VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final Thesis:

HIV and Pregnancy

Narrative literature review- last ten years' articles.

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Table of abbreviations:

HIV	Human immunodeficiency virus
CTLs	Cytotoxic T lymphocytes
WHO	World health organization
PI's	Protease inhibitors
INSTI's	Integrase strand transfer inhibitors
ART	Antiretroviral therapy
NRTIs	Nucleoside reverse transcriptase inhibitors
AZT	Zidovudine

NNRTI's	non-nucleoside/nucleotide reverse transcriptase
sdNVP	Single dose nevirapine
3TC	Lamivudine
NVP	Nevirapine
TDF	Tenofovir
RTV	Ritonavir
ATV	Atazanavir
RAL	Raltegravir
DTG	Dolutegravir
EFV	Efavirenz
PMTCT	Prevention mother-to-child transmission

1. Summary:

The human immunodeficiency virus acts mainly in CD4+T cells, spreads in the body for years, possibly without symptoms until deterioration. Medical treatment developed against the enzyme's reverse transcriptase, integrase, and protease that play a crucial role in viral replication. Viral test is indicated for every pregnant woman, while in the past, only special populations deserved it. When a woman's result is positive, viral load, CD4+ count, and viral genetic tests are done. In the treatment of this population, massive progress has been made. Monotherapy became Combination therapy prescribed for life contrary to the past when it was just indicated during pregnancy. Close monitoring and rapid tests are available today to control the treatment and prevent transmission to their children. Despite the high disease rate in developing countries, we see better management in developed countries with better financial resources, knowledge of society, and a wider range of medications. It is hard to overcome the gap because of the globally known problems: lack of finances, stigmas, lack of support, and limited government resources. Despite all this, we see an ongoing global fight against the virus that has progressed positively. Today approximately eighty-five percents of positive women receive drug treatment, and the percentage of mother-to-child transmission with appropriate treatment is less than 1 percent. The gap between the countries is still huge, but the attempts to reduce and overcome the spread of the disease are succeeding with more resources and advocacy.

2. Keywords: human immunodeficiency virus, HIV mechanism, HIV in pregnancy, Africa, evolution of HIV, HIV treatment, HIV prenatal care, screening tests, resource-limited, high-income, postpartum HIV, HIV worldwide.

3. Introduction:

The human immunodeficiency virus (HIV) is a sexually transmitted disease that has infected over 75 million people over the years, with numbers increasing constantly. It is estimated that 1.5 million HIV-positive women and girls become pregnant yearly. The virus was first identified in the 1980s when homosexual men exhibited immunodeficiency symptoms, and since then spread to all populations. With a constant global fight against its spread, while the numbers of HIV-positive people in the general population are rising, there is a decrease in mother-to-child transmission. Over the years, with experience and knowledge, many changes happened in the attitude and treatment strategies. This article was conducted to answer what changes had occurred in treating the special population of positive pregnant women. Additionally, most positive pregnant women come from low-income countries like Africa. The treatment and attempts to lower the numbers are improving there but not to a satisfactory extent like in high-income countries. What is the reason for the differences between countries? Are there any differences in the treatment strategy? What are the obstacles, and how do professionals try to overcome them? This literature review will try to answer all the relevant questions here.

4. Methodology:

For this work, articles were searched from PubMed, UpToDate, and NIH-national Library of Medicine for the most updated articles in the medical field. Dedicated sites that only deal with HIV and everything connected to it, like mechanism etiologies, statistics treatment, and screening-HIVinfo.NIH.org of the Office of AIDS Research, CDC, and world health organization. The thesis based on literature only for the past ten years. From 2013-2023. First, most informative articles were chosen regarding HIV aetiology, its mechanism, and how it affects the general population. The next step is to concentrate on pregnant women worldwide positive for HIV and their treatment development over the years. While reading, it was discovered that significant gaps exist between countries' management worldwide, so research expanded to add to the differences between low and high-income countries.

5.1. Mechanism of Human Immunodeficiency Virus:

In according to understand the strategy of vertical transmission prevention and the treatment of positive HIV pregnant women, it is crucially important to understand deeply what HIV is, what are its essential components and what is its mechanism of action.

HIV is an enveloped retrovirus that contains two positive copies of stranded RNA. The virus uses reverse transcriptase enzyme to convert its RNA into DNA within mucosal tissues for further cell infection and transmission. When viral DNA forms, the virus can enter the cell's nucleus (1). The main steps of the HIV life cycle described in the following lines are summarized in *Figure 1*. Firstly, the human immunodeficiency virus focuses its activity against activated CD4+ T cells, which usually, in physiological conditions, are used to protect our body against infections, other cells that the virus can target are macrophages, dendritic cells, and monocytes, which release their inner capsid on the cell surface Creating local condition. The virus replicates by the body's cell replication system to create more HIV proteins, those proteins are then cleaved, and mature virions are released to other cells in the body. While encountering an infection, cells with infected and changed DNA begin to duplicate before going further to lymphoid organs and infecting other cells, causing an increase in HIV viral load within the body. This "acute phase" can be accompanied by no symptoms at all or involves generalized and non-specific "flu" like symptoms, such as lymphadenopathy, rash on the skin, and malaise. HIV can be detected as early as the 10^{th} day after getting the infection, with the detection of antibodies peaking possibly on the 30^{th} day. After the "acute phase" of HIV, Viral load starts to decrease by the adaptive immune system. It is assumed to be mainly related to the development of HIV-specific CD8+ cytotoxic T lymphocytes (CTLs) (2), and viral load can remain stable for up to 10 years with constant replication rate, the increase with time of the mutated CTL cells and the progressive loss of CD4+ T cells, leading to immunological abnormalities resulting After several years in severe deterioration of health conditions that can be observed.

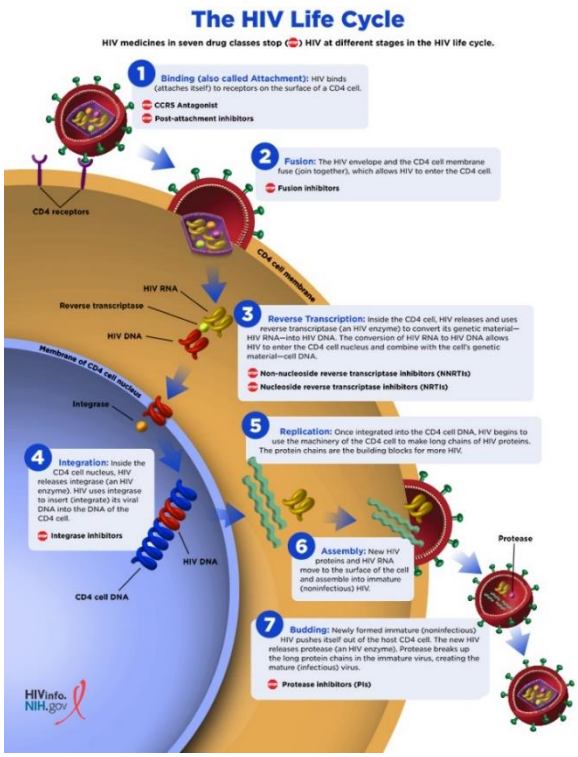

Figure 1: the most essential steps of HIV life cycle and replication—schematic picture.

[I] The HIV life cycle. National Institutes of Health. U.S. Department of Health and Human Services; 2021. Available from: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle

5.2. Main chemokines and proteins of Human Immunodeficiency Virus:

The complex mechanism of human immunodeficiency virus infection is known; it involves binding to specific receptors on the surface of immune system cells. The two receptors that HIV prefers to bind to enter the host cells are the chemokine receptors CCR5 and CXCR4 (2). The binding of HIV particles to one of these receptors influences the cell types they will affect, a phenomenon known as tropism.Research has shown that CCR5-tropic particles predominantly replicate in monocytes or macrophages, but they can also affect dendritic cells and use them as a means of trafficking to lymph nodes. Conversely, CXCR4-tropic particles are known to replicate more efficiently in T cells. It is important to note that after infection with HIV, the CCR5-tropic virus particles are the ones that are most likely to be present in the body, as they are transmitted immediately through sexual contact and can find their way into the epithelial layer of the urinary tract. However, CXCR4-tropic virus particles may also be observed as the infection progresses.In some cases, individuals may have mutations in the CCR5 gene that are associated with decreased susceptibility to HIV infection. Even if such individuals engage in sexual contact with an infected person, there is a high probability that they will not become infected.

Three central genes are responsible for the replication of HIV: "Gag," "Pol," and "Env." "Gag" is the gene responsible for producing P24 protein units that form the nuclear capsid of HIV particles. "Pol" encodes the three critical enzymes involved in the replication of HIV: reverse transcriptase-forming DNA from RNA, integrase-integrates HIV DNA into host cell DNA, and protease-cleaving proteins. "Env" protein is responsible for the production of gp160, a precursor of the glycoproteins gp120 and gp41, activated after the cleavage of the gp160 and responsible for the attachment and fusion of the virus into the targeted T cells, respectively (3). The gene for gp120 mutates rapidly, a phenomenon known as antigenic variation. In particular, the "V3 loop" of gp120 is highly immunogenic, forming different types of antigens. Antibodies like IgM antibodies produced in response to gp120's antigens may be unable to neutralize HIV antigen particles effectively due to their rapid diversity and slower antibody production. Medications that target these enzymes have been developed to control HIV infection by trying to overcome their functions.

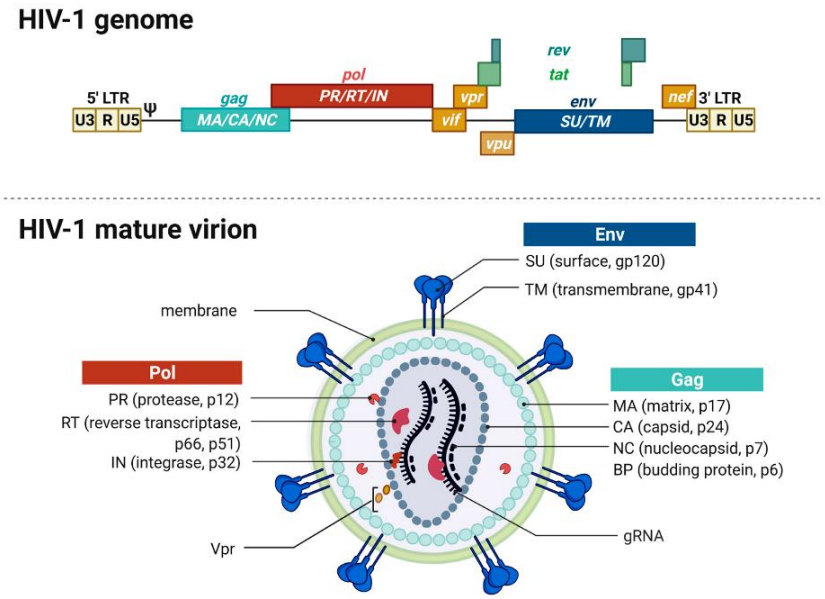

Figure 2: HIV main genes and their main vital components.

[II] van Heuvel Y, Schatz S, Rosengarten JF, Stitz J. Infectious RNA: Human immunodeficiency virus (HIV) biology, therapeutic intervention, and the quest for a vaccine. MDPI. Multidisciplinary Digital Publishing Institute; Available from: https://www.mdpi.com/2072-6651/14/2/138

5.3 Human Immunodeficiency Virus transmission pathways in the general population:

"Every two minutes in 2021, an adolescent girl or young woman was newly infected with HIV worldwide" (4). That fact is concerning because HIV has been present for decades in our world. After good management and a dramatic decrease in the numbers worldwide, we see an

increase again, especially after the COVID-19 pandemic, which shifted the management concentrations worldwide directly and ultimately against COVID-19 itself and did not give the ability to continue treating HIV in the same quality. However, maybe the world is already referring to it as a chronic viral illness and not frightening as it used to be. The transmission of HIV in the general population occurs through the exchange of bodily fluids, including blood by sharing needles or syringes, semen, and vaginal secretions due to unprotected direct sexual contact, and by vertical transmission from an infected mother to her baby before, during childbirth due to untreated or high maternal viral load HIV or after pregnancy from mother's breast milk while breastfeeding. The vertical transmission mechanism will be discussed later. Thereby, the groups at significantly higher risk from the general population for being HIV positive include homosexual men, intravenous drug users, sex workers, and Infants of HIV-positive mothers. The UNAIDS organization declared that ninety-four percent of the cases outside sub-Sahara resulted from those high-risk populations; in contrast, in sub-Sahara, fifty-four percent of the cases are from risk groups (28).

In low- and middle-income countries, it is estimated that half of the people (50%) living with HIV are women, with the proportion being higher in sub-Saharan Africa.

5.4. <u>Mother-to-child transmission:</u>

The vertical transmission between a mother to her child since it was first identified depends mainly on high viral load, viral phenotype, stage of the disease in the mother, and prolonged membrane rupture (more than four hours). It accounts for most pediatric HIV infections. Without interventions, the risk of mother-to-child transmission ranges from fifteen to forty-five percent (6) In the antenatal and intrapartum periods. Postpartum breastfeeding of the baby even increases the percentage of transmission to the child. Usually, throughout the pregnancy, the placenta protects the fetus from maternal HIV transmission and acts as a barrier (5). But if trauma, drug use, or any blood clotting disorders occur, it can decrease the placental protection, and virus transmission to the baby in this situation is much higher. The most frequent window for HIV prenatal transmission is the third trimester, particularly the last 14 days before delivery (5). HIV can enter the placental trophoblast by direct cell-to-cell contact or by endocytosis. This infection process acts on two levels. On one aspect, the inflammatory process of infecting those cells releases pro-inflammatory factors like tumor necrosis alfa, interleukin-1, and interleukin-8. On the other hand, cells produce antiviral particular cytokines and chemokines like CXC ligand-5, protein-1 beta, and leukemia inhibitory factors that will suppress and prevent further replication of the virus., That is why this route has proven as the least common way of vertical transmission. One known cell type

that protects the fetus is the Hofbauer cells, which are placental macrophages that can facilitate HIV passage when the placenta is damaged due to chorioamnionitis, funisitis, placental membrane inflammation, and villous hypercellularity.

During the birthing process, vaginal secretions, and blood full of CD4-infected T cells can be transferred to the neonate through microtears of the skin and get to its mucosal surfaces. The intestine of the fetus has high levels of CD4+ T cells, predominant CCR5+, which increases the transmission rates (6). Due to that, professionals will recommend that women take antiretroviral therapy (ART) before and mainly during the pregnancy to decrease the body's viral load and provide additional protection. In the period after delivery, the most infective way for a woman's child, as already discussed in this article, is through breastfeeding, of course, depending on the viral load of the mother that is present in the milk and found also to be associated with mastitis. Suppose the woman is not appropriately treated, or her viral loads are very high and uncontrollable. In that case, it is recommended for women from high-income countries with clean water sources to feed their babies with formulas, which are already broadly used worldwide by many mothers regardless of any disease. In low-income countries with high HIV prevalence, where clean water is not achievable in most cases, and the costs for buying formulas are high due to increase poverty, it is recommended to breastfeed their babies to prevent other severe conditions (6). In women that are with lifelong ART treatment, it is recommended by the world health organization (WHO) to breastfeed exclusively for the first six months of the baby's life to supply all the essential nutrients that come from the mother's breast milk and add complementary feeding until twelve months of age.

5.5 <u>Human Immunodeficiency Virus screening and further tests during pregnancy:</u>

HIV testing is recommended for every sexually active woman. In the past, HIV tests were indicated only once just for people at risk or as an available option for women who were interested in the test. Today, because of the increasing rates of HIV, lower costs, and the treatment becoming tolerable and manageable with more available resources, every pregnant woman is doing an HIV test as part of the "opt-out" approach, which means the antibody-antigen screening test is done as part of the whole routine tests needed to be done at the beginning of the pregnancy without questioning. Those tests today are very rapid compared to the time they took in the past. It can be done in outpatient settings, not necessarily in laboratories, and even in labor. Results are available from one hour later to 24 hours, depending on the urgency. Further tests are done for deeper checks and final confirmation (24). Additional test for women is done after the first test in some geographic areas with high

HIV rates or risk populations like sex workers, women with other sexually transmitted diseases, and women with new sex partners for verification of not carrying the virus because pregnancy increases the risk for catching the disease. The second HIV test is done in the third trimester, recommended before 36 weeks of gestation to determine the mode of delivery, vaginal or planned cesarean (27). A third HIV test, the rapid screening test, is done right before the delivery. These recommendations are valid for women aged 19-64 (7). In almost every clinic, the professional teams these days, in contrast to the past, are skilled at explaining in detail what the virus is, what a positive or negative result means, giving the patient all the available information about the treatment options, and most importantly allowing her to ask all the questions to lower the stress level, give a feeling of partnership and recruit the patient as much as possible quickly and safely to start the treatment immediately, already at the clinic (24). In many resource-limited countries, especially in Africa, a lot of pregnant women will arrive only for the first antenatal meeting, skipping all other tests further in the pregnancy process, which limits the opportunity to have a full prevention treatment and increases vertical transmission dramatically (22). In a general setting, as soon as women are diagnosed with HIV, there are generally few steps that are recommended to take, especially during pregnancy. First, checking for the HIV-RNA viral load levels and determining the woman's disease stage is crucial. If the woman is already on ART, checking viral loads every three to four months during pregnancy is recommended. If the women start ART on the first antenatal clinic appointment, she is asked to check viral loads two to four weeks after starting medical treatment. Then monthly until reaching undetectable viral load and then, every three months, routine checkup. CD4+ T cell count measures are also required. For women consistent with treatment for more than two years with a count of >300 cells/mm^3 no need to monitor appointments during pregnancy. However, women with inconsistent medication consumption, CD4+ count of fewer than 300 cells/$mm^{3,}$ or newly diagnosed patients must monitor their counts every three months during pregnancy (25). Complete blood count with platelet count and chemistry with metabolic functions to check for liver and kidney functions. Before prescribing any medical treatment, genotypic and phenotypic resistance tests are needed to define the type of the virus, the presence of any mutations, and accommodation for the best medication combinations. However, here we see another gap between countries. Resistance testing is much less available in low-income countries, whereas in developed countries is more accessible to identify the strain of HIV and if it is resistant to one or more medications. Therefore, the lack of information regarding the HIV-specific strain makes it difficult to provide the most specific and appropriate treatment.

Perhaps certain given drugs do not cover the virus and will not overcome it. In resource-rich settings, it is recommended to do a resistance drug test to adjust the best medical combination. On the other hand, it is not recommended in limited source countries. However, we see increasing resistant HIV mutations, especially in women who come late in pregnancy or are not adherent to their medical treatment (22). Usually, broad-spectrum medications are prescribed in those situations. Some studies also recommend checking glucose levels earlier than the routine 24-28 weeks of gestation in women that use protease inhibitors (PI's) and Integrase strand transfer inhibitors (INSTI's)ART due to the increased risk of diabetes, but it is not definitive (25). Hepatitis A, B, and C tests should also be done due to common coinfection because of the same ways of transmission. If one of the results is positive, the women are transferred to consultations for further management of both viruses. Also, an increased risk of Mycobacterium Tuberculosis is seen. Therefore, positive HIV pregnant women are sent for latent tuberculosis tests. There is no significant increase in congenital infections in the baby. Nevertheless, positive HIV women are usually exposed to cytomegalovirus in the past; thus, it is recommended to do antibody screening tests to prevent serious congenital anomalies in their babies, like deafness (27). Drug toxicities tests during pregnancy are also done according to the specific side effect of the drugs prescribed for the women. Important to say that if a woman is already on ART with suppressed viral loads before conception, it is recommended to continue with the same treatment regimen and be under medical supervision. If a woman is on ART but has a high viral load, professionals should advise the patient on adherent strategies. If there is no decline in viral loads after eight weeks, the medical regimen is replaced with the next one. On all the recommendations mentioned above, all the other routine tests done during pregnancy, including other sexually transmitted diseases investigations are recommended except invasive tests like Amniocentesis and Chorionic Villus Sampling.

5.6. <u>Antiretroviral therapy and differences between low and high-income countries:</u>

The next step, after tests completion, ART is the gold standard treatment, which is available to all populations and age groups, including pregnant women, breastfeeding mothers, and children of infected mothers for the management and control of HIV but unfortunately without any current full cure option. The drug treatment of positive pregnant women with HIV and newborns has undergone many changes and developments which will be discussed here. ART during gestation has been shown to reduce the risk of mother-to-child transmission of HIV significantly. With the appropriate use of ART, the risk of transmission can be dramatically reduced to less than one percent (5). Thus, with the understanding that proper

treatment of positive HIV women should take place antepartum, intrapartum, and postpartum for the mother and her baby, and can lead to optimal results. Over the years, the U.S food and drug administration confirmed approximately thirty drugs from different groups to treat HIV. The standard treatment has been available worldwide since the 90s, using a single or later combination of medications to keep the viral load suppressed within the affected person, allowing the immune system to manage the infection better. In the past, the primary use of HIV medications was to prevent mother-to-child transmission. Today the medications are used not only to avoid vertical transmission but to treat the mother's disease level and symptoms, with all the other indications already existing, for example, for prophylaxis to prevent the acquisition of HIV from an infected person (mother-to-child transmission) or after exposure to a positive HIV person (sexual contact for example). Therefore, after confirmation of a positive HIV mother, the clinician should immediately offer a treatment that will dramatically reduce the transmission rates and will increase the rates of healthy baby delivery with benefit to the mother's quality of life.

Prophylaxis treatment has been available in many wealthy countries in North America and Europe already from the 1990s; however, those prophylactic regimes were not readily available to people living in many low and middle-income countries, especially countries in Africa which suffered the most from HIV spread until the mid-2000s (08). That fact is severe due to the knowledge that more than eighty-five percent of HIV-positive pregnant women come from those African countries. In low and middle-income countries, many drugs, like the first-line medications, were unavailable like in the West because of high costs; thus, infected people got treatment with second lines or inappropriate regimens. In those countries that could not afford treatment for every positive woman due to the limited number of medical resources and availability, there was a need for criteria to determine who could start treatment, and this was determined by the viral CD4+ T cells levels of the woman with a limit of CD4 <200 cells/mL. But unlike the rich countries, even getting the opportunity for those relevant tests was complicated, and not every woman that needed it got to do it (09). This left many positive women without proper treatment or awareness of their disease. Over the years, the number of tests, even in the poorest countries in the world, has been gradually increasing due to donations from voluntary organizations and the WHO in particular to fight the global HIV pandemic (08). Nowadays, The WHO recommends ART for all pregnant women living with HIV, without relation to their CD4+ T cell count or viral load (14). ART is recommended to be initiated as early as possible during pregnancy; the best period to start is before the end of the first trimester to maximize its effectiveness in preventing vertical transmission.

Four main drug groups are used as core medications in different combinations today. Nucleoside reverse transcriptase inhibitors (NRTIs) medications like zidovudine (AZT) that is also the first medication invented to manage HIV, Lamivudine, and Tenofovir. All act as competitive agents which bind to the viral reverse transcriptase and inhibit the DNA chain elongation, as a result blocking the replication of the virus. Usually, two NRTIs together are taken twice a day; in the past, there was a recommendation for one NRTI. With time, it was understood that two NRTI are required. Today some NRTIs are not first-line medications due to severe side effects discovered like neuropathy, mitochondrial toxicity, and lipodystrophy (010), usually taken once per day. The non-nucleoside/nucleotide reverse transcriptase (NNRTI's) group, containing the drugs Nevirapine, rilpivirine, doravirine, and efavirenz, whose primary function is not to let reverse transcriptase viral enzyme add new nucleotides for the elongation of the viral DNA. Due to their long half-life, those medications are administered once per day and should be under therapeutic drug monitoring to prevent toxicity or any unwanted reactivity. In contrast to NRTIs, no significant adverse symptoms were seen (010). INSTIs, medications in this group are dolutegravir, raltegravir, and elvitegravir; their mechanism of action is to block the integration of the viral DNA into the cell's genome. PIs class of drugs like atazanavir and darunavir, inhibit the cleavage of the Gag-Pol polyproteins which are very critical for the maturation of the HIV virions maturation, resulting in immature virions that cannot progress the disease. PIs alone needed to be consumed at least three times per day, with short half-life and low bioavailability of cytochrome P4503A4 enzyme which made it complicated to take and for the patient to adhere to the treatment. In the past, when combination therapy was not available, AZT was the first monotherapy for positive HIV pregnant women (21). In contrast, If the mother was not treated during the whole pregnancy phases, a single dose of non-nucleoside reverse transcriptase inhibitor called nevirapine (sdNVP) was used right before the delivery, and given to the mother. However, concerns have arisen over the efficacy of sdNVP in repeat pregnancies due to the Detection of mutations development that caused resistance to Nevirapine among women who previously received sdNVP (011). Because HIV can mutate when it replicates, it can become resistant to a single medication used against it. In contrast with the use of multiple antiretroviral drugs at once, as we are using today, we see significantly reduced chances of the virus becoming resistant to any of the drugs. From 2006 the preferred medication combination was: one nucleoside reverse transcriptase inhibitor-AZT 300 mg, Lamivudine (3TC)150 mg with a no nucleoside reverse transcriptase inhibitors like Nevirapine (NVP) 200mg, or a PI medication. When acute side effects from AZT were

seen, AZT was replaced with Tenofovir (TDF), especially in rich source countries. Only then, medications that used to act as the first line in the West became available in developing countries. After more investigation in the professional field a few years later, the recommended combination is two NRTI backbones like TDF 300 mg + 3TC or Emtricitabine 300 mg once daily with caution for renal insufficiency, PI medication: ritonavir (RTV) with Atazanavir 300mg (ATV) which increases the bioavailability of P4503A4 enzyme and the half-life of Atazanavir 100 mg once daily (12, 13) and INSTI- raltegravir (RAL) 400 mg twice a day or dolutegravir (DTG) 50 mg per day (recommended especially in ART naïve pregnant patients and the acute HIV phase). This combination is less toxic and has been confirmed to be with fewer side effects. NRTIs like AZT became alternative treatments in the second-line therapy in contrast to the past when it used to be the first-line regimen. Additionally, NNRTIs like efavirenz (EFV), taken orally, are alternatives in first-line treatment following risks of neural tube defects. These alternative medications in rich countries are usually used in resource-limited countries today by the WHO recommendations. In the past, ART was administered in constant doses without any changes during pregnancy. Now with the understanding that pregnancy is a physical situation that significantly influences the physical state, hormonal state, and stress level with the hyperinflammatory state of the body that can change the pH ad pharmacokinetics, it is required to adjust the medications during pregnancy if needed by therapeutic drug monitoring as recommended in unique population HIV treatment guidelines, especially in the second or third trimester to keep the antiretroviral amount in the mother before delivery (15).

Intrapartum ART involves constantly continuing ART already used before or during pregnancy. This allows us to give the woman the opportunity to give birth vaginally if her viral load is <1000 copies/mL for four weeks before her due date and not only deliver her using cesarean section as it used to be in a lot of the cases in the past when the medical treatment was not effective as today, and there was not enough knowledge like in our times (16). It is essential to say that in the United States, the preferred way of delivery for HIV-positive pregnant women until today is still cesarean section to avoid any transmission risks. In limited-resource countries, this practice is not applicable, and the mode of delivery in most cases, no matter what the viral load is, is vaginal delivery (22)

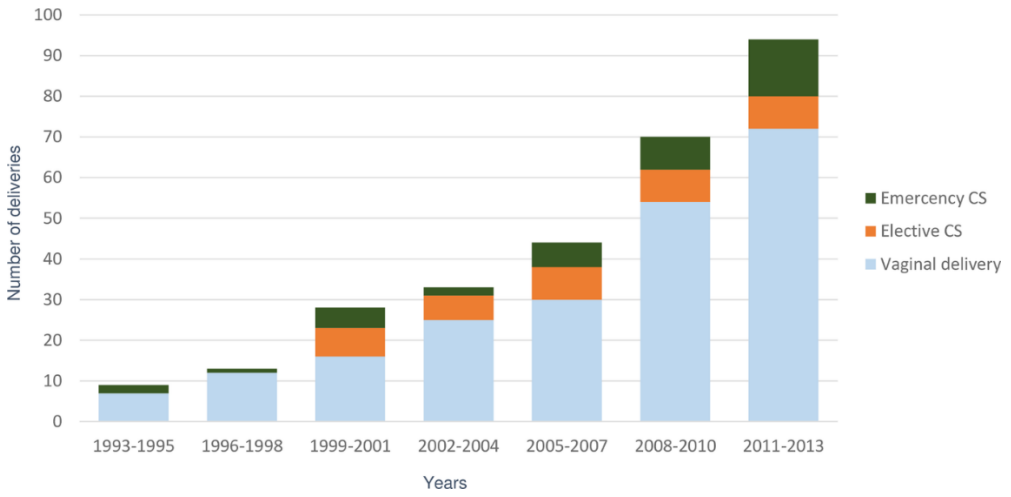

Figure 3: In a study conducted in Finland among HIV-positive pregnant women between 1993-2013, the preferred way for women to give birth is via the vaginal route. Over the years, the diagram shows the emergence of cesarean sections. Still, at the same time, and more importantly, the ratio between births to HIV-positive women and cesarean sections versus natural births is increasing. This shows that vaginal births are relatively possible and even preferred. The main reasons for cesarean sections included previous cesarean sections, breech position, hepatitis C virus unrelated to HIV, according to the mother's request, suspected asphyxia of the fetus, and bleeding.

[III] Aho I, Kaijomaa M, Kivelä P, Surcel H-M, Sutinen J, Heikinheimo O, et al. Most women living with HIV can deliver vaginally-national data from Finland 1993–2013. PLOS ONE. Public Library of Science; 2018Available from: https://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0194370

For women that were not on treatment during pregnancy or whose viral load is unknown, it is recommended to administer AZT intravenously during labor and delivery to reduce the amount of virus load in the genital tract as much as possible and prevent transmission chances during delivery for at least three hours in total, including one-hour loading dose of 2mg/kg and continuous dose of two hours of 2mg/kg. (17)

The postpartum period involves continuing ART consumed before and during pregnancy after the delivery and administering prophylactic treatment to the baby to reduce the risk of transmission through breastfeeding. Breastfeeding recommendations are mentioned already above in this article. In limited-resource and high-resource countries, even with the new plans implanted, we see a loss to follow-up in postpartum periods, with much higher percentages in limited-resource countries in all pregnancy points with women do not continue their treatments (23). In countries like sub-Saharan Africa, we see a decline in motivation due to attrition of the mother after months of follow-ups; in these countries, there is not much supply of clinics like in countries in the West, and they are usually far from the residential areas, and it takes much effort from these women to get to the clinics from their homes. Low levels of

stress after a healthy baby is born, lack of support from the environment and the husband, fear of stigma, and financial problems that still play a prominent role in adherence to postpartum treatment continuation (26).one of the way we see to overcome those obstacles, especially in the African countries which are with the highest HIV positive women in the world is to combine the facilities for antenatal care and ART care clinics to one place, this makes it easier for ART initiation with much fewer delays (23). Qualifications of a dedicated professional team, from doctors to nurses, whose entire purpose is to deal with these medical issues and to engage in advocacy and treatment. Additional home visits, letters, and messages to encourage the women to continue the treatment planned.

Successful implementation of prevention mother-to-child transmission (PMTCT) interventions depends not just on drugs as it was in the past but including access to a range of factors, healthcare, execution of testing and treatment services, and consultation with professionals before, during, and even after pregnancy for future reproductive plans and adherence to ART throughout the whole life. Women living with HIV require comprehensive care and multidisciplinary support to ensure optimal health outcomes for themselves and their children. This approach is already existing for many years in high-income countries but arrived later to limited-resource countries where the rates of HIV-positive pregnant women there were extremely high, and the implementation of this approach was hard due to a lack of clinics, sources or basic understanding of the professional teams in the maternal clinics how to establish good care or how to approach and encourage the patient to adhere the treatment plan. In 2016 the central goal of the organizations acting against HIV transmission was the 90-90-90 program. This means that by 2030 ninety percent of the people infected will be aware of that, ninety percent will be able to access treatment, and ninety percent of people infected will have suppressed viral loads (20).

5.7. <u>The A, B, and B+ programs:</u>

With the purpose to overcome the human immunodeficiency epidemic and preventing new HIV cases, with the substantial differences between the countries of the world, and the HIV cases that were growing, it was decided by the United Nations and the WHO to create a plan that would be convenient and easy to implement both in the personal aspect of the patient's self-care and in the financial aspect for struggling people and countries as Africa. The WHO developed a new program in 2010, including two regimens by the names "Option A" and "Option B," and two years later, in 2012, established the upgraded program used until today called "Option B+." those three regimens were recommended especially for pregnant HIV-

positive women. All contained combination prophylaxis due to understanding this drug cocktail's efficacy but under different conditions for their applications.

Initially, the treatment differed from woman to woman, depending on her viral load. Not every pregnant woman needed to continue a lifelong consumption of antiretroviral medications. Options "A" and "B" treatment criteria were based on the mother's CD4+ count and disease stage.

With option "A," pregnant-positive HIV women are allowed to start with prophylactic treatment as early as 14 weeks of gestation only if their CD4 cell counts >350 cells/mm3 (18), including AZT during pregnancy, before delivery sdNVP, during the delivery process, additionally to AZT Lamivudine (3TC) is given. After the delivery, the child is required to receive nevirapine prophylaxis for four-six weeks after birth or throughout the breastfeeding period. Then the treatment will stop a week after the final breastfeeding. But, if the mother's CD4 cell counts ≤350 cells/mm^3 or is in stages 3-4 of the disease, lifelong antiretroviral triple medication treatment is recommended with infant nevirapine prophylaxis for six weeks.

Some changes were applied with the development of option "B" treatment. A fixed type of triple-drug treatment was supplied to the HIV-positive pregnant woman without any medication changes during the stages of pregnancy with flexibility on the drug type consumed according to the country's financial resources and availability of drugs; She should continue the treatment until delivery or until one week after the secession of breastfeeding with infant NVP or AZT prophylaxis of up to six weeks to all babies regardless the way of feeding. Once started with one drug, no replacement to the other. Mothers were recommended to continue the ART beyond breastfeeding cessation if their CD4 cell count was ≤350 cells/mm^3 or the disease stage by the criteria was stages 3–4 (19). Option "B" was an upgrade from option" A" because the medications were not changed, with doses staying constant along the treatment course, allowing professionals and patients to establish better treatment management and continuation. With time, professionals understood that the conditions for the consumption and adherence to the medications were too complicated and unattainable because not all over the world had the appropriate resources for testing eligibility for drug treatment according to the existing criteria. They looked for a plan that would simplify the process and will be more accessible to the entire world's community. In 2012 came out a new treatment plan that HIV's medical plans are based on until today- Option "B+" Compared to the other programs, this program allowed any pregnant woman who is positive for HIV to start treatment immediately at any stage of pregnancy, with no relation of her disease level or CD4+ cell viral load (20). Moreover, in contrast to the other

programs where the recommendation is to stop the treatment after the period of pregnancy or breastfeeding, here, the unequivocal recommendation is to continue the maternal therapy for life. This option gives the patient a significant advantage because she will not need periodic CD4+ level tests for treatment continuation, increasing adherence rates to the treatment plan even after pregnancy. As we see, and formally from 2015, option B+ has decreased the overall maternal mortality rates in many low- and middle-income countries. Some studies have supported the belief that it is the most effective of the three regimens for preventing mother-to-child transmission of HIV (8).

6. <u>Study results:</u>

	High-income countries	Low-income countries
Distribution of the 1.5 million pregnant women diagnosed with AIDS this year	10%	90%
HIV testing	High performance High availability of all tests needed: rapid tests, CD4+ count tests, deeper RNA tests, resistance genetic tests	High performance low availability of all necessary tests but with increased supply in the last few years. Resistance tests are less available.
ART coverage	81% of women receiving ART. reduction of 2% since 2019	81%- reduction of 2% since 2019
Place of delivery	Formal settings: clinics/hospitals, low costs, and ability to arrive quickly to the facilities	Informal settings: villages, informal housing. Due to poverty, there are not many clinics close to villages. Many women decide to deliver their babies in informal sites.
Loss to follow-up 12 months after delivery	74%- due to reduces stress, lack of time, and stigmas.	73%- lack of family support, inability to buy drugs or come to follow-ups.

Preferred delivery mode	Cesarean- less dangerous, with a lower transmission rate. Mainly in the U.S., although choice has become more accessible for the patient, she can also have a vaginal delivery.	Vaginal- there are no financial and health resources for other ways of delivery.
Mode of feeding	Formulas- very popular in the general population; women can afford them.	Breastfeeding- Children in poverty receive many nutrients and have no option to buy formulas.
With ART therapy transmission	<1%	<5%
Treatment line	First-line medications are chosen. Due to affordable choice, treatment will be specific to the strain discovered in the genetic and viral tests.	Alternative first-line medications or second-line medications. Usually broad spectrum and not specific to the strain. Less expensive but still has a good effect on the patient
Preferred treatment plan	B+	B+

6.1. Table 1: main differences in positive HIV pregnant women treatment between low and high-income countries

	ART in the past	ART today
ART therapy	Monotherapy	Combined therapy
Dosing	Changed doses during points of pregnancy.	Constant doses during the whole pregnancy. If needed, dosing adjustments
Purpose of treatment	Prevent mother-to-child transmission	To treat the mother's disease condition and to prevent mother-to-child transmission.
Who can start treatment?	Usually, only women with CD4+ of <350 cells/mm^3	Every woman, regardless of her CD4+.

Time of the treatment	Usually during pregnancy and in the breastfeeding period. Some women continue treatment for life.	Every woman is recommended to continue treatment for life.
Medication changes	Medication before pregnancy can be changed during pregnancy	It is recommended to continue with the same medicines were before the pregnancy, during the pregnancy
First line therapy	Zidovudine along pregnancy/ single dose nevirapine before delivery	Combination of two NRTI backbones, PI and INSTI

6.2. Table 2: the differences during the years in the understanding and treatment with ART.

7. Discussion:

This article shows the development that has been made during the years in the treatment of pregnant women that are HIV positive. If in the 80s, when the virus was just discovered, it was a terminal illness; slowly, with worldwide health system improvement and awareness, health professionals refer to it as a chronic viral disease that people can live with. Until this day, there is no cure for the disease. In the past decades, approximately thirty different drugs have been developed for life improvement for patients. If in the past, monotherapy was the first gold strategy that was later developed for multiple drug cocktails that are also available for pregnant women, contrary to the past when women needed to change their medical plans not to hurt the fetus. Today, in contrast to the past, treatment focuses not just on transmission prevention but also on medical teams looking for the mother's best health in the existing conditions. Multidisciplinary teams have evolved on purpose to fight HIV directly and understand that many facts like financial, mental, and social aspects are part of the treatment. Still, in our days, there are gaps that we as professionals are trying to reduce so that the disease does not spread, and we can provide a better future for women and their children. In poor countries, obtaining rapid tests, recruiting patients, and providing the best drug treatment is more difficult. There, the popular treatment is second-line therapy because of their low costs or drugs that work on various types when we don't know which virus strain the woman has. On the other hand, in rich countries, the services are available to anyone who wants them. Every woman is tested at the beginning of her pregnancy. If she is positive, comprehensive tests are done, such as CD4+ count, viral loads, genetic viral tests, and the treatment is given by the first-line drugs on the first antenatal care.

The goal of the World Health Organization is that every woman in the world, no matter what country or class she comes from, will receive the same level of care and adequate resources for her treatment and management of the disease. Over the years, more tests have reached

poor countries, the number of drugs has expanded, and there has been a significant jump in the number of women being treated with ART today in poor-resource countries. A number that is almost equal in to rich countries. It is seen that since covid-19 pandemic broke out, a decrease in pregnant women positive for HIV care has decreased. This is worrying because the years before showed improvement in the fight against HIV. Since 2019 there has been a decline of 2% in women using ART during pregnancy both in rich and poor countries. The goal until 2030 is that 90% of affected people will be aware of their virus, consume ART, and will suppress their viral loads.

8. Conclusion:

It is shown that one of the main goals of professionals all over the world is to overcome the human immunodeficiency virus pandemic by preventing mother-to-child transmission. The world has been fighting this virus for approximately forty years. Developing medications and changing treatment strategies, antiretroviral therapy is an essential component in the prevention of mother-to-child transmission of human immunodeficiency virus. Begin with medication treatment at early stages of pregnancy is of great importance in lowering the chance of vertical transmission. Implementing prevention mother-to-child-transmission interventions requires a comprehensive approach, including access to testing, deceasing the costs of all medications to allow better access, and support services, to ensure successful outcomes for women living with human immunodeficiency virus and their children. One of the key understandings is that all over the world the treatment became multidisciplinary including in some cases not just the doctor but also psychologists, social workers, doctors from few disciplines. There is still a lot to do, but it seems like the world is walking on a path that will keep decreasing the transmission rates by evenly caring for the global women's population.

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