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REVIEWS

Review of Medical Approaches for the Prevention of Perinatal Transmission of HIV Infection

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Although advancements in antiretroviral therapies have reduced the rates of HIV transmission, HIV remains an international public health concern. Perinatal HIV transmission continues to be one of the most common modes of transmission, with most new pediatric HIV infections beginning in utero. In this review, we provide background on the current standard of care in HIV-positive pregnant women. This includes a discussion of antiretroviral monotherapy vs polytherapy, vaginal delivery vs elective cesarean delivery, and avoidance of breastfeeding in the prevention of perinatal transmission of HIV infection. We also review several methods of HIV treatment that are currently under investigation, including shock and kill, block and lock, and gene editing techniques. Further, we discuss the significance of perinatal HIV transmission from a public health perspective both on a global level and on a local level in Washington, DC.

Introduction

In 1981, AIDS was discovered in a case study that followed the manifestation of a rare type of Kaposi sarcoma in 8 otherwise healthy young men who had sexual intercourse with men.[1] The isolation of a novel retrovirus belonging to the human T-cell leukemia virus family, now termed *HIV*, was later identified as the etiologic agent of AIDS.[2] Since 1981, HIV/AIDS has been one of the world's leading public health crises. As of 2019, approximately 75.7 million people have received an HIV diagnosis, and approximately 32.7 million people have died of AIDS-related illnesses worldwide.[3]

HIV infection slowly and progressively attacks the body's own immune system. CD4+ T lymphocytes are responsible for mediating cellular immunity and the body's response to foreign pathogens.[4] Progressive loss and transmutation of CD4+ T lymphocytes are the trademark of HIV infection, eventually leading to uncontrolled replication.[2] Left untreated, HIV progresses through 3 distinct phases. Phase 3, AIDS, is the final stage of infection and is distinguished by a CD4+ cell count of less than 200 cell/mm or the

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development of opportunistic diseases such as esophageal candidiasis, *Mycobacterium avium* complex, *Pneumocystis jirovecii* pneumonia, or other infections classically associated with AIDS.[5] Without proper treatment, the prognosis for people living with AIDS is very poor, with a 2-year survival probability of 48%.[5]

HIV is classified as a sexually transmitted infection that is spread via exchange of blood; semen; preseminal, vaginal, or rectal fluids; or breast milk.[6] The most common methods of HIV transmission include sexual intercourse, intravenous drug use with shared needles and/or syringes, and perinatal transmission, which is defined as transmission in utero or shortly postpartum.[6] Most new pediatric HIV-1 infections worldwide occur predominantly via perinatal transmission. Untreated perinatal HIV infections carry a very high mortality rate, with one study finding that 52% of children with perinatal infections died by 1 year of age.[7] HIV viral loads in infants are typically measured to be 10 times as much as those seen in adults, highlighting the severity of disease progression and outcome in infants.[8]

Despite being considered one of the most widespread and detrimental infectious diseases in recent history, no curative treatment for HIV/AIDS exists to date. However, there is some promising evidence that it may be possible, and advancements in modern medicine and antiretroviral therapies (ARTs) have turned HIV into a manageable diagnosis. By adhering to proper treatment, people living with HIV (PLWH) can live a healthy life with a normal lifespan. The objective of this review is to cover the current standard of care as well as prospective preventive and treatment measures for controlling, reducing, and ultimately eliminating perinatal transmission of HIV infection.

Discussion

Standard of Care

HIV testing is recommended in all women who are pregnant, and all women who are looking to get pregnant, irrespective of risk factors. HIV testing is important in the early diagnosis, treatment, and prevention of perinatal transmission. Of the 1.7 million people who acquired HIV in 2019, 150 000 infections were among children.[3] Of the HIV-positive pregnant women in 2019, 85% received ART.[3] Moreover, breastfeeding is associated with decreased risk of malnutrition and diarrhea, which are leading causes of infant mortality in low- and middle-income countries.[9] For some HIV-positive pregnant women, the risk of infant mortality due to malnutrition outweighs the risk of HIV transmission, thereby underlining the clinician's responsibility to provide HIV-positive pregnant women with prenatal care, ART, and support services to prevent perinatal transmission.[9] In HIV-positive pregnant women who lack clinical intervention, the rate of perinatal transmission ranges from 15% to 45%, thereby demonstrating the necessity of perinatal care.[10] Several interventions have been assessed and determined to reduce the rates of perinatal transmission.

Antiretroviral Therapy

In HIV-positive pregnant women, ARTs using nucleoside reverse transcriptase inhibitors (NARTIs) have proven to be successful in reducing the rates of perinatal transmission. Structurally, NARTIs are thymidine analogs, but they have an azido group instead of a hydroxyl group at the 3' carbon of the deoxyribose.[11] The NARTIs' azido group prevents phosphodiester linkages, inhibiting DNA replication. NARTIs selectively bind to HIV reverse transcriptase, thereby preventing viral DNA from integrating into the host DNA and stopping perinatal transmission. However, NARTIs result in decreased mitochondrial DNA, thus increased risk of hematological toxicity, myopathy, lactic acidosis, and hepatic steatosis.[11]

In 2010, the World Health Organization published guidelines recommending ART for HIV-positive pregnant women before birth, during labor, and after birth for the prevention of perinatal transmission.[12] By achieving viral suppression, or less than 200 copies of HIV per mL of blood, ARTs can preserve strength of the immune system, increase a patient's quality and length of life, reduce HIV/AIDS-associated death, and prevent HIV transmission.[7, 13] With proper treatment and adherence, a PLWH's viral load can become so low it is both undetectable and nontransmissible.[6] The first-line ART drugs include zidovudine and nevirapine. Connor et al[14] conducted a double-blind, placebo-controlled clinical trial on the efficacy and safety of zidovudine in decreasing the rates of perinatal transmission. The study included 477 HIV-positive pregnant women. Connor et al[14] determined the rates of perinatal transmission in the placebo group and zidovudine group to be 25.5% and 8.3%, respectively, and that zidovudine decreased the relative risk of perinatal transmission by 67.5%. Recently, combination ART has been debated to be more effective than zidovudine and/or tenofovir alone, suggesting that monotherapy may not completely suppress viral replication. The US Department of Health and Human Services (DHHS) recommends a combination 2-drug ART, alongside an integrase inhibitor or protease inhibitor, during pregnancy.[15] Yet, Lorenzi et al[16] determined that patients treated with a 2-drug ART with or without a protease inhibitor had increased risks of adverse events, including intracerebral hemorrhage and biliary tree malformation in newborns. Similarly, Mandelbrot et al[17] assessed the safety and efficacy of combination zidovudine and lamivudine therapy compared with zidovudine monotherapy. The authors determined that the risk of transmission in combination zidovudine and lamivudine therapy was 5 times lower than that of zidovudine monotherapy, but there was increased risk of neutropenia, anemia, and death due to neurologic complications related to mitochondrial dysfunction.[17] Therefore, the women's risks and benefits associated with antiretroviral monotherapy vs polytherapy should be detailed. Nevertheless, ART is highly recommended during pregnancy, because it has been successful in reducing the risk of perinatal transmission.

For HIV-positive, ART-enrolled women who have viral loads of less than 400 copies/mL, intravenous zidovudine is not required during labor. Warszawski et al[18] assessed 5271 HIV-positive, ART-enrolled women and compared those who received intravenous zidovudine during labor vs those who did not. The rates of perinatal transmission in HIV-positive, ART-enrolled women with and without zidovudine were 0.6% and 0.0%, respectively.[18] However, these rates only applied to HIV-positive, ART-enrolled women who had viral loads of less than 400 copies/mL.[18] The pregnant women's viral load is a risk factor for perinatal transmission, thus early diagnosis and treatment are necessary. Moreover, clinicians should consider the patient's viral load before delivery in determining the need for intravenous zidovudine during labor.

For HIV-positive, ART-enrolled women who had viral loads of less than 400 copies/mL, neonatal zidovudine monotherapy from birth to 6 weeks of life is recommended. Guay et al[19] conducted a study in Kampala, Uganda, and determined that infants administered zidovudine from birth to 6 weeks of life and nevirapine at 2 mg/kg from birth to 1 week of life decreased perinatal transmission to 13% compared with 40% among infants administered zidovudine alone.[19] Therefore, the standard practice for infants born to mothers who did not receive ART during pregnancy and/or had viral loads of more than 400 copies/mL is combination zidovudine for 6 weeks and nevirapine for 1 week.[19]

Although ART is an effective treatment for HIV, compliance plays a significant role in its effectiveness. This is especially important in HIV-positive women enrolled in combination ART, wherein nonadherence is associated with drug-resistant mutations and poorer health outcomes due to the drugs' differing half-lives.[20] Iacob et al[21] demonstrated that adherence between 80% and 100% may be enough to achieve viral suppression, but ART compliance varied between 27% and 80%. It is imperative to address factors contributing to nonadherence to reduce HIV infection and transmission, such as access to health care, adverse drug reactions, socioeconomic status, and stigma. Lack of access and high costs of prenatal care can serve as barriers against treatment. The stigma surrounding HIV infection may deter individuals from HIV testing, thereby missing an opportunity for diagnosis, treatment, and prevention. In a 2007 study conducted in Cape Town, South Africa, Simbayi et al[22] found that 1 in 4 participants never told a friend about their HIV status, 1 in 3 participants felt they were treated differently by friends and family after disclosing their positive HIV status, more than 1 in 3 participants experienced discrimination from disclosing their positive HIV status, and 1 in 5 with HIV/AIDS lost their home or job because of their status. Noncompliance is multifactorial and understanding the factors influencing nonadherence may provide further insight into methods that can improve the disparities and health inequalities underlying HIV treatment.

Mode of Delivery

The mode of delivery—vaginal or cesarean delivery—plays an important role in perinatal transmission of HIV infection. Since 1999, the American College of Obstetricians and Gynecologists has recommended that all HIV-positive, ART-enrolled pregnant women deliver via cesarean. Andiman et al[23] determined that cesarean delivery decreased the risk of transmission in patients receiving zidovudine monotherapy and not receiving zidovudine monotherapy by 50% and 87%, respectively. Recently, the recommendation from the American College of Obstetricians and Gynecologists that the risks from cesarean delivery outweigh the risks from perinatal transmission has been challenged by obstetricians. The viral loads of HIV-positive, ART-enrolled pregnant women play a role in clinicians' recommendation for vaginal vs cesarean delivery. Briand et al[24] identified 4300 HIV-positive, ART-enrolled pregnant women with viral loads of less than 400 copies/mL (2120 had vaginal delivery, 1234 had elective cesarean delivery, and 946 had nonelective cesarean delivery) and 417 HIV-positive, ART-enrolled pregnant women with viral loads of more than 400 copies/mL.[4] The researchers determined that the risk of transmission between vaginal delivery and cesarean delivery did not differ, as long as the HIV-positive, ART-enrolled pregnant women had viral loads of less than 400 copies/mL.[24] In 2014, the DHHS Perinatal Antiretroviral Treatment Guidelines were updated, stating HIV-positive, ART-enrolled pregnant women who have viral loads of less than 1000 copies/mL in late pregnancy may proceed with a vaginal delivery, because the risk of perinatal transmission in this cohort is low.[25] In contrast, HIV-positive pregnant women who did not receive ART during pregnancy and/or had a viral load of more than 1000 copies/mL are advised to schedule a cesarean delivery.[6] For HIV-positive pregnant women, the safest way to deliver, either vaginal or cesarean delivery, is determined by their prenatal care and viral load.

Infant Feeding

Breastfeeding not only transfers proteins, such as antibodies, that enhance the infant's immune response, but it can also transfer HIV, increasing the risk of disease transmission. Alternatively, combination feeding (human milk and formula) also increases the risk of HIV transmission by decreasing the child's development of their immune system as well as their acute immune response against HIV infection, as compared with breast milk or infant formula alone.[26] Nduati et al[27] conducted a randomized clinical trial in Nairobi, Kenya, and found that using infant formula decreased the risk of HIV infections in children by 44%. The Centers for Disease Control and Prevention recommends that infants in resource-limited countries only be fed breast milk. In resource-rich countries, breastfeeding should be avoided if there are alternative approaches, such as infant formula, milk banks, cross feeding, and flash heating.[6] Flynn et al[28] determined that the risk of transmission was significantly reduced in mothers who breastfed, but only if their infants received nevirapine during the first week of life. Therefore, clinicians should

recommend avoidance of breastfeeding, alongside neonatal combination zidovudine, for 6 weeks and nevirapine during the first week of life. Moreover, education on perinatal transmission via breastfeeding, routine viral load testing, and appropriate support services should be provided. In some cultures, breastfeeding postpartum may be expected of the mother or sexual health may be a taboo topic, further impeding the education on HIV transmission and treatment. Therefore, it is imperative to recognize social and cultural implications that may influence rates of perinatal transmission and treatment.

Prospective Approaches for Treatment of HIV Infection

Although DHHS Perinatal Antiretroviral Treatment Guidelines have succeeded in reducing the rates of perinatal transmission of HIV infection, recent studies have underlined new approaches for prevention of perinatal transmission. Tang et al[29] determined that syncytin, a glycoprotein capable of inducing mammalian cell fusion, is capable of infection by non–CD4-expressing cells. They identified syncytin's ability to facilitate HIV spread through nontraditional ways. Specifically, syncytin is constitutively expressed in the placenta's trophoblast layer, increasing the likelihood of perinatal transmission events during pregnancy, dissemination of HIV, and areas of viral reservoirs in other tissues.[29] Current research on syncytin and HIV infection is limited, but further investigation can help provide insight into syncytin as a target of therapy, thereby reducing the rates of perinatal transmission of HIV infection.

Additionally, Pollara et al[8] studied the ability of passive immunotherapy to eliminate viral reservoirs of HIV in pediatric populations. They determined that bio-specific HIV dual-affinity re-targeting (DART) X CD3 molecules were efficient in recruiting and averting T cells found in umbilical cord blood to aid in the elimination of HIV infection.[8] DART molecules bind cell surface antigens while simultaneously engaging CD3, a protein complex on cytotoxic T lymphocytes. Stimulating cytotoxic T lymphocytes promotes their lysing abilities, eliminating virally infected cells.[30] Pollara et al[8] identified the efficacy of DART molecules in umbilical cord blood T cells compared with adult T cells was lower. They looked to enhance efficiency through using CD16 DART molecules as well, but further research is needed before applying this approach in pediatric populations affected by perinatal HIV infection.[8]

Current research for HIV-positive individuals has been based on 2 strategies: developing a sterilizing cure with full elimination of HIV provirus from the body and latent reservoirs or a functional cure through immunologic support and control of HIV-persistent cells. A latent reservoir is typically referred to as a site or cell type where replication of a virus can persist, despite prolonged periods without replication. Latent reservoirs are larger for HIV-positive patients who are receiving ART for short periods of time; larger reservoirs can

lead to decreased rates of success of HIV treatment and higher rates of HIV infections.[4] Meanwhile, patients who are treated with ART immediately upon infection generally have a smaller reservoir.[4]

Shock and Kill, Block and Lock, and Gene Editing Techniques

Moranguinho and Valente[4] evaluated 3 strategies for the treatment of HIV infection: shock and kill, block and lock, and gene editing techniques.[4] The basis of these methods is eradication of the latent reservoir, removal of cells with the HIV provirus, and blockage of elements related to HIV replication. The shock and kill approach focuses on eliminating all HIV proviruses capable of replicating from the latent reservoir. The shock and kill strategy attempts to delete the latent reservoir of HIV-positive cells through activation (ie, shock), then purging (ie, kill). The technique uses latent reversal agents to promote transcription of latent cells, thereby alerting the patient's immune system to recognize the active virus and tag it for destruction. In clinical trials, latent reversal agents have been effective in preventing HIV reactivation. However, there have been no significant changes in latent reservoir size, suggesting its ineffectiveness in prevention of perinatal transmission of HIV infection.[4]

In contrast, the block and lock approach focuses on targeting the HIV- or host-specific factors, inducing a state of irreversible latency. Block and lock uses a latency promoting agent (LPA), instead of ART, to eliminate viral transcription completely or to decrease viral transcription to low levels unrecognizable by the patient's immune system. Thereafter, integrated proviruses will be present but dysfunctional due to the destruction of transcription function. There are several proteins and complexes that can be inhibited during the transcription pathway that have been studied as targets for permanent suppression of HIV transcription, such as FACT, mTOR, BRD4, and HSP90. Block and lock proved to be the most successful when using a Trans-activator of transcription (TAT) inhibitor. TAT is a protein that acts on the gene promoter, activating HIV gene expression early during the infection. It increases the level of transcription of double-stranded DNA, significantly enhancing the efficiency of viral transcription. By inhibiting TAT, disease expression may be diminished. Didehydro-cortistatin A (dCA), a well-evaluated TAT inhibitor, has been shown to prevent HIV activation and viral production by inhibiting transcriptional elongation and blocking the feedback loop driving viral production. TAT inhibitor, alongside an ART, may improve the efficacy of the block and lock approach.[4]

Further, several gene editing techniques have been studied to treat HIV-positive individuals. The gene editing techniques alter HIV transcription and translation processes, suppressing HIV replication. The CRISPR/Cas9 system targets specific regions of a virus genome, excising and replacing target regions using a guide RNA. The stem cells are obtained, then edited and modified before reinfusing them into the patient. First, Mancuso et al[31] evaluated the adeno-associated virus 9 (AAV9)–CRISPR/Cas9 gene editing construct

approach with guide RNAs in rhesus macaques. Through AAV9-CRISPR/Cas9, the researchers increased the delivery and expression of guide RNAs, improving the efficiency of the removal of fragments of integrated proviral DNA. Through droplet digital polymerase chain reaction studies of lymph nodes, Mancuso et al[31] identified a 95% reduction in the intact SIV DNA compared with 20% in non-CRISPR/Cas9 treatment. Therefore, continued research using the AAV9-CRISPR/Cas9 approach in larger populations should be considered, especially in the prevention of perinatal transmission of HIV infection.

Second, Dash et al[32] combined CRISPR/Cas9 and long-acting, slow-effective release antiviral therapy (LASER ART), resulting in elimination of HIV infection in a population of humanized mice. The researchers determined that LASER ART alone resulted in viral rebound, but when coupled with CRISPR/Cas9, it resulted in cleavage of viral genomes at highly conserved regions, mitigating the chance of reemergence. Dash et al[32] identified 9 of 23 mice in 3 independent studies that lacked viremia after the combination approach. The study highlighted combination LASER ART and CRISPR/Cas9's ability to eliminate latent viral reservoirs in humanized mice populations, but has not been attempted in human populations due to safety, feasibility, and ethical concerns.[32] Third, Moranguinho and Valente[4] identified 2 HIV-positive patients in remission, both of whom were taking ART, then provided a stem cell transplant with a homozygous deletion of the CCR5 delta 32 allele. CCR5 codes for white blood cell surface receptors and plays a key role in the normal human immune response. HIV uses CCR5 to enter white blood cells, so by deleting the CCR5 delta 32 allele, one pathway of infection may be eliminated. After the homozygous deletion, the patients were no longer given ART, and no viral load rebound was detected. In 2018, a team of scientists in China genetically engineered twins to be resistant to HIV using CRISPR/Cas9 by editing the CCR5 gene in early human embryos.[33] This was led by He Jiankui despite a ban by China's National Health Commission on research of "human *in vitro* embryos after the 14th day of existence, and its subsequent implantation into a human uterus."[33] Currently, CRISPR/Cas9 continues to be a controversial debate due to its safety, feasibility, and ethical concerns. However, it has shown promising results in its effectiveness in treating HIV-positive animal models.

Public Health and Significance

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS)[34] created the 90-90-90 targets:

- By 2020, 90% of all PLWH will know their HIV status,
- By 2020, 90% of all PLWH will receive ART,
- By 2020, 90% of all PLWH receiving ART will have viral suppression.

To achieve 90-90-90, 73% of HIV carriers must have suppressed viral loads, and as of 2019, 14 countries achieved this target, with Switzerland and Eswatini achieving 95-95-95.[34] The updated 2030 targets indicated 86% of HIV carriers have suppressed viral loads.[34] There are large discrepancies between countries in achieving these targets due to differences in sociocultural factors, stigma, education, and access to care.

UNAIDS reports that "increased access to [ART] has averted an estimated 12.1 million AIDS-related deaths since 2010" and in the United States, there has been a 95% reduction in mother to child transmission of HIV nationally with ART, with transmission rates as low as 1%.[34,35] Because of the success of ART in the United States, it is often thought the HIV epidemic is over. However, this is not the case, with for example Washington, DC, being disproportionately affected by HIV. Between 1994 and 2013, Washington, DC, was found to have the highest prevalence of transmitted drug resistance (22.5%) amongst other cities in the United States, Europe, and Australia, where ART was also implemented long-term.[36] From 2013 to 2017, HIV-related causes accounted for 27.1% of total deaths in Washington, DC.[35] Kassaye et al[36] found that immigration patterns from African countries played a role in increased HIV rates in the Washington, DC, metropolitan area. In 2016, Mayor Muriel Bowser announced the 90/90/90/50 Plan to End the HIV Epidemic in the District of Columbia by 2020 plan[35]:

- By 2020, 90% of PLWH in DC will know their status,
- By 2020, 90% of PLWH in DC will be in treatment,
- By 2020, 90% of PLWH in DC who are in treatment will reach viral suppression,
- By 2020, new HIV diagnoses will be reduced by 50%.

As of 2019, in Washington, DC, 90% of PLWH knew their status, 80% of PLWH were in treatment, and 87% of PLWH who were in treatment reached viral suppression.[35] As of 2020, the 90/90/90/50 plan was updated to 95/95/95, with the additional goal of having fewer than 130 new diagnoses of HIV per year.[37] Although there have been many advances in treating HIV/AIDS, it is evident HIV is still prevalent in certain regions of the world, including the Washington, DC, community. By understanding the social implications of perinatal transmission, preventive methods can be implemented to further lower the rate of HIV transmission.

Conclusion

In the United States, the rate of perinatal transmission of HIV infection has declined because of evidence-based guidelines supporting ART, viral load determination in vaginal delivery vs cesarean delivery, and avoidance of breastfeeding. In 2018, 5000 women with HIV gave birth in the United States,

but only 32 infants were diagnosed with perinatally acquired HIV, showing an incidence of 0.8 per 100 000 live births.[38] In 2018, Washington, DC, had an HIV prevalence of 1.8%, with women making up 26.1% of PLWH.[35] Koay et al[39] determined that ART before birth, during labor, and after birth; cesarean delivery; and avoidance of breastfeeding continue to be effective measures in reducing perinatal transmission of HIV infection. HIV-positive, ART-enrolled women have a low risk of HIV transmission, so avoidance of intravenous zidovudine during labor and cesarean delivery may be safer options for this cohort. While ART is effective in preventing transmission, noncompliance results in immunosuppression secondary to rebound viremia, which is associated with increased HIV-related morbidity and mortality.[4] Therefore, access to prenatal care and support services to prevent perinatal transmission should be underlined. Moreover, the father's role in perinatal care and prevention of perinatal transmission is limited, but additional research investigating prevention and treatment of HIV infection in fathers may provide benefits toward reducing perinatal transmission further.

Although the HHS Perinatal Antiretroviral Treatment Guidelines have succeeded in helping to decrease the rates of perinatal transmission of HIV infection, total eradication of HIV infection has not been achieved with ARTs. Continued research is necessary to eliminate HIV infection, thereby eliminating the risk of perinatal transmission. Shock and kill was slightly promising, but increased concerns related to unreliability and tremendous strains on the immune system because it activated the HIV from the patients' latent reservoirs. Block and Lock is more promising, because it relies on TAT inhibition. Block and Lock alongside LPAs do not appear to create severe adverse events, and thus should be considered as a prospective approach for treatment of HIV infection. Moreover, LPAs suppress HIV replication, thus continued research investigating combination approaches using LPAs should be considered, as well as other proteins that may be effective in inhibiting the transcription process. CRISPR/Cas9 targets CCR5, the major HIV coreceptor for transmission. Through CRISPR/Cas9, gene modification may be effective in treating patients with HIV infection. However, the risks associated with stem cell transplants and other gene editing techniques far outweigh the benefits of remission of HIV infection. Nonetheless, researchers are looking to improve efficacy with CRISPR/Cas9 approaches, as well as resolve the ethical issues so that they can proceed to clinical trials.[4]

HIV is a worldwide epidemic, most prevalent in Western and Central Africa, but still concerning in various other regions of the world, as demonstrated by HIV infection rates in Washington, DC. Resolving the HIV epidemic can involve multiple approaches, from learning more about the virus' effect on the immune system to addressing medication nonadherence and expanding access to treatment. Implementation of preventive measures, therapies, education, and social support help decrease the rate of perinatal transmission. HIV has

a high incidence, prevalence, and mortality rate, thus finding a safe and efficacious treatment option is necessary in preventing transmission and providing insight to treating other comparable diseases.

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