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CHARACTERISTICS OF CHILDREN LIVING WITH HIV IN A REFERRAL CENTER IN IRAN: A CROSS-SECTIONAL STUDY

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Abstract. *Background*. With an estimated 38.4 million people worldwide living with HIV in 2021, including 2.73 million children, there is a pressing need to understand and address HIV transmission and its impact on children's health. This study aims to describe the demographic characteristics, clinical profiles, and outcomes of Iranian children living with HIV referred to one of the largest center for counseling HIV patients in Iran. *Materials and methods.* In this descriptive cross-sectional study, we assessed clinical and biological markers in HIV-infected children treated at the counseling center for behavioral diseases in a referral Hospital in Tehran. The study included a total of 60 records of children and adolescents under the age of 18, spanning from 2004 to 2020. We collected detailed clinical and laboratory data, including demographic information, treatment history, comorbidities, opportunistic infections, adherence to treatment, side effects of HIV treatment, and laboratory test results. Additionally, the study investigated any history of COVID-19 infection during the follow-up period, which coincided with the pandemic. *Results.* Out of the 60 patients included in the study, there were 23 females (38.3%) and 37 males (61.6%), with a mean age of 10.03 years. About 16.7% of patients had at least one comorbidity, including epilepsy, ADHD, autoimmune hepatitis, ITP, allergic asthma, alopecia areata, and cystic fibrosis. Among the mothers of these children, 93.9% were HIV-positive. Out of the 60 mothers, 6.7% were not infected with the virus, 60% were receiving treatment, and 10% had passed away. Treatment adherence was acceptable in 93.3% of patients. Opportunistic infectious diseases were experienced by 36.7% of patients, with oral candidiasis being the most common. Hospitalizations occurred in 21 patients, primarily due to pneumonia, fever, weakness, lethargy, and oral thrush. *Conclusions.* Investigating the demographic, clinical profile, and long-term outcomes of pediatric HIV is crucial for policymakers to effectively address the ongoing HIV epidemic. Given the significant knowledge gap on pediatric HIV in Iran, further studies in this area are necessary to improve understanding and inform strategies for the prevention, management, and treatment of HIV in children in the country.

Key words: *HIV, pediatric care, adolescents, HIV infection, antiviral therapy, Iran.*

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ХАРАКТЕРИСТИКА ДЕТЕЙ, ЖИВУЩИХ С ВИЧ В ИРАНЕ, ПО ДАННЫМ СПЕЦИАЛИЗИРОВАННОЙ КЛИНИКИ: ПОПЕРЕЧНОЕ ИССЛЕДОВАНИЕ

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Резюме. *История вопроса.* Учитывая, что в 2021 г. во всем мире по приблизительным оценкам будет насчитываться 38,4 млн человек, живущих с ВИЧ, включая 2,73 млн детей, существует острая необходимость решения проблемы передачи ВИЧ и изучения влияния ВИЧ-инфекции на здоровье детей. Целью данного исследования является описание демографических характеристик, клинических профилей и результатов лечения иранских детей, живущих с ВИЧ, направленных в один из крупнейших центров консультирования пациентов с ВИЧ в Иране. *Материалы и методы.* В настоящем описательном перекрестном исследовании мы оценили клинические и биологические маркеры у ВИЧ-инфицированных детей, находящихся на лечении в консультационном центре по поведенческим заболеваниям специализированной больницы в Тегеране. В исследование включено в общей сложности 60 записей о детях и подростках в возрасте до 18 лет с 2004 по 2020 г. Мы собрали подробные клинические и лабораторные данные, включая демографические сведения, историю лечения, сопутствующие заболевания, оппортунистические инфекции, приверженность лечению, побочные эффекты от лечения ВИЧ и результаты лабораторных исследований. Кроме того, в ходе исследования изучалась любая история заражения COVID-19 в течение периода наблюдения, который совпадал с пандемией. *Результаты.* В исследование было включено 60 пациентов, в том числе 23 ребенка женского пола (38,3%) и 37 – мужского пола (61,6%); средний возраст 10,03 года. Около 16,7% пациентов имели по крайней мере одно сопутствующее заболевание, включая эпилепсию, СДВГ, аутоиммунный гепатит, идиопатическая тромбоцитопеническую пурпуру, аллергическую астму, очаговую алопецию и муковисцидоз. Среди матерей таких детей 93,9% оказались ВИЧ-положительными. Из 60 матерей 6,7% не были инфицированы вирусом, 60% получали лечение, а 10% скончались. Приверженность лечению была приемлемой у 93,3% пациентов. Оппортунистические инфекционные заболевания наблюдались у 36,7% пациентов, наиболее часто встречался кандидоз полости рта. Госпитализация имела место в анамнезе у 21 пациента, основными ее причинами были пневмония, лихорадка, слабость, летаргия и молочница полости рта. *Вывод.* Исследование демографического, клинического профиля и долгосрочных последствий ВИЧ-инфекции у детей имеет решающее значение для эффективного противодействия продолжающейся эпидемии ВИЧ. Учитывая значительный пробел в знаниях о ВИЧ у детей в Иране, необходимы дальнейшие исследования в этой области для улучшения понимания и обоснования стратегий профилактики, ведения и лечения ВИЧ у детей.

Ключевые слова: *ВИЧ, педиатрическая помощь, подростки, ВИЧ-инфекции, противовирусная терапия, Иран.*

Introduction

In 2021, an estimated 38.4 million people worldwide were living with HIV, of which 2.73 million were children aged 0–19. Approximately 850 children were being infected daily. In Iran, according to UNAIDS, 59 314 people were living with HIV in 2019 of which 862 were children under 15 years. Additionally, the country experiences around 4100 new infections and 2500 AIDS-related deaths each year [25, 27].

HIV transmission from a mother to her child can occur during pregnancy, childbirth, or breastfeeding, referred to as perinatal transmission [21]. The majority of children with HIV infection acquire it through perinatal transmission or by breastfeeding during their early years of immune, neuro-cognitive, and physical development. Adolescents who contract HIV typically acquire it through sexual transmission [6].

The most typical symptoms and signs of HIV in children include recurrent upper respiratory tract infections, lymphadenopathy, and skin manifestations. Furthermore, children with HIV are more susceptible to various opportunistic infections such as tuberculosis, bacterial pneumonia, diarrhea, oral candidiasis, and Kaposi's sarcoma [20]. Opportunistic infections are a major contributor to both illness and death in individuals with HIV. Although antiretroviral therapy (ART) has reduced the occurrence of opportunistic infections, it still contributes to hospitalizations and deaths in those with HIV. Thus, preventing opportunistic infections in those with HIV is crucial in reducing disease burden and associated mortality [24].

ART enables individuals with HIV to have a life expectancy similar to the general population and has a significant impact on controlling the progression of HIV disease. However, it can also result in various complications, such as metabolic syndrome, dyslipidemia, cardiovascular disease, osteoporosis, and renal disease. In the absence of ART, children with HIV may face growth and puberty delays, long-term immune dysfunction, neuro-developmental delays, and other chronic complications of HIV infection [11].

The lack of comprehensive HIV statistics for children in Iran is a significant concern that hampers efforts to address and combat the virus's impact on this vulnerable population. Despite the growing number of HIV cases among children in the country, limited research and data collection efforts have been directed toward understanding the scale and dynamics of this issue [18]. Without accurate statistics, it becomes difficult to design effective prevention and treatment strategies tailored to the specific needs of children living with HIV in Iran. To address the significant burden of HIV disease in Iran, particularly in Iranian children, we embarked on a study to explore the demographic characteristics, clinical profile, and outcomes of children living with HIV referred to the behavioral disease counseling center of Imam Khomeini Hospital, Iran. This research endeavor was prompted by the scarcity of studies conducted in this specific population.

Materials and methods

Study design and participants. We conducted a retrospective cross-sectional study to describe the demographic characteristics, clinical and biological markers, as well as the complications in HIV infected children referred to the counseling center for behavioral diseases in a referral Hospital in Tehran.

The study population consisted of all children under the age of 18 who received treatment for HIV from 2004 to 2020. Inclusion criteria included all available files of children and adolescents younger than 18 years old with HIV from the archives of the counseling center. Patients with incomplete records were excluded from the study. A total of 60 records were assessed and entered into the study.

Data collection and variables. The study extracted detailed clinical and laboratory information from patients' records using a structured form, which was based on previous research [1, 5]. The form captured data including demographic information (sex, current age, age at diagnosis, height and weight), immunization history, treatment history for HIV, history of maternal infection and treatment, and comorbidities (such as cancers, renal, cardiovascular, dermatologic, metabolic and neurological disorders). Opportunistic infections included any history of infections that exploit an unnatural opportunity to induce diseases such as a compromised immune system including pneumonia, candidiasis, Tuberculosis (TB), cytomegalovirus (CMV), and herpes simplex virus (HSV) [20].

Adherence to treatment was defined, based on previous studies, as the patient consistently attended scheduled visits and followed the prescribed medication regimen over the past year [12]. History of treatment failures was defined as a viral load of > 200 copies/ml after 6 months of treatment [4]. Moreover, we assessed for any side effects of HIV treatment (such as allergic reactions — nausea/vomiting, loss of appetite, fatigue, lipodystrophy, mood changes, and dermatological disorders).

Laboratory test results included the initial and final CD4 count, HBS Ag — anti-HBS Ab (ELIZA), HCV Ab (DiaSorin, Spain), CMV Ab (IgM, IgG), PPD test, toxoplasma Ab (standard ELIZA), blood sugar, creatinine and hemoglobin levels, and lipid profile.

In addition, as the patients' follow-up took place during the COVID-19 pandemic, we investigated any history of COVID-19 infection in the study population.

Ethical considerations. The study received ethical approval from the Ethic Committee of Tehran University of Medical Science (The ethic code. IR.TUMS.IKHC.REC.1398.037). To protect participant confidentiality, personal identifying information was not collected and each participant was assigned a unique identification number. This study was observational and did not interfere with patients' routine treatments.

Statistical analysis. The data analysis was performed using the Statistical Package for Social Sciences (IBM SPSS) version 26.0. Quantitative variables were described using measures of central tendency such as mean, and standard deviation, while qualitative variables were summarized using absolute frequency and percentage. The results were presented in tables.

Results

There were 23 female patients (38.3%) and 37 male patients (61.6%) with a mean age of 10.03 years and a standard deviation of 4.60. The youngest patient was one-year-old and the oldest was 18 years. Fifty-one patients were under family care (85%), six patients were receiving healthcare assistance (10%), and three patients were under guardianship (5%). Ten patients had at least one comorbidity (16.7%). Specifically, amongst those diagnosed with comorbidities, there were two cases of epilepsy (3.3%), two cases of attention deficit hyperactivity disorder (ADHD) (3.3%), one case each of autoimmune hepatitis (1.7%), ITP (1.7%), allergic asthma (1.7%), alopecia areata (1.7%), and cystic fibrosis (1.7%).

Fifty-six children were born from HIV-positive mothers (93.9%). Among the remaining four children who were born from healthy mothers, two didn't have any identified risk factors, one had received a blood transfusion after inguinal surgery and the last one had been a victim of rape.

Out of 60 mothers of these children, four (6.7%) mothers are not infected with the virus, 36 mothers (60%) were receiving treatment, six (10%) mothers had passed away while there is no information regarding the status of other seven mothers (11.7%).

Fifty-six patients (93.3%) had an acceptable adherence to treatment and had regular visits to the clinic as required. Out of four patients who were not committed to treatment, three guardians were

identified as addicts and the fourth child had lost his mother and was under the supervision of the welfare system and had regular visits but ever since he has been under the guardianship of a family he had not visited for check-ups. Patients' characteristics were listed in Table 1.

Twenty-two patients (28.37%) had experienced at least one episode of opportunistic infectious disease during their illness, including oral candidiasis (20%), herpetic lesions (5%), and varicella zoster (3.33%). In addition to these, there was one occurrence of each of the following diseases: Candida vaginitis, molluscum contagiosum, vaginitis, urinary infection with Enterobacter, and warts on the lower limbs. Recurrent otitis was observed in 3.33% of patients. Twenty-one patients were hospitalized at least once with the following presentations and symptoms: Seven patients (11.6%) had fever, weakness, lethargy, and Oral thrush, seven patients were (11.6%) hospitalized due to pneumonia, two patients (3.33%) had seizures and at least one patient experienced one of the following conditions: asthma attack (1.66%), diarrhea (1.66%), herpes zoster (1.66%), syncope (suspected seizure) (1.66%), TB (1.66%), to receive cell pack (1.66%), ear surgery (1.66%), lethargy (1.66%), petechiae and epistaxis (1.66%), shingles (1.66%), encephalopathy (1.66%), Stevens–Johnson syndrome (1.66%) and inguinal hernia surgery (1.66%).

Table 1. Demographic characteristics and clinical profile of children living with HIV, 2004–2020

Characteristics	Subcharacteristics	N (%)
Age, year, mean±SD		10.03 (4.60)
Age at diagnosis, year, mean±SD		3.81 (3.53)
Sex	Male	37 (61.6%)
	Female	23 (38.3%)
Child's care	Family care	51 (85%)
	Welfare care	6 (10%)
	Guardianship	3 (5%)
HIV-positive mother		56 (93.3%)
History of hospitalization		21 (35.0%)
Positive PPD		2 (7.7%)
Positive Toxo IgG		7 (17.5%)
Positive HBs Ab		17 (41.5%)
Positive HBs Ag		0 (0%)
Positive HCV Ab		0 (0%)
Positive CMV IgG		34 (81%)
Positive CMV IgM		4 (11.1%)
Mothers HIV-treatment	Not available	7 (11.7%)
	No treatment	7 (11.7%)
	Under treatment	36 (60%)
	Passed away	6 (10%)
Treatment adherence	Acceptable	56 (93.3%)
	Not enough adherence	4 (6.7%)
CD4 count before treatment, mean±SD		855.51 (1153.46)
Latest CD4, mean±SD		1074.39 (619.38)
Length of ART, month, mean±SD		69.96 (40.29)
FBS, mean±SD		88.45 (12.46112)
Cr, mean±SD		0.5612 (0.11954)
Hg, mean±SD		11.25 (1.57895)
TG, mean±SD		118.575 (64.4304)
Cholesterol, mean±SD		132.9487 (34.51007)
LDL, mean±SD		74.75 (33.94588)
HDL, mean±SD		36.9375 (15.62863)

Patients records were screened for possible coinfections and the results are as follows: Out of 18 patients with PPD records, only two patients exhibited positive PPD with dimensions of 16mm and 6mm while others tested negative. The result of the other virus's immunoglobulin screening is documented in Table 1. Also, the initial and final treatment regime of patients is listed in Table 2 and 3. A summary of ART side effects, and regime change causes is available in Tables 4, 5 respectively.

None of the included patients reported prior infection with COVID-19. Two children passed away between 2004–2020. One was under foster care, and the guardians were unaware of the child's medical condition, which resulted in a lack of treatment. The second case was a known case of TB and Cystic Fibrosis, who was hospitalized due to pneumonia and passed away subsequently.

Discussion

This study aimed to investigate the demographic characteristics, clinical profile and outcomes of HIV-infected children who received treatment at the counseling center for behavioral diseases in Imam Khomeini Hospital between 2004 to 2020. The prevalence of opportunistic infections was found to be (28.3%). While all HIV-infected individuals are susceptible to a wide variety of opportunistic infections [30], the prevalence and incidence of HIV-associated opportunistic infections can vary considerably [17, 19]. Most publications on the frequency of opportunistic infections among HIV-infected children come from North America and Europe, leaving the burden of opportunistic infections among HIV-infected children in low- and middle-income countries inadequately reported [22]. In these regions, TB, oral candidiasis, varicella zoster, pneumocystis pneumonia, bacterial pneumonia, herpes zoster, and dermatophyte infections are the most prevalent opportunistic infections [3, 15]. The present study identified oral candidiasis (20%) as the most common

opportunistic infection, followed by herpes (5%), and varicella zoster (3.33%).

Opportunistic infections are the primary causes of morbidity and mortality in HIV-positive children, accounting for 94.1% of HIV-related deaths [20]. In this study, the hospitalization rate for HIV-infected children was 35%, with the most common reason being delayed diagnosis of infected children and failure to identify infected mothers in a timely manner, leading to candidiasis, weakness, lethargy, and fever during their initial visit to the medical center (11.6%). Another significant cause of hospitalization was pneumonia, accounting for 11.6% of all hospitalizations in the study population. Similar results were observed in a study conducted in Thailand, where 35% of children were hospitalized [10]. Moreover, two cases of pediatric HIV resulted in mortality (3.33%). The first patient wasn't receiving therapy, however, there is no available record of the cause of the patient's death. The second patient was a known case of TB, who died due to pneumonia while hospitalized.

Despite the advances in ART for HIV patients, we are yet to reach the point of no mortality in this disease. A recent systematic review of pediatric HIV mortality showed 7.9% all-cause cumulative death among patients [2]. In our study, 3.33% of patients passed away, including one due to lack of treatment and the other due to pneumonia.

HIV-infected children usually get infected vertically through mother-to-child transmission during pregnancy, delivery, or breastfeeding. Brahmbhatt et al. [8] showed that more than 20% of children born from infected mothers are infected with HIV at birth and during breastfeeding. In our study, more than 90% of pediatric HIV cases were born from infected mothers.

Although pediatric HIV treatment has made a lot of advances since the beginning of the pandemic, the general lack of well-tolerated age-appropriate formulations remained a major challenge. There are limited approved ART options for pediatric HIV infection, and their possible effects on neurocognitive development are still under investigation [23]. In our study, the initial and final treatment regimens prescribed for the patients were collected. Our results demonstrated that 76.7% of patients received at least zidovudine and lamivudine as their initial therapy and 48.4% as their final treatment. Recent pediatric guidelines suggest using two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus dolutegravir (DTG). Further studies could be done to assess the reasons behind zidovudine and lamivudine being the first choice of physicians on the NRTIs list and the less frequent use of DTG in the treatment regimen for children. Our results show an increase in mean CD4 count from 855.5±113.46274 to 1074.393. As more than 90% of patients had acceptable adherence to treatment, we can suggest that ART treatment had an impact on CD4 cell count.

Table 2. Current ART regimens among children living with HIV, 2004–2020

ART Regimens	N (%)
LPV/r, ZDV, 3TC	7 (11.7)
ZDV, 3TC, NVP	13 (21.7)
ZDV, 3TC, EFV	16 (26.7)
ZDV, 3TC, DTG	3 (5)
ZDV, 3TC, ATV/r	1 (1.7)
LPV/r, TDF, FTC	2 (3.3)
TDF, FTC, EFV	2 (3.3)
EFV, 3TC, ABC	2 (3.3)
3TC, LPV/r, TDF	1(1.7)
DTG, TDF, FTC, LPV/r	1 (1.7)
3TC, LPV/r, ABC	3 (5)
3TC , TDF, DRV/r	1 (1.7)
3TC, ABC, DRV/r	1 (1.7)
TDF, FTC , DTG	4 (6.7)
3TC, ABC, DTG	2 (3.3)
TDF, FTC, ATV/r	1 (1.7)

Note. LPV/r: Lopinavir/Ritonavir, ZDV: Zidovudine, 3TC: lamivudine, NVP: Nevirapine, EFV: Efavirenz, DTG: Dolutegravir, ATV/r: Atazanavir/ritonavir, ABC: Abacavir, TDF: Tenofovir disoproxil fumarate, FTC: Emtricitabine, DRV/r: Darunavir/ritonavir.

Table 3. Initial ART regimes in children living with HIV, 2004–2020

ART Regimens	N (%)
ZDV, 3TC, NVP	24 (40.0)
ZDV, 3TC, EFV	22 (36.7)
ZDV, 3TC, LPV/r	4 (6.7)
3TC, NVP, ABC	1 (1.7)
TDF, FTC, EFV	3 (5.0)
3TC, LPV/r, TDF	1 (1.7)
3TC, EFV, ABC	3 (5.0)
3TC, ABC, LPV/r	2 (3.3)

Table 4. ART-related side effects in children living with HIV, 2004–2020

Drug side effects	Type	N (%)
No identified side effect		39 (65)
Side effects	Vomiting	7 (33.3)
	Diarrhea	3 (14)
	Decrease in hemoglobin levels	2 (9.5)
	Skin lesions	2 (9.5)
	Steven Johnson syndrome	1 (4.7)
	Insomnia and restlessness	2 (9.5)
	Aggressiveness	2 (9.5)
	Dizziness	1 (4.7)
	Urinary frequency	1 (4.7)
	Loss of appetite	1 (4.7)
	Sore throat	1 (4.7)

Table 5. Reasons for change of medication regiment in children living with HIV, 2004–2020

Reason	N (%)
No change	37 (61.7%)
Drug resistance	6 (10.0%)
Drug adverse reaction	9 (15%)
Both	5 (8.3%)
Other reasons	2 (3.3%)
Unknown	1 (1.7%)

Failure of treatment is an important topic to address both in adolescents and children infected with HIV, as the risk of mortality significantly increases in this condition. A recent meta-analysis by Endalamaw and his colleagues [13] revealed that about 14.6% of children experience this phenomenon. Moreover, another study from a pilot cohort in South Africa [7] shows that delayed start of ART treatment is a risk factor for treatment failure, and many of these patients experience higher viremia periods, failing to reach viral load suppression levels during their treatment.

The long-time therapy and treatment adherence challenges in HIV disease as a chronic condition are serious issues that should be addressed. This problem can eventually lead to drug resistance and severe life-threatening side effects [14]. Shubber and her colleagues [26] specifically investigated how patients describe their barriers to adherence to ART and reported forgetting and being away from home as the most common reasons. A systematic review on HIV treatment adherence in middle and low-income countries reported more than 75% adherence in most of included studies [29]. In our study, the adherence rate to treatment was 93.3%, which is higher than in previous reports.

In this study, the researchers investigated drug-related side effects. Among the participants, 65% did not experience any identified drug-related side effects. However, vomiting and diarrhea were found to be the most prevalent among those who did. Additionally, the study identified two life-threatening side effects: Stevens–Johnson syndrome and a decrease in hemoglobin.

Although ART is crucial and lifesaving for pediatric patients with HIV, it can also result in various complications such as metabolic syndrome, dyslipidemia, and renal disease. Vargas–Pacherrez's study highlighted that approximately half of the HIV-infected patients in Bahia experienced metabolic syndrome [28]. In our study, although there were cases with higher-than-normal levels of lipid profile and blood sugar, the overall mean of cases in each of these markers did not exceed the maximum value within their respective ranges.

Determining the coexistence of TB and HIV is crucial in pediatric HIV as studies have shown that about 17% of pediatric TB mortality occurs in HIV-positive children. The complexity of the situation is further compounded by the matter of drug interaction in these patients and that these children may derive less benefit from Bacillus Calmette–Guerin (BCG) vaccine [16]. In our study, only two cases of co-accordance of HIV and TB were identified. However, this prevalence might be underestimated as we encountered some missing data in this aspect. Lack of available data regarding the coexistence of HIV with other viral diseases including hepatitis B virus (HBV), hepatitis C virus (HCV), and CMV was less common. None of the patients were exposed to HCV. Although more than 40% of patients had prior exposure to HBV, none of them were infected with it at the time of data collection. More than 80% of patients were previously infected with CMV but only 10% were actively infected. These results are consistent with the results obtained in a study of Varo et al. who found CMV IgG was the most common positive result in all age groups (in 73% of children < 1 year, and 100% in all other groups). Three patients were CMV IgM positive (3.3%), suggesting acute infection. In a similar study from Malawi, HSV-2 IgG was positive in four patients (4.4%), and HBs Ag in two (2.2%) among 91 HIV-Infected Malawian Children [9].

The results of the present study should be interpreted considering several limitations, such as a small sample size, incomplete patient records, and the lack of follow-up records in some cases. To address these limitations, large-scale investigations with designs ensuring the obtaining of complete patient records and follow-up data are needed.

Conclusion

Our study contributes significant insights into the demographic and para-clinical characteristics of HIV-infected children in Iran, shedding light on their long-term outcomes and potential complications. The findings from our research provide valuable information that can inform policymakers and healthcare professionals in their efforts to address the ongoing HIV epidemic within the country. This may involve implementing comprehensive prevention programs, expanding access to HIV testing and treatment services, and providing specialized care for HIV-infected children. Furthermore, our study highlights the critical need for further research in the field of pediatric HIV in Iran. Despite the progress made in recent years, there remains a severe lack of knowledge regarding the specific needs and experiences of this vulnerable population. Future studies should aim to fill these knowledge gaps, focusing on areas such as optimal treatment approaches, long-term monitoring, and the impact of socioeconomic factors on HIV outcomes in children.

Conflict of Interest

The authors confirm that they have no conflict of interest.

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