Perinatally Acquired HIV: Viral Evolution and its Implications for Adolescents

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This literature review explores the implications of viral evolution on the health outcomes of adolescents with perinatally acquired HIV, offering recommendations for enhancing public health practices. Since the emergence of HIV in the 1980s, perinatal transmission from parent to child has become increasingly prevalent in developing countries. Antiretroviral therapy (ART) has greatly improved the life expectancy of children with perinatally acquired HIV, allowing them to reach adolescence. ART plays a critical role in suppressing HIV and reducing the risk of transmission. Nevertheless, low adherence or lack of treatment can lead to viral evolution and drug resistance, posing significant threats to adolescents. Challenges faced by adolescents with perinatally acquired HIV are multifaceted, including increased viral evolution and difficulties in adhering to ART. The impact of stigma, behavioral factors, and social and familial dynamics contribute to low adherence rates. Global inequities and systems-level challenges further complicate the situation, particularly in resource-limited settings. Adequate public health infrastructure and innovative approaches, such as long-acting injectable ART, are imperative to address these structural barriers and reduce drug resistance among adolescents. Comprehensive data collection and longitudinal studies are needed to understand the long-term consequences of perinatally acquired HIV and its impact on viral evolution. A multidisciplinary approach involving healthcare providers, virologists, and social scientists is crucial to meeting global HIV goals and addressing the specific needs of this vulnerable population.

Keywords

human immunodeficiency virus • parent-to-child transmission • pediatric HIV treatment • adolescent health • global health

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Introduction

HIV (human immunodeficiency virus) is a chronic, treatable virus that originally spread across the globe in the 1980s. One critical route of HIV infection is perinatal transmission, where HIV is transmitted from a parent to their child during pregnancy, labor and delivery, or breastfeeding. Today, most children who acquire HIV via this route (also called vertical transmission) have access to lifesaving treatment and live into their adolescence and beyond. Adolescence is an important time for this population, given the potential for HIV evolution as a result of behavioral changes and life transitions. This literature review explores how HIV evolution impacts the health outcomes of adolescents living with perinatally acquired HIV globally. Drawing upon existing research, I seek to synthesize the biological implications of life-long HIV infection and the behavioral challenges for adolescents in order to make recommendations for future public health practices that improve health outcomes for adolescents living with HIV.

Basic Principles of HIV, Treatment, and Viral Evolution

HIV is a disease that attacks the body's immune system. It can be spread through sexual contact, sharing needles to inject drugs, and during pregnancy (CDC, 2022). This paper will focus on the latter, also called perinatally acquired HIV. Perinatally acquired HIV can occur prepartum (through the placenta), intrapartum (through the exposure of the infant's skin to maternal blood and vaginal secretions), and postpartum (through breast milk) (Ahmad, 2010). The use of antiretroviral therapies (ART) in pregnant individuals living with HIV lowers the chance of perinatal transmission to less than 1% (NIH, 2023b). Without ART, the transmission rate is about 30% (Ahmad, 2010). There is no cure for HIV, so someone infected with HIV will have the disease for the duration of their life. (CDC, 2022)

ART is a treatment regimen that typically includes a combination of three HIV drugs belonging to at least two of the seven different drug classes (NIH, 2023a) The HIV drug classes are 1) Non-nucleoside reverse transcriptase inhibitors (NNRTIs), 2) Nucleoside reverse transcriptase inhibitors (NRTIs), 3) Protease inhibitors (PIs), 4) Fusion inhibitors, 5) CCR5 antagonists, 6) Integrase strand transfer inhibitors (INSTIs), 7) Post-attachment inhibitors (NIH, 2021). Each class is grouped by the mechanism it uses to fight HIV and inhibit viral replication (NIH, 2021).

The modern ART drug regimen was released in 1996 (NIH, 2018). It suppresses HIV, allowing people living with HIV (PLWH) to live long, healthy lives. Antiretroviral treatment is an effective treatment for HIV because it prevents the virus from replicating, therefore preventing within-host genetic evolution in the virus (Bandera et al., 2019). A longitudinal study looking at 18 patients over 5 years showed that patients with low-level viremia who adhered to ART saw no genetic evolution for HIV over this period (Vancoillie et al., 2017). Additionally, ART adherence prevents the transmission of HIV, decreasing the odds of between-host evolution (Alizon & Fraser, 2013).

When an individual living with HIV does not receive ART treatment, or when adherence to treatment is low, it can lead to virus evolution. Genetic evolution of HIV can be dangerous because it can lead to HIV treatment resistance. By constructing a viral phylogeny (a diagram of evolutionary relationships) of HIV in an individual, we can better understand the history of HIV infection. By taking a viral sample at two different time points, scientists can compare phylogenies and detect HIV viral evolution through the presence of a temporal signal or new

population structure (Bandera et al., 2019). This technique has been used to compare viral evolution over long follow-up periods in ART-naive patients and patients taking ART (Bandera et al., 2019; Brodin et al., 2016). Phylogenies constructed from this study suggest that ART prevents viral evolution because treated HIV lacks novel phylogenetic structures (Brodin et al., 2016). When undertreated HIV evolves and creates a drug-resistant mutation, these mutations differ significantly. Transmission and replication fitness vary greatly and are often influenced by the viral genetic background (Bandera et al., 2019). Drug resistance emerges through suboptimal ART adherence, which occurs when the drug is taken inconsistently and becomes ineffective. This occurs because drug resistance mutations that code for reverse transcriptase or protease can become dominant within several months of the initiation of treatment (Rong et al., 2007). Resistant strains of HIV can be spread from a parent to their child through vertical transmission (Leitner, 2019). Additional drug resistance, therefore, has serious implications for teens living with perinatally acquired HIV.

Treatment Challenges For Adolescents with Perinatally Acquired HIV

This section will focus on the impacts of the aforementioned HIV evolution on the treatment and health outcomes of adolescents living with perinatally acquired HIV. Historically, children born with HIV in the 1980s and 1990s were prescribed suboptimal treatment regimens that were the standard of care at the time (such as monotherapy or dual therapy). These treatments were ineffective because they can lead to viral rebound. The aforementioned population, now adults, are more likely to have multi-class drug resistance (Yusuf & Agwu, 2020). Today's teens living with HIV have always been recommended ART, however, many still face barriers that prevent them from obtaining treatment or maintaining medication adherence. Adolescents who acquire HIV perinatally are an important population to study from an evolutionary lens. This group is at higher risk for drug resistance due to "early ART initiation, exposure to multiple treatment regimens, and long-term treatment exposure" (Yusuf & Agwu, 2020). First, the unique HIV treatment challenges for adolescents living with perinatally acquired HIV will be outlined. Subsequently, the behaviors that lead to drug resistance, and how public health efforts can address these root causes, will be explained.

Adolescents living with perinatally acquired HIV face increased challenges in HIV treatment compared to their teen or adult counterparts living with behaviorally acquired HIV. Second-line therapy is used when a PLWH develops treatment failure to their initial ART drug regimen (Alene et al., 2019). In 2019, it was shown that among adolescents living with perinatally acquired HIV in South Africa who had been retained in care for over 10 years, over 40% were on second-line ART. Teens on second-line ART had poorer immunological outcomes, including higher CD4 counts and lower viral suppression rates compared to individuals on their initial ART treatment. (Anderson et al., 2019). The majority of adolescents living with HIV reside outside of the United States. Even in this developed nation, about 18–25% of adolescents with early acquired HIV (perinatally or behaviorally) experience triple-class drug resistance (Yusuf & Agwu, 2020). Given high rates of resistance, the World Health Organization recommends regular viral load testing for adolescents (Broyles, 2023). This is challenging given the cost and access barriers that exist with this type of medical care.

Another modern challenge in treating adolescents with HIV is proper ART dosing. Puberty in adolescents may affect drug metabolism. Oftentimes, information from ART clinical trials performed with adults is extrapolated to adolescents. This is an issue in the area of HIV treatment because adolescents, one of the populations with the highest potential for drug resistance, are not sufficiently represented in ART research (Yusuf & Agwu, 2020).

Low Adherence among Adolescents

A significant source of HIV evolution and drug-resistant mutations is low adherence to ART. The full effect of viral suppression cannot be reached if ART is taken irregularly. Low adherence can lead to the progression of HIV, opportunistic infection, HIV transmission, and drug resistance (Hudelson & Cluver, 2015). One study measuring virological suppression among adolescents and adults in southern Africa showed that adolescents were significantly less likely to reach 100% adherence within a year of starting treatment compared to adults (Nachega et al., 2010). Another retrospective study in South Africa showed that older adolescents (ages 15–19) were more likely to have unsuppressed viral load compared to adults (Evans et al., 2013). Perinatally infected youth are also more likely to be prescribed less potent drug regimens due to drug resistance, therefore, missing a dose may have more of an impact on ART efficacy (MacDonell, 2012).

Adolescents living with perinatally acquired HIV experience very specific barriers to ART adherence, which I will examine through a socio-ecological lens. Compared to teens who acquired HIV behaviorally, teens with perinatally acquired HIV cite feeling "sick to the stomach" or feeling bad as a main barrier to taking ART medication (MacDonell et al., 2012). This could be because perinatally infected youth may be more likely to be prescribed more complicated drug regimens that have more side effects compared to other teens living with HIV. Also at the individual level, barriers to adherence include HIV-related stigma, forgetfulness, depression, and substance use. On the interpersonal level, lack of caregiver assistance, late-in-life parent disclosure of the child's HIV status, and lack of caregiver support with clinic visits are all recorded barriers to ART adherence. On the community level, reported barriers include long travel times to clinics, long wait times, or lack of peer support groups (Ammon et al., 2008). The next section will address the systems or government-level barriers that exist, and how public health infrastructure could be improved in order to address the needs of adolescents living with perinatally acquired HIV.

Global Inequities and Systems-Level Challenges

While both familial and individual barriers impact low adherence in adolescents living with perinatally acquired HIV, larger-scale public health infrastructure challenges also impact adherence rates. Patterns of drug resistance among adolescents living with perinatally acquired HIV can also be attributed to inadequate public health infrastructure in developing countries where perinatally acquired HIV occurs most often. Systems or policy-level barriers vary depending on the country. In the United States, low adherence has been associated with food insecurity, as hunger can exacerbate ART side effects (Young et al., 2018). Additionally, in a survey of nearly 400 adolescents living with HIV in the United States, non-adherent teens were significantly

more likely to report problems with medical insurance and problems with transportation to clinic visits (Rudy et al., 2009). Though this survey did not include teens living with perinatally acquired HIV, the findings illustrate the systemic barriers faced by young people who rely on US health systems.

The main focus of adolescent HIV research lies outside of the US in lower and middle-income countries. 90% of children living with perinatally acquired HIV live in sub-Saharan Africa (Frigati et al., 2020). In these areas, comorbidities are especially common among adolescents living with perinatally acquired HIV, making this population even more complex to treat (Frigati et al., 2020). Notably, as children with HIV age into teenagers, they are less likely to be retained in care, especially after the age of 15. The healthcare transition describes a teen's experience of moving from pediatric to adult healthcare settings (Ritchwood et al., 2020). Healthcare transitions often occur at younger ages (15 or below) in resource-limited areas and between 17 and 24 in high-resource settings (Ritchwood et al., 2020). A study conducted in South Africa showed that outcomes post-healthcare transition were worse in older adolescents, evidenced by a decline in viral suppression within three years of the transition (Davies et al., 2017). One systematic review of transition outcomes from pediatric to adult care reported that transition outcomes were worse for adolescents who already had unsuppressed viral levels in pediatric care. This shows that adolescents who are already vulnerable to drug resistance are often hit hardest by the healthcare transition, increasing the potential for viral evolution.

Further Recommendations and Conclusion

In order to meet the 95–95–95 goals set by UNAIDS, which aims to have 95% of people living with HIV to know their status, receive ART, and have viral suppression, the needs of adolescents living with HIV must be addressed. In the United States, clinical approaches for adolescents living with perinatally acquired HIV should emphasize a holistic care model that addresses food insecurity, problems with insurance, and inadequate transportation. Existing literature suggests some recommendations to ameliorate the global disparities and negative health outcomes for adolescents living with HIV. Interventions that educate healthcare providers on how to promote self-management among pediatric patients could improve healthcare transition outcomes (Mutumba, 2019). Very recent advances in long-acting injectable antiretroviral therapy may be the answer to low treatment adherence among adolescents, but more research is needed to understand the acceptability and feasibility of this strategy (Toska, 2023). One approach to improving health outcomes for youth with perinatally acquired HIV is to collect more comprehensive data and increase longitudinal studies following teens into adulthood. There is hardly any data on the global incidence and prevalence of adolescents living with perinatally acquired HIV (Yusuf & Agwu, 2020). This is an important limitation in this area of research in part because it deprives global policymakers of easily citable metrics they could use to pass legislation. Additionally, there is scant longitudinal research on teens living with HIV. Without such research, we do not know exactly how HIV evolves in a host for their entire lifetime (Yusuf & Agwu, 2020). The lack of virological insight makes it difficult to know whether current ART medication strategies are sufficient to maintain long-lasting health for adolescents living with perinatally acquired HIV. Providers, virologists, and social and behavioral scientists must work in tandem to address the complex and specific needs of adolescents with perinatally acquired HIV.

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