Beyond the ABCs: How to Prevent HIV

Drs Quarraisha & Salim Abdool Karim developed a gel to prevent sexually acquired HIV infections in women, empowering women to protect themselves

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A **virus** is a microscopic organism which consists of a **genome** (genetic material) enclosed within a **capsid** (a protein coat), and sometimes, an additional outer protein **envelope**. Scientists estimate that there are around 10,000,000,000,000,000,000,000,000,000,000 viruses on Earth. That's 31 zeroes…there are a *lot* of viruses!

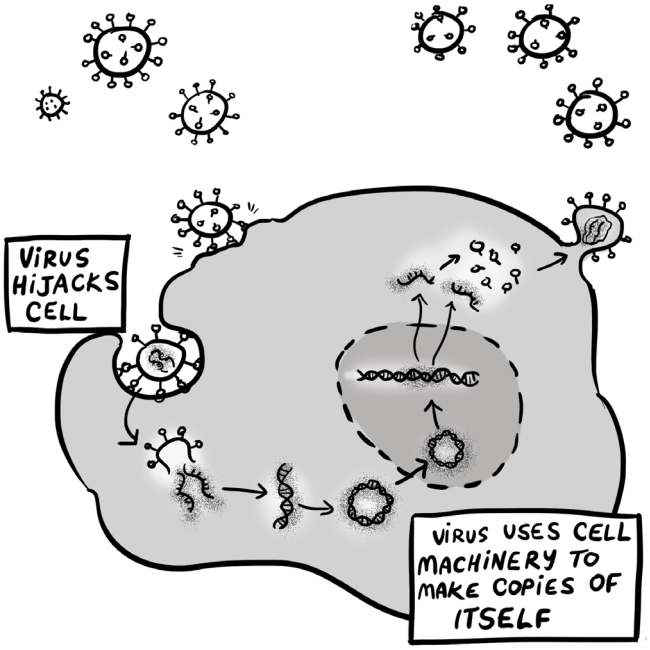
Technically, viruses aren't alive: they can't **reproduce** (make copies of themselves) on their own. Instead, viruses infect living host cells, and multiply in number using the cell's own machinery and resources. These viruses are tiny – instead of being measured in metres or centimetres, they are only **nanometres** (a billionth of a metre) in length. Most viruses are harmless, but some of these miniscule molecular machines can infect living organisms, such as bacteria, plants, and animals, causing diseases like the common cold, rabies, and COVID-19.

In humans, one example of a deadly virus is the **human immunodeficiency virus** (HIV).

Meet HIV: the virus behind AIDS

HIV is a spiky, roughly spherical virus with a diameter of about 120 nanometres. For scale, that's about 60 times smaller than a red blood cell in the human body. HIV also happens to be a **retrovirus**, a type of virus that can insert its genome into the cells it infects.

HIV can only infect CD4+ cells – that is, a cell with a CD4 **receptor** (a type of protein found on the surface of cells). Examples of CD4+ cells include white blood cells, such as **macrophages** (which swallow foreign substances, like cancer cells) and **T-helper cells** (which release **cytokines**, a signalling molecule which activates the immune system). When HIV encounters a CD4+ cell, it binds to the CD4 receptor, fuses with the cell membrane, and releases its genetic material into the host cell.



Unlike the double-stranded DNA found in human cells, HIV's genome consists of single-stranded RNA molecules. Although RNA and DNA are quite similar, they are different in structure, and

consequently for HIV to reproduce, it must use a r**everse transcriptase**, an **enzyme** (a specialized protein), to convert its RNA genome into a DNA version, known as a **provirus**. This provirus then integrates into the host cell's DNA, using a second enzyme called **integrase**. There, the provirus lies dormant, waiting for the host cell to replicate its DNA. Each time the host cell reproduces, it inadvertently produces new HIV particles, which results in two main effects: (1) the host cell is destroyed, and (2) the new HIV particles will go on to infect additional CD4+ cells.

This cycle will continue to repeat again and again. Normally, the human body has between 500 to 1,500 CD4+ cells per cubic millimeter (mm^3) of blood. An HIV infection will steadily weaken the immune system over the years, by causing a drop in the number of CD4+ cells available to fight infections. Eventually, the human body is unable to produce enough new CD4+ cells to replace those being destroyed by HIV.

When there are under 200 CD4+ cells/mm^3, the immune system becomes severely compromised, causing **acquired immunodeficiency syndrome** (AIDS). In this state, the body is more vulnerable to infections that a healthy immune system would be able to fight off, like the common cold and pneumonia, increasing the likelihood of death.

When it comes to preventing HIV/AIDS, the ABCs aren't enough

For decades, researchers have been trying to better understand, prevent and treat HIV/AIDS.

Since HIV spreads largely by the transfer of bodily fluids, such as blood, breast milk, and semen or vaginal fluids during sexual intercourse, experts in Uganda were the first to recommend the **ABCs** to prevent HIV infection: **abstinence** (to avoid having sex), **being faithful** (to reduce exposure to HIV by having a single partner) and using a **condom** (to prevent the transfer of semen).

But the ABCs aren't a perfect HIV prevention strategy, and indeed, have many societal problems associated with them. In fact, two researchers, Dr. Quarraisha Abdool Karim and Dr. Salim Abdool Karim, have been looking beyond the ABCs to prevent HIV infections.

"In 1989, we had good descriptions of AIDS in industrialized countries, and in West, Central and East Africa, but there was very little data on HIV in South Africa," says Dr. Quarraisha, a public health researcher at Centre for the AIDS Programme of Research in South Africa (CAPRISA). "One of the first things in studying epidemics is to understand what the magnitude of the problem is, and its characteristics – who is getting infected by AIDS?"

To answer this question, the Karims carried out population-level surveys to better understand HIV/AIDS in South Africa, and how factors, such as gender and age, played a role in this epidemic.

They quickly learned that women, especially teenagers, were more likely to have HIV infections, and tended to acquire HIV five to seven years earlier than men.

"What became clear was that women understood the risk, but they were unable to negotiate the ABCs – because all of these are dependent on male cooperation," says Dr. Quarraisha, pointing out the gender power imbalance in relationships. In many parts of the world, it can be difficult for

women to insist on following through on the ABCs as they are financially dependant on their sexual partners, an issue that the Karims couldn't directly address through their research.

"We heard this repeatedly [from women]: 'give us something we can use – that is safe and effective.' That's what led us down the path of **microbicides**," says Dr. Quarraisha.

A **microbicide** is a compound that can be applied as a gel or cream inside the vagina or rectum to act as a barrier against sexually transmitted infections, like HIV.

Currently, doctors prescribe a combination of medications to slow down HIV infections, allowing the immune system an opportunity to recover. These medications include the **anti-retroviral** drug, Tenofovir, which slows down HIV reproduction by blocking its reverse transcriptase enzyme. The Karims thought that Tenofovir could be adapted for use in a microbicide, and could potentially be used as a new HIV prevention technology for women.

"We needed to develop a completely new solution because none of the existing solutions addressed the problem," says Dr. Salim, a physician and global health researcher at CAPRISA. "It was a part of Quarraisha's approach: how do we empower women to protect themselves?"

Over two decades, the Karims built a proof-of-concept technology

It took almost two decades for the Karims to finally develop a viable 1% Tenofovir gel microbicide, which women could apply to their vaginas as an HIV prevention strategy. This microbicide was to be taken in two doses: approximately 12 hours before and after sexual intercourse.

The Karims' next step was to test their Tenofovir gel.

"We wanted to do a study that would give us an answer as to whether this gel was safe, and does it prevent HIV? We needed to do the study with enough people to answer both questions," says Dr. Salim.

In 2007, the Karims launched a large-scale study, called CAPRISA 004, to test their Tenofovir gel in over 800 HIV uninfected, sexually active women living in South Africa.

Remarkably, the Karims found that their 1% Tenofovir gel microbicide was 39% effective in reducing the risk of HIV transmission during sexual intercourse. While 39% may not seem like a high number, this was in fact a significant breakthrough. The Karims had demonstrated, for the first time, that Tenofovir gels prevented sexually acquired HIV infections in women, and provided an option for women to protect themselves.

This proof-of-concept was hailed as one of the "Top 10 Scientific Breakthroughs of 2010" in the Science journal, and led the Karims to win multiple awards, including the 2020 John Dirks Canada Gairdner Global Health Award. It also earned the Karims multiple standing ovations at the 2010 XVIII International AIDS Conference.

"Scientists are generally very conservative – they're not a very excitable lot. It's not a rock concert," says Dr. Quarraisha, remembering the very tangible excitement in the air during her talk where she first unveiled their breakthrough findings.

Notably, the Karims' findings laid the foundations for **pre-exposure prophylaxis** (PrEP): a standard HIV prevention strategy that was first recommended by the World Health Organization in 2015, where people at risk for HIV take a daily Tenofo-

vir-containing pill to lower their risk of infection.

Looking ahead

The Karims' long-term vision – trying to stop HIV infections in young women – has not changed since almost thirty years ago. Today, they continue to study different aspects of HIV/AIDS, including the shortcomings of their breakthrough product.

Despite its success, the Karims note that their Tenofovir gel has a low level of efficacy, and its success is highly dependent on women using the gel, which is often difficult to apply. Instead, the Karims are now using a newer, stronger version of Tenofovir, called Tenofovir Elafenamide, to develop an arm implant to place in women, like a contraceptive implant.

"This little tube will release Tenofovir Elafenamide at a very slow level continuously. So, for a whole year, this little implant will be releasing the drug," says Dr. Salim. "We are studying whether this new potent form of Tenofovir, put in an implant, will be more effective in preventing HIV."

The Karims are also studying whether there are additional biological factors which may explain why women had different rates of success with their Tenofovir gel microbicide.

"Science is a very slow process, with incremental knowledge gains," says Dr. Quarraisha. "If you want to be a scientist, you must be persistent, and you must be very passionate about wanting to find the solution. It's not something that will happen instantly. If we knew the answers, we wouldn't need the research."

"If it were easy, everyone else would have already done it. The fact that you take on a difficult problem that does not have an easy solution means that you have to spend years battling through your failures – and how you learn from each failure to do things better the next time, is central to it," says Dr. Salim. "Each failure is one step closer to success."