International AIDS Society Releases New HIV Cure Strategy

The updated report summarizes progress to date, identifies gaps and outlines recommendations for HIV cure research over the next five years.

December 6, 2021 By Liz Highleyman

Coinciding with World AIDS Day on December 1, the International AIDS Society (IAS) has launched a new global scientific research strategy for working toward a broadly applicable cure for HIV. The report, titled "Research Priorities for an HIV Cure: IAS Global Scientific Strategy 2021," was published in Nature Medicine.

"Over the past decade, HIV cure research has greatly intensified, but it remains clear that we will not cure HIV until we better understand where and how the virus hides and we also get much better at measuring the HIV reservoir," Sharon Lewin, MD, of the Peter Doherty Institute for Infection and Immunity in Australia, who cochairs the IAS Towards an HIV Cure program, said in a statement.

The past decade has been marked by progress toward achieving a functional cure for HIV—meaning sustained viral remission without antiretroviral therapy—but the field has seen several disappointments.

While antiretrovirals can keep HIV replication suppressed as long as treatment continues, the virus inserts its genetic blueprints into the chromosomes of human cells and establishes a latent reservoir that is unreachable by antiretrovirals and usually invisible to the immune system. These so-called HIV proviruses can lie dormant in resting immune cells indefinitely while on treatment, but they usually start churning out new virus soon after antiretrovirals are stopped.

The only two people widely regarded as cured of HIV—the late Timothy Ray Brown ("the Berlin Patient") and Adam Castillejo ("the London Patient")—received bone marrow stem cell transplants from donors with an uncommon genetic mutation (CCR5-delta32) that makes immune cells resistant to HIV entry. But this procedure is too dangerous for people who don't need it for treat life-threatening cancer. A few other patients who received stem cell transplants from donors without this mutation temporarily controlled HIV after stopping antiretrovirals, but eventually the virus rebounded.

Over the years, researchers have identified a small number of people who manage to naturally control HIV without antiretroviral treatment. Some (known as elite controllers) have never taken antiretrovirals, while others (known as posttreatment controllers) have been able to maintain viral control after stopping therapy. The latter is more likely if treatment is started very early. The prospects may be best for infants. In 2013, researchers reported a case of a baby in Mississippi who received antiretrovirals soon after birth but later fell out of care and stopped treatment. The child managed to control HIV for more than two years off treatment, but here, too, the virus ultimately rebounded.

More recently, researchers have described two women—Loreen Willenberg ("the San Francisco Patient") and the anonymous "Esperanza Patient" in Argentina—who appear to have eliminated HIV without antiretroviral treatment and may even have achieved a natural cure.

While such cases are exceptional, they offer proof of concept that a functional cure is possible and offer clues that may help researchers achieve long-term viral remission in other people living with HIV.

"It is clear that an HIV cure is achievable. The past five years of following the science have taught us that," said IAS president Adeeba Kamarulzaman, MBBS, of the Centre of Excellence for Research in AIDS at the University of Malaya in Malaysia.

"The recent case of the cured Esperanza patient adds a new dimension to our understanding of HIV controllers, those people who naturally control HIV without antiretroviral therapy," she continued. "The challenge is to identify how commonly elimination of all intact virus occurs in elite controllers and what the mechanism is that makes that possible. We can then work out how we can replicate it on a broad scale. We need an HIV cure that works for everyone so we can end the HIV pandemic."

The third edition of the IAS cure research strategy was developed by a 68-member International Scientific Working Group. It reflects on progress to date, identifies gaps in the research agenda and outlines recommendations for HIV cure research over the next five years.

The HIV reservoir is now seen as an evolving, rather than static, source of virus not reached by antiretrovirals, the report notes. Researchers have identified important differences among people living with HIV, such as biological sex, that may affect reservoir location and dynamics.

Technological developments—such as the ability to better detect tiny amounts of hidden virus—allow for a better understanding of how HIV latency is established and how the virus is reactivated after treatment interruption.

What's more, new drugs and interventions are being developed and have shown early promise in preclinical animal models. These include the "poke and clear" strategy (previously known as "shock and kill"), which involves waking up dormant virus using latency-reversing agents, and the "block and lock" approach, which aims to keep proviruses asleep indefinitely. Experimental interventions include broadly neutralizing antibodies, therapeutic vaccines, engineered immune

cells and gene therapy. Many experts think combination approaches are likely to yield the best outcomes.

The IAS HIV cure program aims to strengthen international multidisciplinary collaborations, promote the involvement of early-career researchers and scientists from countries most affected by HIV, alleviate regulatory and logistical challenges associated with drug development and enhance community engagement and advocacy.

“Communities should be empowered and supported through education and engagement at all levels of the research process to help shape the HIV cure research agenda and allow for potential study participants to have a voice in trial design,” the report states. “Attention must focus on broad representation (for example, age, race and ethnicity, gender and sexuality, geographic location, risk behaviors) in research.... Further, ethical questions of equity and justice related to the distribution of safe and effective cure interventions must consider acceptability, scalability and cost-effectiveness.”

“In the next decade, we expect to see a greater understanding of HIV reservoirs, an increasing number of clinical trials and hopefully reports of individuals who achieved long-term remission with less intensive and more widely applicable strategies,” the report concludes. “Fortunately, the resources for such work remain available, and the field is highly committed to making the long-term commitments necessary to develop an effective and scalable remission or cure strategy.”

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