Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus with Zidovudine Treatment [1]


In 1994, Edward M. Connor and colleagues published "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment." Their study summarized how to reduce the transfer of human immunodeficiency virus, or HIV, from pregnant women to their fetuses with Zidovudine, otherwise known as AZT. HIV is a virus that weakens the immune system by destroying white blood cells, a part of the body’s immune system. Fifteen to forty percent of infants born to HIV-positive mothers become infected during fetal development, labor and delivery, or breast-feeding. From April 1991 to December 1993, Connor and his colleagues researched HIV-positive pregnant women who took AZT, a drug that treats but does not cure an HIV infection. In their article, Conner and colleagues showed that AZT decreased the maternal-infant transmission of HIV and helped decrease infant mortality due to the viral infection.

Zidovudine, also known by Retrovir, azidothymidine or AZT, is a medication used to treat HIV infection in adults and to prevent maternal-fetal transmission of the virus. On 19 March 1987, the Food and Drug Administration [8], or the FDA, approved AZT as the first medication to treat HIV. The FDA is a US government agency that supervises the safety of consumable goods, such as food, prescription drugs, and supplements. The FDA approved AZT after one human trial, in which one group of people got the drug and another group got a placebo. A placebo is a medication with no physiological effects taken by the control group, or the group that does not receive treatment to determine a medication’s efficacy. The FDA typically requires three human trials before approval of a drug, but the people taking the placebo were dying quickly and needed treatment to stay alive.

AZT works in vitro [7] to prevent HIV from reproducing and lowers the viral load, or the amount of virus detectable in blood. The viral load of an HIV-positive person is an integral factor in viral transmission. Suppressing the viral load reduces the chance of virus transmission from an HIV-positive individual to a HIV-negative individual. The authors of "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment," here after referred to as "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus," used AZT to reduce the viral load in pregnant women who tested positive for HIV type 1. HIV types 1 and 2 are the two main strains of HIV. HIV type 1 is the most widespread type, whereas HIV type 2 is less prevalent and less disease causing. HIV type 1 leads to acquired immunodeficiency syndrome, or AIDS, more often than HIV type 2. AIDS is a syndrome in which the immune system can no longer fight off illness or infection. The authors focused their attention on type 1 because HIV type 1 is more virulent than type 2.

The article has four sections, an introduction, methods, results, and discussion. In the introduction, the authors preface the article with background information on maternal-infant transmission of HIV. In the methods section, they explain the design of the drug trial. In the results section, the researchers discuss the efficacy of the drug trial on reducing instances of maternal-infant transmission of HIV and the effects on the health of both the women and the infants in the trial. Lastly, in the discussion, the authors discuss the aftermath of the drug trial.

In 1994, the article "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment" appeared in The New England Journal of Medicine. The authors were Edward Connor, Rhoda Sperling, Richard Gelber, Pavel Kiselev, Gwendolyn Scott, Mary Jo O'Sullivan, Russell VanDyke, Mohammed Bey, William Shearer, Robert L. Jacobson, Eleanor Jimenez, Edward O'NeIl, Brigitte Bazin, Jean-Francois Delfraissy, Mary Culnane, Robert Coombs, Mary Elkins, Jack Moye, Pamela Stratton, and James Balsley. Connor was a scientist and researcher who worked in concert with the AIDS Clinical Trials Group, a research organization [8] focused on HIV and AIDS. Connor’s research focused on infectious diseases in children. Balsley was a medical doctor whose research focused on AZT and worked in concert with the AIDS Clinical Trials Group namely working to test AZT’s safety and efficacy. Connor’s and Balsley’s colleagues who contributed to the article worked with the AIDS Clinical Trials Group, as well.

In the introduction, Connor and his team begin their article by noting the severity of HIV in infants and children. The authors note that the most common way HIV infects children is through maternal-infant transmission. They note that anywhere from fifteen to forty percent of infants delivered by HIV-positive mothers contract the virus in utero, during birth, or through breast-feeding. The researchers add that prevention of maternal-infant transmission of HIV is important because HIV can be fatal for children. Next, the authors discuss AZT, the drug used in their trial. They state that AZT passed previous safety and efficacy trials for pregnant
women when used for short periods. That means that researchers found evidence that AZT worked to treat HIV infection in previous drug trials. They note that AZT can cross the placental wall, which means that the drug can reach the fetus in utero. The authors detail the structure of the drug trial. In their methods section, Connor and his colleagues state that their trial was double-blind, meaning that the pregnant women did not know if they were receiving AZT or the placebo, and the physicians did not know if they were administering AZT or the placebo. Double-blind studies reduce biases in research, because people cannot anticipate a certain result. Using a placebo creates a control group so that researchers can assess whether the drug causes observed effects rather than psychosomatic, or placebo, effects.

Next, Connor and his colleagues then note how they selected the women included in the drug trial. The authors selected pregnant HIV-positive women between fourteen and thirty-four weeks pregnant for the trial. They add that the women in the trial all had a CD4 count higher than 200. A CD4 count measures the number of CD4 positive cells in the bloodstream. CD4 cells are specialized white blood cells that fight infection. When the CD4 count is lower than 200, a person is classified as having AIDS. Though not stated in the article, the authors selected women without AIDS because women with AIDS are immune compromised and are prone to infections. In addition, the authors selected women with normal blood work results and no other risks that could cause the fetus to be unhealthy. The women had to pose no other risk to the viability of the fetus, such as a hormone imbalance or high blood pressure, to be included in the trial. Connor and his colleagues excluded women whose fetuses were more likely to die from congenital or developmental problems from the trial. Lastly, the authors excluded any woman who received immunotherapy, radiation therapy, or received an experimental anti-HIV vaccine in the past to determine the sole effects of AZT without interacting with any other treatment. They did not select any woman who posed a risk to her fetus that could alter the outcome of their research for the drug trial.

As their methods section continues, Connor and his colleagues talk about the dosage of AZT they used in the drug trial. The authors note that for the women in the AZT group, or the women assigned the drug AZT, they orally administered 100 mg of AZT five times a day. That means that the pregnant woman took 500 mg of AZT daily. The AZT administered during pregnancy was to prevent the transmission of HIV during fetal development. During labor, Connor and his colleagues gave the woman two mg per kg of their body weight of intravenous AZT for the first hour, then one mg per kg if their body weight per hour after the initial hour. That means a woman who weighed fifty kg received one hundred mg of AZT for the first hour of labor and fifty mg of AZT for every hour after until she gave birth. That was to prevent the transmission of HIV during delivery. The authors note that they gave newborns two mg per kg of their body weight oral AZT every six hours for six weeks, starting eight hours after birth. That means, a newborn weighing three kg received six mg of oral AZT eight hours after birth for every six hours until it was six weeks old. Dosage of AZT after birth was to suppress any HIV that transferred to the infant to prevent infection with HIV. Women received the study drug, either AZT or placebo, for a median of eleven weeks before giving birth. After giving birth, treatment started within twelve hours of birth for eighty-four percent and within twenty-four hours for ninety-six percent of infants. Forty-six infants stopped treatment before completing the six weeks of therapy, twenty-two in the AZT group and twenty-four in the placebo group, eleven in each group stopped because of toxic effects and seven reached a study end-point one in the AZT group and six in the placebo group.

Connor and his colleagues then explain how they monitored the health of the pregnant women during their drug trial. They monitored the women every four weeks until the thirty-second week of the woman’s pregnancy, and then the researchers began to monitor them weekly after the woman’s thirty-second week of pregnancy. The researchers note that they monitored the women by performing sonograms and non-stress tests to ensure that the women were healthy enough to continue with the trial. A sonogram is a visual imaging technique that can visualize structures inside of the body, such as a developing fetus. The authors used sonograms to make sure the fetus was developing properly and that the pregnant woman had no signs of organ problems. Connor and his colleagues used non-stress tests to ensure that the heart rate of the fetus was normal. They also performed final checks on the women six weeks after delivery and again six months after delivery to ensure normal development.

The methods section of the article continues as the authors talk about how they monitored the infants after birth. The authors state that they monitored the infants up until seventy-eight weeks of age, or approximately a year and a half. The researchers added that they took blood samples from the infants and tested them for HIV at twelve weeks, twenty-four weeks, and seventy-eight weeks after birth. They classified infants as HIV-positive if one blood sample tested positive for HIV.

Following the detail of their methods, Conner and his colleagues discuss how many infants were born to the women in the trial in their results section. They note that out of the 477 pregnant women enrolled in the study, 409 women gave birth to 415 live-born infants, including 403 singletons and six sets of twins. Thirty tested HIV-positive. The authors conclude that the lower number of HIV-positive neonates in the AZT group indicate that the drug blocked the maternal-fetal transfer of HIV more effectively than the placebo. Because the trial included subgroups of women, women of different races, ages, and drug history, the researchers further conclude that maternal age, race, and drug history did not affect the efficacy of AZT. Furthermore, they state that the neonate’s birth weight or biological sex did not affect the drug’s efficacy.
Connor and his colleagues then discuss the differences in CD4 counts between the AZT group and the placebo group. They observed a significant increase in CD4 cells of the women after they gave birth in both groups, but they observed a greater increase in the AZT group. An increase in CD4 count indicates that immune function increased, whereas a decrease indicates further deterioration of the immune system. The increase of CD4 cells in the women in the AZT group showed that AZT blocked the virus from replicating and destroying CD4 cells.

As the authors continue with their results, they detail the fetal, neonatal, and infant deaths that occurred during the trial. Eight fetal and neonatal deaths occurred during the trial, five in the AZT group and three in the placebo group. In their article, the researchers do not consider AZT responsible for their deaths. The causes of death were determined to be premature labor and fatal developmental disorders. Aside from the fetal and neonatal deaths, seven infants died after birth, one due to trauma and six from HIV infection. Of the six who died from HIV, two infants came from the AZT group and four came from the control, or placebo group.

Next, the authors compare the results of the non-stress tests and sonograms between the AZT group and the control, or placebo group. The non-stress tests and sonograms taken during the trials showed no differences between the two groups. That means that the drug did not alter the heart rate or the physical appearance of the neonate. The authors note similar weight, length, and head circumference measurements in both groups through eighteen months after birth. Both groups had similar instances of structural abnormalities.

In the discussion section, Connor and his colleagues examine the effects of AZT on maternal-infant transmission of HIV. The authors state that by administering AZT to HIV-positive pregnant women, they were able to decrease the maternal-infant transmission of HIV by two-thirds. That means that HIV-positive women who want to give birth can take AZT to lessen the chances of transferring an HIV infection to their infant. The authors speculate that the drug may have reduced the pregnant woman’s viral load, which lowered the risk of fetal exposure. Some infants became HIV infected despite treatment. The researchers hypothesize that may have occurred due to HIV transmission before treatment, the women not complying with the treatment regimen, inefficient suppression of the virus by the medication, or unique characteristics or mutations of the HIV strain that particular woman had.

As of 2019, scientists have cited “Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment” over 1900 times. In a letter written in response to the article the author stated that because of the drug trial, scientists began planning for similar studies in Africa, Asia, and South America. As of 2018, health care workers use AZT to prevent maternal-infant transmission of HIV worldwide. As of 2019, health care workers use AZT to prevent maternal-infant transmission of HIV worldwide.

"Reduction of Maternal-Infant Transmission of HIV" helped decrease the maternal-infant transmission of HIV and helped decrease infant mortality due to viral infection. According to the National Institute of Health, or the NIH, a US agency responsible for public health research, AZT successfully prevents maternal-fetal transmission of HIV in most women. As of 1996, AZT used in concert with other antiretroviral, or HIV-fighting, drugs, in a regimen called highly active antiretroviral therapy, or HAART. As of 2019, HAART is the preferred method of HIV treatment because it is more effective than taking a single antiretroviral medication. In 2017, the NIH stated that there is no evidence that AZT causes birth defects. [15]

**Sources**


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