfect recipe for persistence because it allows the virus essentially to persist just as information, and in this form, it is unaffected by immune responses and antiretroviral drugs," Dr. Siliciano observed.

However, if these cells become activated again, as some of them likely do every day, viral replication will resume.

Research data show that all HIV-infected patients who were tested had these latently infected, resting CD4 cells, the longevity of which has been confirmed. The number of these cells decreases extremely slowly in patients who are on antiretroviral therapy and who have had viral levels below the clinical limits of detection for years. "At this rate of decay, it would take over 70 years to clear this reservoir," he noted.

There are two main hypotheses on the persistent, very low level of viremia seen in HAART patients who have clinically undetectable viral levels.

One scenario is that viral replication continues despite the therapy. That would be of concern, because it would enable viral evolution leading to resistance and eventual treatment failure, he said.

Another hypothesis is that antiretroviral therapy stops ongoing viral replication, and the residual viremia that patients experience is a reflection of the release of virus from stable reservoirs—that is, cells that were infected before the therapy was initiated, such as those long-lived memory T cells.

The second hypothesis has a number of testable predictions, Dr. Siliciano said. First, the virus in the blood should genetically resemble that in the reservoir. Indeed, phylogenetic testing supports this prediction, showing that at least some of the circulating virus in such patients is similar and even identical to that in the resting cells.

Second, the residual viremia should not be accompanied by evolution (that is, change in the viral genome), which requires replication. Here, too, phylogenetic testing shows no evidence of the emergence of evolution in the form of new resistance mutations in the residual virus.

Third, and most important, is that intensifying HAART by adding another drug should not reduce the residual viremia, because there is no ongoing replication to inhibit, he said. Intensification studies have found no additional reduction in viral load.

"We cannot exclude a small contribution from ongoing replication, but it is clear at this point that the major problem is the release of virus from stable reservoirs," Dr. Siliciano said.

To identify these reservoirs, he and his colleagues have been focusing on the residual virus in the plasma released from the reservoirs. In about half of the patients in the study, this viral population is dominated by just a few viral clones, which suggests that there is a common source. However, the researchers have not been able to identify the clones in the resting CD4 cells, suggesting that there is another source.

"Our current hypothesis is that this represents the rare infection of a stem cell or progenitor cell, and that this cell can divide after infection," Dr. Siliciano said. "The idea is that there is a second major source of residual viremia, perhaps in a cell that has some capacity for self-renewal. It is certainly a disturbing [idea] and will require much further research."

Dr. Siliciano said he had no conflicts of interest regarding his presentation. ■

Stakeholders Regroup After Failure of Latest AIDS Vaccine

BY SUSAN LONDON
Contributing Writer

MEXICO CITY — The development of an AIDS vaccine is likely to take a long time, and research needs to be more selectively focused on the most promising candidate vaccines, given the recent failure of the latest leading candidate to prevent infection in a large, international trial, according to the findings of a report aimed at setting priorities for AIDS vaccine research.

Experts at the International AIDS Conference discussed the status of AIDS vaccine efforts at a press conference to unveil the AIDS Vaccine Blueprint 2008. The document, published by the International AIDS Vaccine Initiative (IAVI), is the fifth biennial report of its kind. It comes at a time when optimism in the field is waning, after early closure of the STEP trial of the failed vaccine last year and cancellation of the PAVE 100 trial of a new vaccine this year.

The blueprint delineates the current challenges in developing an AIDS vaccine, and provides interim milestones for each. "This is a way to measure [progress], to hold people accountable," explained Dr. Seth Berkley, president and CEO of IAVI.

The blueprint calls for pruning the vaccine pipeline. "We believe that the majority of the 30-odd candidates that are in the pipeline should be prioritized based on their probability of success," he said. This recommendation is not new, he acknowledged, but the document goes further, detailing how it should be done by requiring vaccine candidates to be superior to ones that have failed in preclinical testing.

In recent years, more stakeholders have rallied behind the blueprint, which will be critical going forward, according to Dr. Peter Piot, executive director of UNAIDS in Geneva. AIDS vaccine development "is not going to be something that can be done by one organization. It requires a coalition," he said.

"Science is never a straight line. Failure is part of the game," noted Dr. Alan Bernstein, executive director of the Global HIV Vaccine Enterprise in New York. As disappointing as the STEP trial's results were, the trial has been a success in the sense that it provided, and continues to provide, a wealth of data that will help inform future trials.

Given the retroviral nature of HIV and the lack of much precedence in developing vaccines against retroviruses, he applauded recent efforts by several organizations to stimulate diverse approaches to the problem. "I think that's urgently needed," he said. "We all should not be crowding though the same door."

Putting the AIDS vaccine effort into context, Dr. Berkley noted that the development of a vaccine typically takes decades. "So in a sense, this is par for the course, but particularly for a virus that is probably more difficult than any we have ever worked with before."

Advancing HIV vaccine research will require not only new talent, but also stable, predictable, and flexible financing, he continued. Flexibility "is important because … we need to be able to jump on advances and quickly drop things that aren't promising." This ability to be flexible will be critical to maintaining incentives that keep companies engaged in the effort.

In response to calls to end the vaccine research effort, Dr. Piot emphasized that the disease's toll remains staggering. "If the world can be satisfied with 2.7 million people infected per year—7,500 per day—then I am not so sure where the standards are for declaring something a total disaster," he commented.

Shutting down the AIDS vaccine trial sites in Africa would be "a big mistake," agreed Dr. Omu Anzala, chairman of microbiology at the University of Nairobi (Kenya) and director of the Kenya AIDS Vaccine Initiative. He noted that these sites—representing considerable infrastructure and capacity that have been put into place over half a decade—not only stand ready for future trials, but also continue to conduct epidemiological and basic HIV research. "It is this information that will then feed into HIV vaccine discovery and also feed into drug discovery," he pointed out.

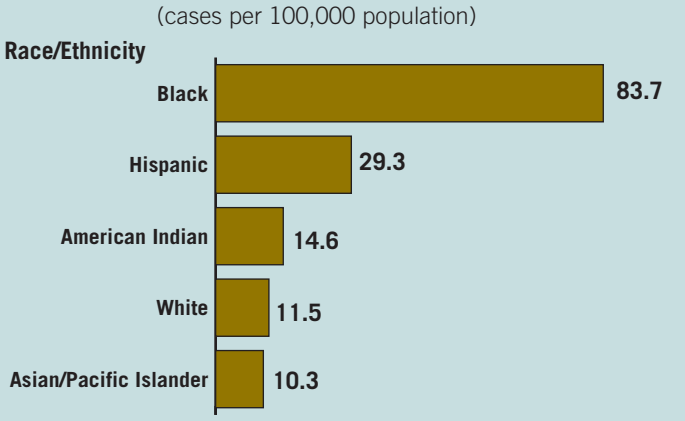
Dr. Anzala agreed with his colleagues that the failure of a single vaccine is not cause for condemning the entire AIDS vaccine initiative. Noting that he comes from a country known for long-distance running, he likened the search for an effective vaccine to a marathon in which perhaps 100 runners start and many fall by the wayside—but eventually one wins. "We cannot stop now," he concluded.

The speakers reported that they had no conflicts of interest related to the press conference. ■

DATA WATCH

Most New HIV Infections Occurred In Blacks in 2006

(cases per 100,000 population)



Note: Postcensus estimates by the U.S. Bureau of the Census of 50 states and the District of Columbia.
Source: JAMA 2008;300:525.