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The Effect of Antiretroviral Therapy on Placenta Size and Fetal Development

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ABSTRACT

HIV, or human immunodeficiency virus, is a virus that targets the human body's immune system and weakens it so that it struggles to defend against other pathogens designed to harm the body. In order to enhance immune health and decrease the transmission of HIV, patients who have HIV are treated with antiretroviral therapy, or ART, a treatment that seeks to reduce the replication of HIV by disrupting a specific portion of the HIV replication cycle. However, while it does reduce the vertical transmission of HIV between mother and fetus, the use of antiretroviral therapy during pregnancy can have adverse impacts on the size of the placenta and the development of the fetus. Through the study of various research papers, a distinct connection between the use of antiretroviral therapy and the placenta size and fetal development was made. Analyzing the placenta and birth characteristics of fetuses from both women with and without HIV, overall the placentas of mothers with HIV taking ART drugs had smaller diameters, weights, and areas, along with an irregular shape, than mothers without HIV; the fetuses of mothers with HIV taking ART drugs had smaller weights at birth, weeks of gestation at birth, and birth weight centile than fetuses of mothers without HIV. Exploring the impacts of antiretroviral therapy on placenta size and fetal development, this comprehensive research aims to assist researchers in creating safer and improved antiretroviral drugs to treat mothers with HIV that promote both the health of the mother and the development of the child.

Introduction

HIV, short for human immunodeficiency virus, is an enveloped retrovirus consisting of two copies of a single-stranded RNA genome; classified as either HIV-1 or HIV-2, the virus fuses with cell membranes of CD4+ T cells (white blood cells) and integrates itself into the host genome, allowing it to rapidly make copies of itself to infect other cells and kill the CD4+ T cell host itself. HIV infection can be diagnosed through a fourth-generation assay, which identifies specific HIV antibodies and antigens, a rapid test, which uses blood or saliva to identify the infection quickly, or a PCR test, which displays how much of the virus is in the blood; more often than not, a combination of these tests is performed to determine if an individual has HIV. In 2019, 38 million people were HIV+, 1.7 million people became affected, and 690,000 people died of HIV disease, with a 24% increase in HIV infections in the population due to growth despite the decreased mortality rates; about 1.3 million women living with HIV become pregnant each year. Statistics display significant racial and ethnic disparities of HIV infection, as black people are twice as likely as Hispanic people and eight times as likely as white people to contract HIV.

While there is no definite cure for HIV, there are effective treatments for the virus. Antiretroviral therapy, more commonly known as ART, is a remedy that decreases the replication of HIV, reduces the sexual transmission of the virus between partners, and could eventually curtail the spread of HIV throughout the population. Highly recommended for all people diagnosed with HIV, especially pregnant people, this treatment continues throughout an HIV+ individuals' lifetime. However, while ART greatly promotes maternal and fetal health by preventing, to a certain degree, the transmission of HIV from the mother to the child, increasing evidence suggests that ART poses risks to the development of the fetus. This research paper seeks to explain the effects of ART on the placenta, the organ that

regulates the metabolic processes for fetal growth, and on the fetus' physical development at birth. Additionally, this comprehensive research on the connection between ART, placenta size, and fetal development can potentially assist researchers in their endeavors to improve ART to treat HIV+ mothers, without affecting the growth of their offspring.

History of HIV and AIDS

Although the first reports of the HIV disease came much later, the history of HIV began in Central and East Africa, specifically in Kinshasa, Democratic Republic of Congo (DRC), and Cameroon. Chimpanzee populations in Cameroon were identified to have simian immunodeficiency viruses (SIVs), which are closely linked to the lineage of HIV-1, suggesting the transmission of the disease to humans from the primates. The HIV-1 group M in humans originated in Kinshasa by the early 1920s and continued migrating all throughout the DRC to the neighboring cities of Brazzaville, Lubumbashi, and Mbuji-Mayi by the late 1930s and Bwamanda and Kisangani by the 1940s and 1950s respectively. The group M virus can be further classified into subtypes, with subtype C constituting over 50% of HIV cases globally as the disease became a pandemic affecting the entire world.

In the United States, the first report of the disease was in 1981 amongst younger, originally healthy homosexual men in Los Angeles, California as an abnormal cluster of Kaposi's Sarcoma and Pneumocystis carinii Pneumonia; this eventually became known as AIDS, short for acquired immunodeficiency syndrome. By 1982, case studies suggested that AIDS was spread through bodily fluids and exposure to contaminated blood, through a report of an infant suffering with the disease after receiving a blood transfusion from a donor with AIDS. HIV was identified to be the cause for AIDS by the US National Institutes of Health team led by Gallo and the Institut Pasteur team led by Montagnier and Barré-Sinoussi, and this discovery pioneered a global research effort to understand the disease and potentially overturn the tragic consequences of its pandemic.

The Virology and Pathology of HIV

As mentioned above, HIV can be classified as either HIV-1 or HIV-2, with the difference characterized by the organization of its individual retrovirus genomes. However, the structure of HIV remains identical for both types with the presence of the fundamental genes *gag*, *pol*, and *env*. The *gag* gene is responsible for the core structural proteins in the capsid and the matrix, which are p24, p7, p6, and p17. The *pol* gene is responsible for the enzymes reverse transcriptase, integrase, and protease; involved in HIV replication, reverse transcriptase converts viral RNA into DNA, integrase fuses the viral DNA into the host DNA, and protease breaks down the polyproteins in the HIV cell. The *env* gene is responsible for the envelope glycoproteins gp120 and gp41, which identify cell receptors on its surface. The HIV cell itself is composed of a lipid membrane encasing the matrix protein, the structural proteins in the capsid, the enzymes, and the RNA genome, with the glycoproteins on the surface of the membrane; it has a diameter of roughly 100 nanometers. Figure 1 details the individual components of the HIV cell.

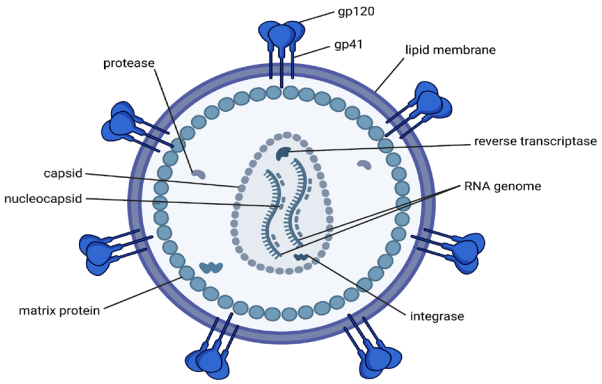

Figure 1. Diagram of an HIV cell with the individual components labeled. Adapted from "HIV", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

The HIV cell is able to multiply and spread rapidly since its individual components all work to produce more viral cells through its replication process. The first step is the attachment of the HIV cell to the host cell; this occurs from the binding of the glycoprotein gp120 to the CD4 receptor on the CD4 cell. Once this happens, the viral cell alters its shape in order for the gp120 to bind to the human chemokine receptors on the surface of the CD4 cell, which can be either CCR5 or CXCR4. Once the cells are bound together by this attachment, the HIV cell and host cell membranes fuse together; this allows the contents of the viral cell, which are the HIV RNA, reverse transcriptase, integrase, and viral proteins, to enter the cytoplasm of the CD4 cell. Next, the reverse transcriptase forms the viral DNA by transcribing the viral RNA into a double helix DNA, which is then transported through the nucleus of the host cell. Once within the nucleus, the DNA is incorporated into the DNA within the CD4+ T cell genome by the integrase, which breaks the nucleotides of each of the 3' ends of the DNA to attach it to the host genome; this enables the formation of proviruses. Then, following cell activation, the provirus DNA is transcribed into a messenger RNA, leading to the formation of regulatory HIV proteins like Tat and Rev, which facilitate HIV RNA transcription. The RNA, enzymes, and proteins exit the nucleus to move to the cytoplasm, where the new HIV cells are synthesized. The structural gene *env* creates the glycoprotein spikes of gp120 and gp41 for the HIV cell surface, while *gag* and *pol* create the nucleus of the viral cell; the core proteins, cleaved by the enzyme protease, create the viral capsid, which encapsulates the viral RNA. This immature virus moves closer to the surface of the cell where it is cleaved into infectious particles by the protease; once budded through the cell membrane, it is matured and released.

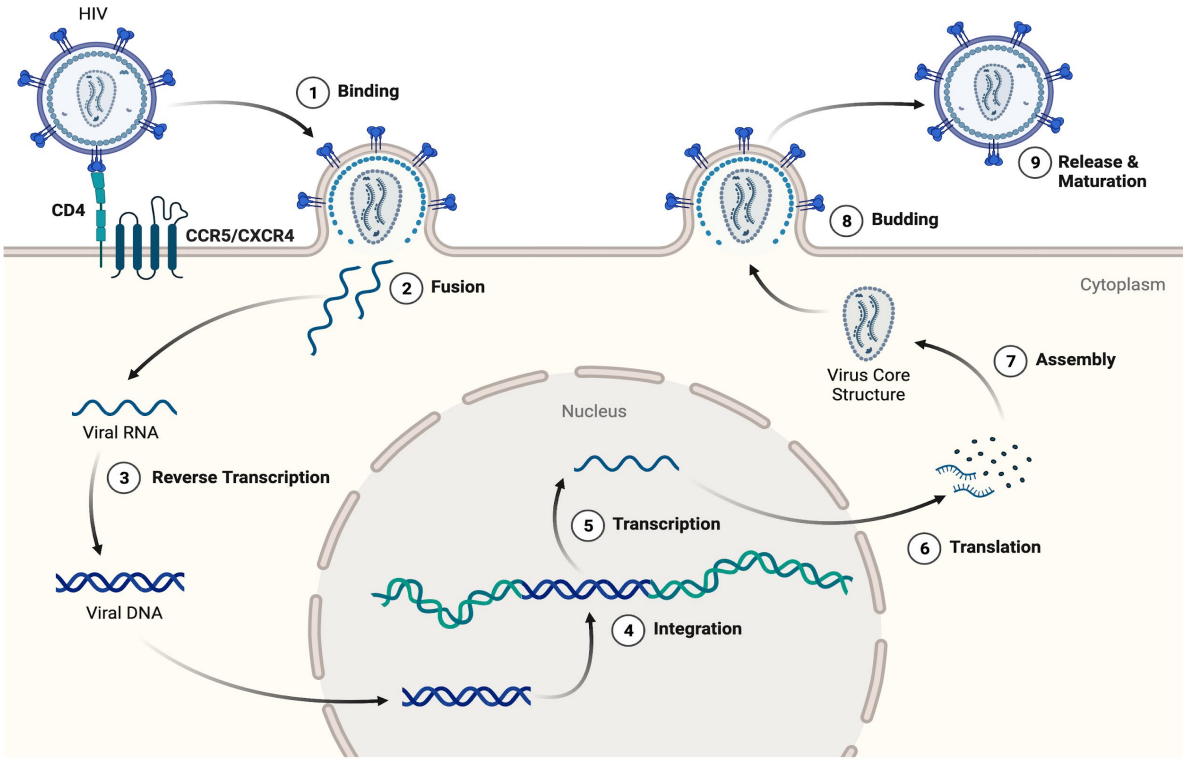

Figure 2. Diagram of the HIV replication cycle. Adapted from "HIV Replication Cycle", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

Antiretroviral Therapy

Antiretroviral therapy, shortened to ART, is drug therapy to stop or slow the replicative process of HIV. The main goals of ART are to, "achieve and maintain suppression of plasma viremia to below the current assays' level of detection; improve overall immune function as demonstrated by increases in CD4+ T cell count; prolong survival; reduce HIV associated morbidity; improve overall quality of life; and reduce risk of transmission of HIV to others (Pau et al, 2014). There are six classes of ART drugs, with over thirty types of medications across all the classes; most often, a combination of drugs is used to combat HIV as these different classes target HIV in different ways. **Figure 3** exhibits the categorization of the various FDA approved ART drugs into its different classes.

Drug Class	NRTI	NNRTI	INSTI	PI	Entry Inhibitors	Attachment and Post-Attachment Inhibitors
FDA Approved Drug	- Abacavir - Didanosine - Emtricitabine - Lamivudine - Stavudine - Tenofovir disoproxil - Tenofovir alafenamide - Zalcitabine - Zidovudine	- Delavirdine - Doravirine - Efavirenz - Etravirine - Nevirapine - Rilpivirine	- Bictegravir - Dolutegravir - Elvitegravir - Raltegravir - Cabotegravir	- Amprenavir - Atazanavir - Darunavir - Fosamprenavir - Indinavir - Lopinavir - Nelfinavir - Saquinavir - Ritonavir - Tipranavir	- CCR5 inhibitors: maraviroc - Fusion Inhibitors: enfuvirtide	- Attachment Inhibitors: fostemsavir - Post- Attachment Inhibitors: Ibalizumab

Figure 3. Table of the six different classes of antiretroviral therapy drugs and the various medications under each. Abbreviations: NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, INSTI = integrase strand transfer inhibitor, PI = protease inhibitor. Information from "Antiretroviral Therapy: Current Drugs" (Pau et al, 2014) and "Types of Antiretroviral Medications" (Pebody 2021).

The first class of antiretroviral drugs the FDA approved are nucleoside reverse transcriptase inhibitors, NRTI for short. These drugs target the HIV protein reverse transcriptase, which converts viral HIV RNA into DNA. By disrupting the conversion of the RNA once incorporated into the viral DNA, NRTIs have the ability to stop the reverse transcription process and HIV replication. As HIV medication works best as a combination of drugs, NRTIs are the backbone of these combinations.

The next class of antiretroviral drugs approved are non-nucleoside reverse transcriptase inhibitors, NNRTI for short. These drugs also target reverse transcriptase, but differently to NRTIs. Rather than disrupting the process of transcription, NNRTIs bind to the enzyme directly, stopping the reverse transcriptase process.

An additional class of approved antiretroviral drugs are integrase strand transfer inhibitors, INSTI for short. These drugs disrupt the integrase enzyme, a protein that activates the union of the host cell DNA and the HIV DNA. Thus, they prevent the integration of HIV DNA into the host cell.

Another class of approved antiretroviral drugs are protease inhibitors, PI for short. These drugs bind to HIV proteases, enzymes that split up cell polyproteins to assemble HIV particles in the cell. They block its activity, resulting in the virus' inability to produce mature HIV particles within the cell.

The next class of antiretroviral drugs approved by the FDA are entry inhibitors, which treat HIV by prohibiting the virus from entering the human cells. The two types of entry inhibitors are CCR5 inhibitors and fusion inhibitors. CCR5 inhibitors disrupt the coreceptor CCR5, which is one of the two receptors on the cell surface HIV must bind with in order to insert itself into the cell. Fusion inhibitors prohibit the combination of the CD4 cell and the HIV envelope protein.

The final class of approved antiretroviral drugs are attachment and post-attachment inhibitors. Attachment inhibitors prevent HIV from attaching to the CD4 receptor on the immune cells by binding to the gp120 portion of the HIV envelope protein. Post-attachment inhibitors prevent the gp120 portion of the HIV envelope protein from transforming itself to attach to the CD4 receptor by binding to the CD4 receptor.

Figure 4 displays the target sites for the various ART drugs within the HIV replication cycle.

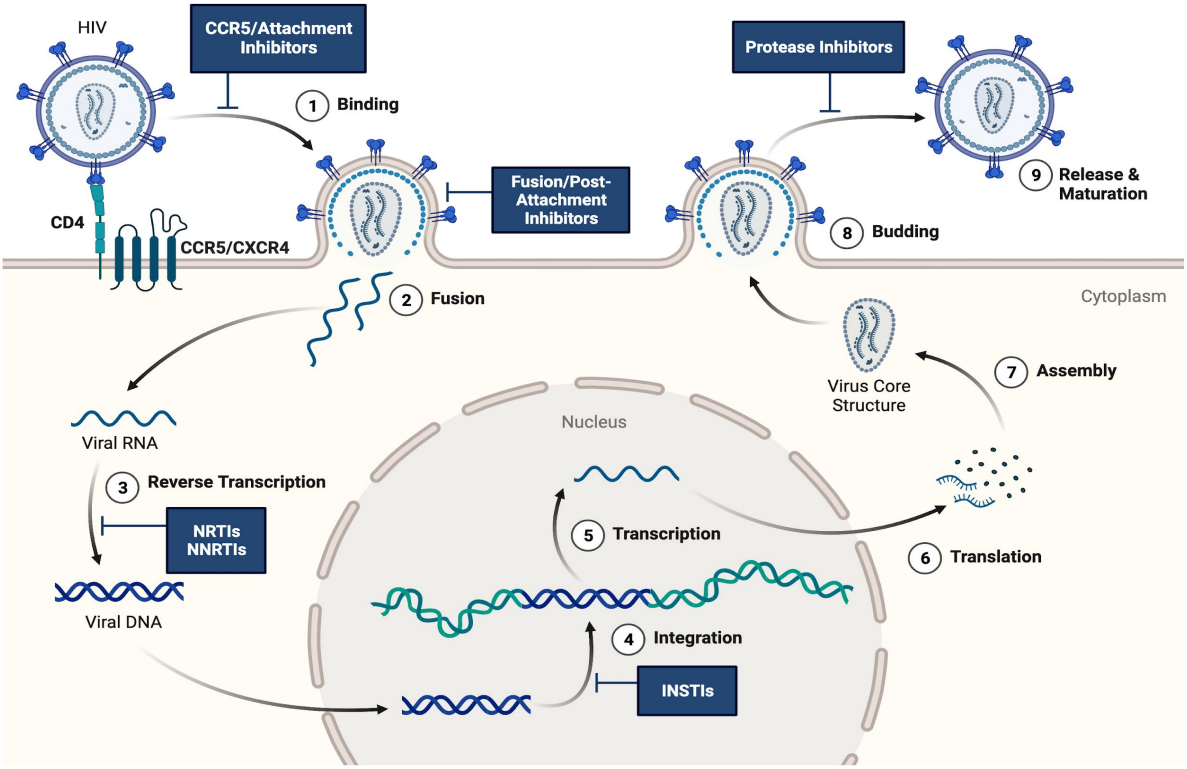

Figure 4. Diagram of the HIV replicative cycle with ART sites labeled. Adapted from "HIV Sites for Therapeutic Intervention", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

The Effect of Antiretroviral Therapy on Placenta Size

People who are HIV+ utilize ART drugs to help them effectively treat their disease. Thus, women who are HIV+ and pregnant take ART drugs in order to reduce the vertical transmission of HIV to their offspring. However, the drugs can have negative impacts on the development of the placenta, the organ that attaches to the side of the uterus during pregnancy and is responsible for maintaining and regulating the essential life processes for fetal growth, which are nutrient and oxygen transfer and waste removal. Compared to HIV- women, HIV+ women taking ART drugs have decreased placenta diameters, smaller placenta areas, and lower placenta weights, suggesting a connection between ART and placenta size. Those undergoing ART are more likely to have smaller placentas, and in general, it can be

concluded that smaller placentas are more frequently found within a population of HIV+ women compared to a population of women without HIV. Moreover, placentas from HIV+ women have a slightly greater deviation from its conventional circular shape. Traditionally, the chorionic plate, which is the fetal side of the placenta, is circular. This ensures optimal growth and development for the placenta and the fetus as that is the section of the placenta where the umbilical cord, the link between the mother and the fetus that facilitates the transfer of oxygen and nutrients and the removal of waste, attaches. However, if the chorionic plate is irregularly shaped, the resulting abnormal placenta structure can be linked to its potentially diminished functionality. There exists a significant correlation between deviations to the standard circular shape of the placenta and the efficiency of the placenta; this further demonstrates how ART detrimentally impacts placenta size by impacting its purpose. Figure 5 displays the association between ART and placenta size by showing its impacts on the diameters, areas, and weights of the placenta as well as on the shape through the measure of the relative symmetric difference from the standard placenta structure.

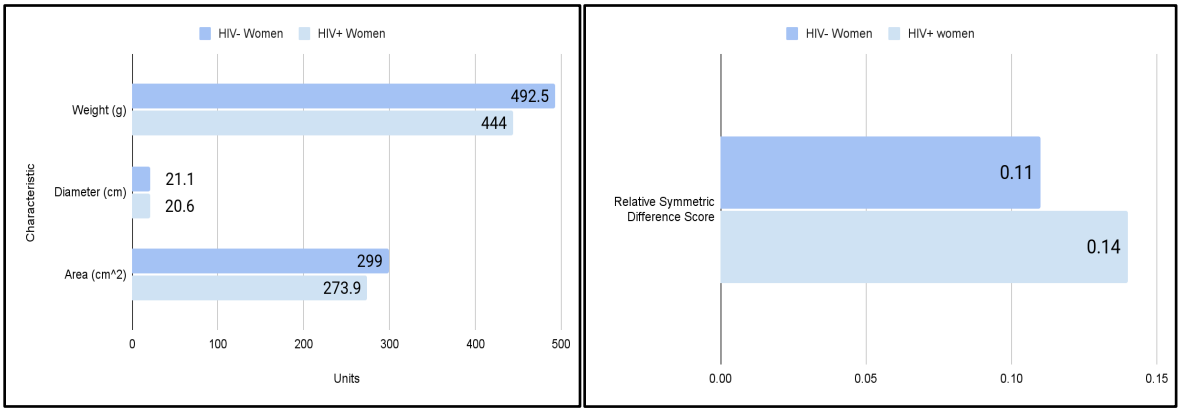

Figure 5. Graph of the characteristics and measurements of the placenta. Information from "Exploring the impact of HIV infection and antiretroviral therapy on placenta morphology" (Yampolsky et al., 2021).

The Effect of Antiretroviral Therapy and Placenta Size on Fetal Development

Ultimately, as the effects of the ART on the placenta can result in reduced placenta functionality and efficiency from the placenta's smaller size and abnormal shape, ART can have a harmful impact on the physical development of the fetus. Compared to HIV- women, HIV+ women taking ART drugs have offspring that have smaller birth weights, are less weeks gestation at birth, and are in a lower birth weight centile, suggesting a connection between ART, placenta size, and fetal development. As placental weight is roughly proportional to the birth weight of the offspring, a lower placental weight will subsequently lead to the offspring having a lower weight at birth as placental growth patterns and fetal growth patterns are intrinsically linked. Additionally, placental weight is roughly proportional to the fetus' weeks gestation at birth; there is a strong correlation between the two as a lower placental weight will result in the offspring having a smaller gestational age. The difference in the birth weight centile, which is the measurement for if the fetus is small, average, or large for gestational age, also indicates the discrepancy in development when comparing offspring from HIV- and HIV+ mothers. The infants from HIV+ mothers are more likely to be small for gestational age compared to infants from HIV- mothers, further showing how ART adversely affects placenta size, which in turn impacts fetal development. Figure 6 displays the association between ART, placenta size, and fetal development by showing their impacts on the birth weight, weeks gestation at birth, and birth weight centile of the fetus.

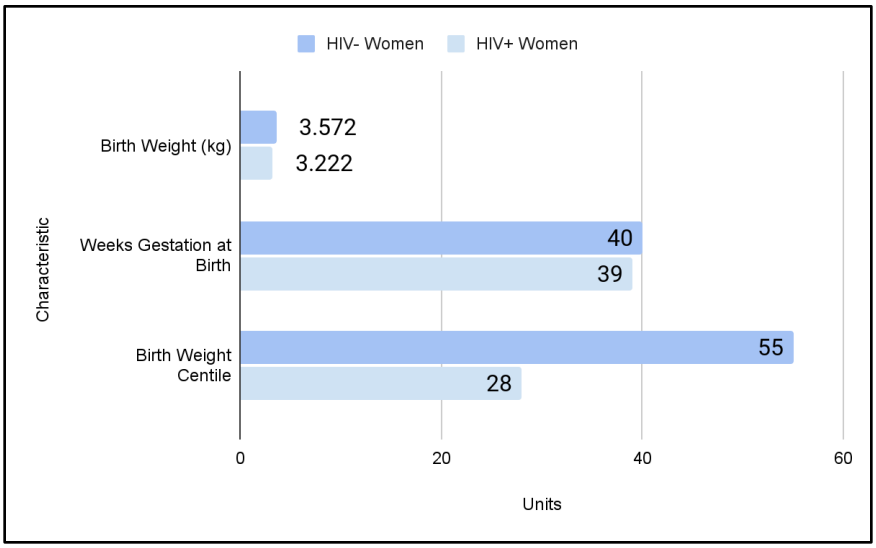

Figure 6. Graph of the characteristics and measurements of the fetus at birth. Information from "Exploring the impact of HIV infection and antiretroviral therapy on placenta morphology" (Yampolsky et al., 2021).

Conclusion

HIV has historically been a disease that has greatly impacted the world. As its virology and pathology was analyzed, various research efforts globally found a treatment for HIV – antiretroviral therapy. ART has been a revolutionary discovery in the fight against HIV and AIDS as it effectively manages the virus in patients and plays a great role in reducing the transmission of the disease to future offspring. However, these drug treatments, when taken by pregnant HIV+ mothers, can negatively impact these future offspring by limiting their development, by means of the placenta and their physical growth. The research articles studied in this paper display a clear link between the use of ART and the placenta size and fetal development, as in most cases, ART leads to smaller placenta sizes and reduced fetal development when looking at the characteristics of the placentas and fetus at birth from women who are HIV- and HIV+. Generally, the placentas of HIV+ mothers had lower diameters, weights, and areas as well as a more irregular shape compared to the placentas of HIV- mothers. Additionally, the fetuses of HIV+ mothers had lower weights at birth, weeks gestation at birth, and birth weight centile compared to the fetuses of HIV- mothers. This research has extensive implications as it intends to help researchers in their endeavors to create safer antiretroviral therapy drugs. Through further research investigating the effects of ART on additional factors that influence fetal development in a larger, more diverse, yet matched population, researchers can further explore how ART can be improved to not only reduce vertical transmission of HIV but also limit the consequences and repercussions on the fetal development of offspring from HIV+ mothers. In conclusion, these findings demonstrate how antiretroviral therapy can significantly affect the development of future generations that warrant continued study.

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