Zidovudine or azidothymidine [1]

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In 1964, Jerome Horwitz synthesized the drug zidovudine, commonly abbreviated ZDV, otherwise known as azidothymidine, or AZT, at Wayne State University School of Medicine in Detroit, Michigan. Horwitz and his colleagues originally developed zidovudine to treat cancers caused by retroviruses. In 1983, Nobel Prize in Physiology or Medicine[6] recipients Françoise Barré-Sinoussi and Luc Montagnier [7] discovered a new retrovirus [8], the human immunodeficiency virus, or HIV, at the Pasteur Institute in Paris, France. HIV weakens the immune system and can be passed from a pregnant woman to her fetus [9] *in utero*, or in the womb [10]. In 1984, scientist Marty St. Clair and her team determined that zidovudine could help treat HIV. Zidovudine was the first medicine discovered to help treat HIV and prevent the transmission of HIV from affected pregnant women to fetuses in the womb [10] by blocking the virus from passing through theplacenta [11].

A retrovirus [8] is a type of virus that attaches to a host cell inside another organism. Many viruses use deoxyribonucleic acid, or DNA, to replicate themselves inside host cells. A retrovirus [8] uses a different type of genetic material called ribonucleic acid, or RNA, to replicate itself. The retrovirus [8] uses reverse transcriptase, an enzyme that facilitates the replication of DNA from the retrovirus's RNA. Once attached to the host cell, a retrovirus [8] injects its own viral RNA, which is a single-stranded molecule that codes for DNA. DNA is a double-stranded molecule that passes traits from parent to offspring. Once the retrovirus [8] injects its RNA into the host cell, the host cell replicates the retrovirus [8] within itself and spreads the virus to other cells within the body. Those new host cells repeat the process.

Before zidovudine was invented, scientists were trying to find a cure for cancer. In the 1960s, scientists theorized that environmental retroviruses caused cancer in humans [12] since they also caused cancer in somebirds [13]. Horwitz, a medical researcher in the US, and his colleagues originally synthesized zidovudine as a medication to fight cancer in humans [12]. The National Institutes of Health [14], or NIH, a US medical and health researchorganization [15] headquartered in Bethesda, Maryland, funded that research with a grant. Horwitz designed the drug to integrate into the DNA in cancer cells and stop the growth of those cells. However, when zidovudine proved ineffective as an anticancer drug during preliminary testing, scientists set it aside until the 1970s.

In 1974, scientist Wofram Ostertag of the Max Planck Institute, a non-governmental and non-profit research institute, in Munich, Germany, discovered that a retrovirus [8] called murine [16] leukemia virus, or MLV, could not replicate itself when treated with zidovudine. After that discovery, scientists classified zidovudine as a nucleoside analog reverse transcriptase inhibitor, or NRTI, class medication. That meant that zidovudine inhibited the function of reverse transcriptase, which is an enzyme that retroviruses use to generate DNA from their own RNA. By blocking the reverse transcriptase, zidovudine prevented the retrovirus [8] from multiplying itself and spreading to other healthy cells in the body. However, there were very few known retroviruses that affected humans [12] in the 1970s, so Ostertag's study did not receive much attention.

That changed in the 1980s with the discovery of a newretrovirus [8], HIV. In the early 1980s, scientists had not discovered or diagnosed HIV in any humans [12]. In 1981, five homosexual men in Los Angeles, California, presented with symptoms of pneumocystis carinii pneumonia, or PCP, a rare lung disease that generally does not affect healthy individuals with functioning immune systems. That same year, *The New York Times* reported forty-one cases of Kaposi's sarcoma, a rare skin cancer that causes skin lesions, in the states of New York and California. By the end of the year, there were 270 reported cases of severe immunodeficiency, or the lack of a working immune system, among homosexual men in the US. Of those 270 men, 121 died. With the emergence of rare cancers and diseases in the population of homosexual men, medical professionals began looking for the cause of those conditions, which they thought was a communicable illness, or an illness that can be transmitted from person to person.

Some researchers noted that the homosexual men were presenting opportunistic infections. An opportunistic infection is an infection that a healthy body's immune system can usually prevent unless it is compromised. Immunodeficiency can lead to various opportunistic infections, which may ultimately result in death. PCP is an example of an opportunistic infection. On 24 September 1982, the Centers for Disease Control and Prevention, or CDC, a US agency headquartered in Atlanta, Georgia, that protects individuals from health and safety threats, used the term acquired immunodeficiency syndrome, or AIDS, for the first time. The CDC used the term AIDS to describe the weakened immune systems of the homosexual men who had increasingly developed opportunistic infections in 1982. However, the cause of AIDS was still unknown.

On 10 December 1982, the CDC reported that an infant who received a blood transfusion acquired AIDS. In the next week, the CDC reported 22 more cases of immunodeficiency and opportunistic infections in infants. On 7 January 1983, the CDC reported cases of women acquiring AIDS through sexual contact with male partners who had AIDS. Those cases all demonstrated that AIDS could be passed from one human to another, meaning that the condition had to be caused by something transmittable,

such as a virus.

On 20 May 1983, researchers Barré-Sinoussi and Montagnier of the Pasteur Institute discovered a retrovirus [8] they named lymphadenopathy associated virus, or LAV, that they thought was the cause of AIDS. In the US, Robert Gallo, a scientist at the NIH, discovered a retrovirus [8] that he named human t-lymphotropic virus type three, or HTLV-III, which he thought caused AIDS. In June 1984, Gallo and Montagnier held a press conference from the Pasteur Institute to announce that LAV and HTLV-III were identical and likely caused AIDS. Both LAV and HTLV-III were the same virus, which was renamed human immunodeficiency virus, or HIV, in 1986.

After the discovery of HIV, a retrovirus [8] that impacted human health through the development of AIDS, researchers and medical professionals returned to zidovudine and its potential as a therapy for retroviral infection. In 1984, St. Clair and her team of scientists began testing different medications and their effects on HIV replication. Scientists were looking to block the replication of the virus. One way to block the replication of a retrovirus [8] is to block the function of reverse transcriptase. St. Clair and her colleagues plated 350 tissue cultures with living cells, the HIV virus, and different drugs to see if any drug hindered the replication of the virus. Sixteen out of 350 of the tissue cultures showed no signs of HIV replication. Those sixteen tissue cultures had been treated with zidovudine. Zidovudine blocked HIV from replicating itself, but it did not kill the virus, so even with treatment, HIV was still present in the cells of treated tissue cultures. That meant that even though zidovudine could treat HIV, it was not a cure.

In 1985, the Burroughs-Wellcome Fund, a private research foundation in Research Triangle Park, North Carolina, performed a clinical trial that demonstrated zidovudine prolonged the lives of individual humans [12] who had HIV. By the end of 1985, each inhabited region of the world reported at least one case of HIV. The Food and Drug Administration [17], or FDA, a US organization [15] that promotes public health by monitoring food and drugs headquartered in Silver Spring, Maryland, approved zidovudine after one human clinical trial because no other drug existed to treat the growing population affected by HIV. According to the CDC, from 1987 to 1992, the number of cases of AIDS from progressed HIV grew from 50,280 instances to 202,520 instances in the US. The FDA approved zidovudine to lower those growing numbers of HIV instances. Zidovudine was typically taken as an oral tablet, but professionals could also administer it intravenously in medical situations like during labor and delivery.

Although zidovudine treated an HIV infection, physicians used it together with other antiretroviral medications as of 1996 because when newer, more effective drugs appeared on the market. Scientists referred to that method of treatment as highly active antiretroviral therapy. Using multiple treatments prevented an individual from developing drug resistance. Drug resistance occurs when the body accustoms itself to a drug and is no longer affected by that drug.

In 1991, researchers in the US tested the efficacy of zidovudine on maternal-fetal transmission of HIV. Pregnant HIV-positive women, or pregnant women who are infected with HIV, can transfer the virus to their fetus [9] *in utero*. In those cases, the infant would be born HIV-positive. Aside from sexual contact and *in utero* transmission from pregnant woman to fetus [9], HIV can be transmitted during breastfeeding or during childbirth through contact with blood. In the 1991 study, researchers showed that zidovudine reduced the rate of maternal-fetal transmission of HIV by two-thirds. In the trial, the researchers gave HIV-positive women 500 mg of zidovudine daily to take orally and then a continuous intravenous drip during labor. The researchers gave newborns oral zidovudine within twenty-four hours of their birth and up to six weeks thereafter. According to the study, the drug was well-tolerated by the pregnant women and did not cause adverse reactions to the infants. On 8 August 1994, the FDA released a statement approving zidovudine to be used to prevent the maternal-fetal transmission of HIV. The zidovudine regimen for HIV-positive pregnant women begins at fourteen weeks gestation [18] and continues into labor, during which they receive an intravenous drip of zidovudine.

Although zidovudine helped treat HIV, researchers noted some harmful side effects related to the drug. At high doses, zidovudine can make an individual's DNA unable to replicate, which can lead to damage of cardiac and skeletal muscles. Physicians in the 1980s and 1990s administered higher doses of zidovudine compared to the doses that individuals infected with HIV take in 2018. In the 1980s and 1990s, physicians typically administered 400 mg of the drug every four hours. As of 2018, individuals infected with HIV take zidovudine orally as a tablet, either ingesting 300 mg twice a day or 600 mg three times a day.

If an HIV-positive pregnant woman was dosing to prevent maternal-fetal transmission of HIV, doctors gave the woman 100 mg five times a day in concert with other antiretroviral drugs. If she was in labor, doctors gave the woman 2 mg per kg of her body weight over one hour, then 1 mg per kg of her body weight every hour until she gave birth and the umbilical cord [19] was clamped. For example, if a woman weighed 50 kg, she would receive 100 mg of zidovudine for the first hour, then 50 mg of zidovudine each hour after that. The NIH recommended that only pregnant women with a viral load less than 400 copies per ml of blood should receive intravenous zidovudine. That means if the pregnant woman had a viral load count less than 400 copies/ml, intravenous zidovudine was not required. Although the amount of zidovudine administered in the late 1980s and early 1990s was higher and could potentially cause negative side effects, physicians still prescribed the medication, as the side effects were preferable to untreated HIV, which is a life-threatening illness. The common side effects of zidovudine included anemia [20], a condition in which the body does not produce enough red blood cells, and general discomfort.

When a pharmaceutical company started selling zidovudine, *The New York Times* described the drug's cost as inhumane. At the time, zidovudine was the most expensive drug in history, originally costing a patient $10,000 annually. However, in 1989, Burroughs-Wellcome, the company that held the patent for zidovudine, lowered the cost to $8,000 annually. About thirty-five

percent of patients with HIV or AIDS did not have health insurance to help cover that cost. For those patients, the drug was unobtainable. The patent for zidovudine expired in 2005, allowing the FDA to approve three cheaper generic versions of the drug. As of 2020, zidovudine is used as part of a regimen to prevent maternal-fetal transmission of HIV. Zidovudine is commonly prescribed under the brand name Retrovir.

Though zidovudine was the first medication to treat HIV, scientists developed several other forms of treatment for HIV. Because of zidovudine, new treatments, and preventative methods, the instances of new HIV diagnoses and rate of maternal-fetal transmission of the virus is generally decreasing each year.

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Subject

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