A nyone who gets tested for sexually transmitted diseases waits in fear of the H-bomb: “You’ve got HIV.” HIV, or human immunodeficiency virus, causes the fatal and incurable disease AIDS.

A quarter century has passed since the first AIDS case was reported in 1981. When the disease was discovered, people held out hopes that a cure would quickly be found. Or perhaps scientists would develop a vaccine that could eliminate this awful disease the way smallpox was eliminated.

But HIV has proven to be a clever foe. No cure has been found, and no vaccine is available. Still, scientists around the world struggle to accomplish these goals. At Arizona State University, researchers are tackling HIV from a new angle. They hope to create a successful and affordable vaccine. They have their work cut out for them. Several characteristics of the virus make it an elusive target for vaccine researchers.

With most diseases, even highly lethal ones, at least some people recover fully. The survivors are immune to future infection from the same pathogen. Scientists study these survivors to figure out which immune responses correlate with protection from the disease. These signature immune responses help them create a vaccine that will provide the same immunity without causing an infection.

“In all research on vaccines from the time of [Edward] Jenner, one of the key things to create immunity is to look for natural cases of immunity,” explains Tsafrir Mor, an ASU biologist. “But HIV is a completely lethal disease. Everybody getting infected dies.”

As a retrovirus, HIV also mutates rapidly. Typically, vaccines only protect against one or a small number of viral subtypes. However, many variants of HIV are circulating worldwide, and a successful vaccine will need to produce an immune response to a large number of them.
THEY GET OTHER SEXUALLY TRANSMITTED DISEASES SUCH

THE HIV virus (at top) is simple in structure. It consists of an RNA core surrounded by a protein coat, or capsid. The RNA contains genetic information for making new copies of the virus. The capsid is surrounded by a membrane-like fatty envelope. Glycoproteins are embedded within that fatty envelope. Glycoproteins are proteins with attached sugar molecules. They can bind with receptors found on the membranes of mucosal cells that line the intestines and urogenital tract. Once bound, the virus is transported from the outside of that lining across the cells. It is released on the inside. This process is called transcytosis. The cell is infected when the viral and cell membranes fuse. The virus is later transferred to immune system cells (middle). ASU scientists now know that specific antibodies can be directed against particular proteins located on regions of the viral envelope. These antibodies can block transcytosis and/or infection from taking place (right).
In addition, HIV attacks the immune system, the very system that should be fighting it. Soon after the virus is transmitted to a person, it attaches to macrophages and dendritic cells. These cells normally aid the immune system by “eating” pathogens. The cells then present pathogen remains on their surfaces to signal the immune system to take action. Instead, HIV uses these cells to hitch a ride back to the lymph nodes, the immune system’s “headquarters.” In this way, HIV uses macrophages like Trojan horses to help it get past our bodies’ defenses.

In the lymph nodes, the virus primarily infects immune cells called helper T cells. These cells stimulate other components of the immune system. HIV can hide out in helper T cells for a long time—sometimes for years—completely invisible to the rest of the immune system. Eventually, the virus starts replicating, destroying its cellular host and rendering it unable to stimulate the immune system to fight back.

Mor puts it even more simply. “The virus is making a fool of our immune systems,” he says.

These problems and others have complicated attempts to develop a vaccine against HIV. Mor and his colleagues are trying a new approach in the hopes of cutting off HIV before it even gets started.

Most vaccines are delivered through an injection. They stimulate the body to produce antibodies that will fight off a particular invader. The vaccines are generally designed to fight off viruses once they have entered the body.

Unfortunately, once HIV gets into the body, it is very difficult to fight. “HIV can remain inside the cell without the immune system being aware of it. And of course, it attacks the immune system,” says Mor.

Mor and his colleagues want to turn HIV away at the gates. The body’s first line of defense is its epithelial cells, which line the outside and inside of the body. Your skin is made up of epithelial cells. So are the mucosal linings of your mouth, nose, lungs, anus, and urinary and reproductive tracts.

HIV is typically spread when secretions from an infected person come in contact with the mucosal cells of another. Normally, epithelial cells form a wall that won’t let anything pass through. However, the body needs to allow some molecules to pass. One of the ways it does this is through a process called “transcytosis.” Molecules bind to receptors on one side of an epithelial cell and are ferried through the cell in structures called vesicles.

HIV can also attach to these receptors, passing itself off as a molecule that should be allowed into the body. It slips through the body’s borders like a traveler with a fake passport. Once inside, the virus gets busy finding host cells to infect so that it can start replicating.

Mor and his colleagues want to stop the virus at the mucosal level so that it never gets a chance to get inside the body. They plan to do this using an oral vaccine that is designed to trigger a mucosal immune response.

“Our approach is very novel,” says Nobuyuki Matoba, a post-doctoral researcher working on the project. “Most vaccines only cope with the pathogen inside the body. For HIV, the conventional approach doesn’t work. You have to activate the mucosal immune system. You can only do that by using the mucosal system, either orally or nasally.”

Where does one even begin to develop this sort of vaccine? The researchers have found a good starting point. Although no AIDS patients have recovered from the disease, there are a few examples of natural immunity. A small number of people have avoided infection despite repeated exposure to the virus. These folks include spouses of infected patients, and sex workers who have multiple clients who don’t use condoms.

“They get other sexually transmitted diseases such as gonorrhea, syphilis, and HPV, but they don’t get HIV,” says Mor. These infection-resisters are known as HEPS—highly exposed, persistently seronegative individuals. Scientists are trying to learn how HEPS manage to resist infection in order to mimic the process.
ASU scientists created a vaccine with two distinct parts. The vaccine combines a nontoxic protein subunit of cholera toxin with a portion of the HIV gp120 envelope protein called 9T0P. The toxin portion allows the vaccine molecule to bind to mucosal cells in epithelial tissues (middle). A complex chain of immune system cells then pass the vaccine molecule through a process that results in production of antibodies by plasma cells (bottom). Antibodies of the IgG type mostly remain in the serum. At the same time, specialized antibodies called secretory IGA are transported across the mucosal barrier into body cavities such as the vagina or intestines. A successful vaccine would result in antibodies that bind to and deactivate HIV before it can enter epithelial cells (top right).
Mor works closely with Morgane Bomsel of the Cochin Institute in Paris. Bomsel has learned that the HEPS are resisting infection at the mucosal level. For example, a typical HEPS female carries IgA-type antibodies in her vaginal secretions. These antibodies block transcytosis. HIV can’t slip through the epithelial cells in her body the way it normally would.

Mor is working to create a vaccine that will produce these antibodies and keep HIV out. Traditional injected vaccines only produce IgG-type antibodies. These antibodies circulate in the blood but do not appear on the mucosal surfaces like IgA antibodies do. However, when a vaccine is delivered directly to the mucosal system (through oral or inhaled delivery) it can produce both IgG and IgA antibodies. The goal is to develop an oral vaccine that will block the virus at the mucosal level and also neutralize HIV inside the body. “Then if the virus slips through the mucosa, we can block it at a later stage,” explains Mor.

The researchers have been looking at a lab-made antibody known as 2F5. It was initially discovered as a neutralizing antibody—one that prevents infection of cells. In laboratory tests, Bomsel has shown that 2F5 can also successfully block transcytosis. When tested in macaques, passive immunization with 2F5 protected the animals from mucosal infection.

The 2F5 antibody targets HIV by recognizing a protein on the virus called gp41. “There is something in the structure of gp41 that allows it to be recognized by the immune system,” explains Mor. As a result, the scientists are using a portion of the gp41 protein in their vaccine to stimulate an immune response. They have combined it with a non-toxic part of the cholera toxin that acts as a mucosal binding agent.

The team has tested the combination on mice using both nasal and injected vaccines. Ideally, the vaccine will be given through multiple routes, Mor says. “We produced both antibody responses, IgG and IgA,” he says. “Of course, just making antibodies is not good enough. You need neutralizing antibodies.” The ASU team sent the mouse antibodies to Bomsel. She tested the antibodies in her lab and found that they do indeed block transcytosis.

The results are extremely promising, but there is still a long way to go. More animal trials are in the works. The trials are needed to ensure that the vaccine is safe as well as effective. Only then can the vaccine be tested on humans.

Testing vaccines for diseases like HIV is more difficult than typical human trials. “There is only way to tell if a vaccine works. You have to give the vaccine to test subjects and then infect those same subjects with the disease. You can’t do that with a disease that’s incurable,” explains Hugh Mason, an ASU biologist. “So you vaccinate a large number of people in a population that’s at risk already. You know there’s a calculable risk that they will get the disease.”

Scientists then follow those people over time. They want an answer to one big question. Do vaccinated people acquire the infection at a lower rate than those who aren’t vaccinated?

Mason is working on plant-based vaccines for the other “H-bombs” in the world of STDs—herpes, human papilloma virus, and, in particular, hepatitis B. Like HIV, these diseases have no cures. Although a vaccine exists for hepatitis B, it is very expensive and difficult to deliver in developing countries where it is most needed.

That’s why the ASU scientists are working to grow all of these vaccines in plants. Plant-derived vaccines can be made much more cheaply than traditional vaccines. Most vaccines are mass-produced in laboratory cultures. This process is efficient but expensive. The majority of HIV infections, like hepatitis B, occur in developing countries. The ASU researchers want to find a way to help these countries develop their own vaccines in a more affordable manner.

“We hope that our research will be practical and possibly run by a commercial entity in time,” says Mor. “But we don’t expect that an HIV vaccine will generate a lot of money. We don’t want it to. We want it to be accessible.”

Matoba expresses the goal even more succinctly. “Every minute, 10 people are infected with HIV, and five people die of AIDS,” he says. “We have to stop it.”

STD vaccine research at ASU is supported by the National Institutes of Health. For more information, contact Tsafir Mor, Ph.D., School of Life Sciences, 480.727.7405. Send e-mail to tsafir.mor@asu.edu or visit the Biodesign Institute web site at http://biodesign.asu.edu/