A cross-sectional study on adherence to antiretroviral therapy among HIV-infected pediatric patients attending medical college and hospital, Kolkata

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ABSTRACT

Background: HIV infection is a serious lifelong health risk, leading to increased illness and death. In children, adhering to antiretroviral therapy (ART) is crucial to reduce these harmful effects. Yet, due to the challenges of pediatric patients and the social issues related to HIV, sticking to ART can be difficult in this group. **Aims and Objectives:** The study was conducted to evaluate the adherence of pediatric patients to their daily ART dosages. We also tried to understand the causes that led to the failure to follow the scheduled dosages and evaluate how these factors affected our study population. **Materials and Methods:** We examined the adherence to ART in 49 patients, aged 2–15, who had been on ART for at least 12 months. They visited the ART center at Medical College and Hospital, Kolkata, between August 01 and September 30, 2022. Ethical clearance was granted by the Institution's Ethics Committee. The participants were chosen through systematic random sampling. We collected data through interviews and chart reviews and analyzed it using SPSS version 19. **Results:** Out of the 49 participants, 34 (69.38%) adhered to ART in the preceding month. For the non-adherent patients (n = 15), the main reasons included conflicting ART dosage timing with school hours and children falling asleep at dosing time. Most (53.1%) were in the 5–10 age groups, with 93.88% in WHO Stage 1 of the disease and 6.12% in Stage II. In 77.6% of cases, mothers were the primary caregivers, and 79.6% of caregivers were HIV positive. Many children (71.43%) were unaware of their disease. Out of the 31 children whose disease status was known to others, grandparents of 23 and siblings of 12 were aware. Six of these children faced stigma from relatives and neighbors. ART adherence was significantly associated (P < 0.05) with the caregiver's occupation (P = 0.006), the child's age when starting ART (P = 0.001), parents' AIDS-related deaths (P = 0.003), and travel time to the ART center from home (P < 0.02). **Conclusion:** Although most children adhered to their ART regimen, there is room for improvement. Caregivers, especially for younger children, play a crucial role. Empathetic education for caregivers and children, tailored to their age, along with regular adherence checks, can enhance medication adherence significantly.

Key words: Anti-retroviral therapy; HIV; Pediatric patients

INTRODUCTION

HIV weakens the body's immune system, making it easier to get infections and cancers.[1] You can get HIV through sexual contact, sharing needles, or from a mother to her child during pregnancy, childbirth, or breastfeeding.[2] In the United States, most children under 13 get HIV from their mothers, but adolescents usually get it through sex.[3] According to the 2023 World Health Organization report, 40.4 million people have died from HIV as of July 13, 2023,

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and 39.0 million still live with HIV from the end of 2022. In 2022, 1.3 million people got HIV, and 630,000 died from HIV-related causes.[1]

In India, the 2021 HIV factsheet says that 0.21% of adults (15–49 years) have HIV, with 24 lakh people living with HIV. In 2022, there were about 62.97 thousand new infections and 41.97 thousand AIDS-related deaths.[4] The UNAIDS HIV factsheet for 2022 reports that 1.5 million children (0–14 years) had HIV. The number of children with HIV has decreased from 310,000 in 2010 to 130,000 in 2022.[5]

HIV treatment, or antiretroviral therapy (ART), is recommended for everyone with HIV, including children and adolescents. However, it can be hard for them to take their medicine as directed. Good adherence to ART, at least 95%, keeps the virus under control. Not following the treatment properly can lead to treatment failure, more sickness, and drug-resistant HIV.[6] Some reasons for not taking the medicine include feeling bad about having HIV (stigma), a busy schedule, side effects from the medicine, family issues, addictions, and the child's age and how they are growing.[3]

We use CD4 cell count and HIV viral load to check if the treatment is working. CD4 count tells us how strong a person's immune system is. A good response to ART means the CD4 count goes up by 50–150 cells/mm^3 in the 1st year, with smaller increases after that. Ideal viral suppression means the HIV level is too low to detect (usually <20 copies/mL).[7]

It is important to stick to ART for effective treatment. Long-term HIV infection can be very harmful. This study looks at how well pediatric patients with HIV follow their treatment, their background, what affects their treatment, and what infections they get.

Aims and objectives
1. To determine the adherence of paediatric patients to their daily ART dosage.
2. To study, the causes that prevents the adherence to the scheduled dosage.

MATERIALS AND METHODS

We used questionnaires and face-to-face interviews with caregivers of HIV-infected children aged 2–15 in Kolkata, India, who attended the Medical College and Hospital's ART center from August 01 to September 30, 2022. We recruited patients every Tuesday and Thursday. All children had received ART for at least 12 months, following national guidelines.

We selected study participants systematically, choosing every fourth patient after randomly selecting the first based on a currency note's last digit. We excluded newly diagnosed patients, critically ill patients, those with other chronic illnesses, and those whose caregivers didn't provide informed consent. Children in NGOs were also excluded. In total, 49 children were included in the study.

Before starting the study, we conducted a thorough literature review and obtained Institutional Ethical Committee clearance on April 27, 2022. We finalized study questionnaires and informed consent forms in multiple languages. Caregivers signed the forms after we explained the study's purpose and their right to withdraw consent without affecting treatment.

We collected data through interviews, chart reviews, and measured adherence. Medical personnel not involved in patient care conducted interviews to ensure unbiased reporting. Confidentiality was a top priority, and caregivers were assured of maintaining the children's disclosure status.

We assessed adherence by recalling missed doses and late doses by more than 2 h and their reasons. Non-adherence meant missing ART doses or being late (>2 h) for more than two doses.

Disease staging followed WHO Clinical Staging of HIV in adults, adolescents, and children.[8] For quality control, we pilot-tested the data collection pro forma on five patients, which was 10% of the expected sample size.

Data were entered into MS Excel and analyzed using SPSS version 19 software, and results were presented in tables. We conducted appropriate statistical tests, with P<0.05 considered statistically significant.

RESULTS

Adherence to ART
Out of 49 study participants, 34 (69.38%) participants were found to be adherent to ART in the preceding month, while 15 (30.61%) were non-adherent. For the non-adherent patients (n=15), the main causes included ART dosage timing conflicting with school hours, and the child fell asleep at the timing of ART dosage (Table 1).

Sociodemographic parameters of patients
The majority (53.1%) of the patients were in the age group 5–10 years, followed by those between 10 and 15 years (34.7%) with 55.1% of the study participants being males. Majority were from rural areas (59.2%). About 46.9% of study participants attended primary school, while 24.5%

attended middle school. Amongst the study population who were orphans, the majority were paternal orphans (77.78%) (Maternal orphan: Children whose mother had expired, paternal orphan: Children whose father had expired, and both categories were mutually exclusive).

The majority of the children were from nuclear families (57.1%). According to the Modified B. G. Prasad scale January 2021 (9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8797132/),[9] the majority of the study population was from the middle class (Class III) (51.0%) (Table 2).

Caregiver characteristics
For the majority of the children, the mother was the primary caregiver (77.6%), with the majority of the caregivers' being in the age group >30–40 years (55.1%). Naturally, the majority of the caregivers' were females (81.6%). Most caregivers' had received secondary education (44.9%), followed by primary education (24.5%). Most caregivers' were homemakers (46.9%), followed by skilled workers (28.5%). About 79.6% of the caregivers were HIV-positive (Table 3).

Disease history
The majority of the study population were in WHO Stage 1 of the disease (93.88%) and 6.12% in Stage II (We did not find children in WHO Stage 3 or Stage 4 in the ART center for the duration of the study). About 71.43% of the children were diagnosed between 2010 and 2014, with an equal number of children being diagnosed in the age group (<18 months) including five prenatal diagnosis (42.86%); and the age group 18 months – 5 years (42.86%). The mean age at diagnosis was 33 months.

About 55.1% of the children started ART from 2015 to 2021, with the mean duration on ART being 56 months (None of the children started ART between the years 2005 and 2009). At the time of ART initiation, 30.61% of children were in the age groups, <18 months and 18 months – 5 years each.

Most (22.45%) of the study participants had the ART regimen combining Lamivudine + Zidovudine + Efavirenz followed by Lamivudine + Zidovudine + Nevirapine (20.41%) (Both are first line therapy). Non-adherence to therapy was observed with the following drug regimens: Lamivudine + Zidovudine + Efavirenz (5/14), Lamivudine + Zidovudine + Nevirapine (3/14), Lamivudine + Abacavir + Lopinavir + Ritonavir (2/14), Lamivudine + Zidovudine + Lopinavir + Ritonavir (3/14), and Lamivudine + Abacavir + Efavirenz (2/14) (Table 4).

Other possible determinants of ART adherence
The majority (71.43%) of the children were not aware of their disease. Among those who were aware (14/49),

10 patients belonged to the age group >10–15 years and four belonged to the age group >5–10 years.

Majority (67.35%) of the children did not have any illness in the preceding 4 weeks. Of the 16 children who fell ill, the majority (56.25%) suffered from acute respiratory infections (ARI).

About 79.6% of the study population visited the ART center at monthly intervals, for check-ups and medication refills. The time taken to reach the ART center from home ranged from <1 h to >2 h with an equal number (32.65%) of the participants taking <1 h and >2 h each.

For the majority of the study population, the mother was ICTC positive (89.80%); and for 55.1%, the father was positive. For 27 patients (55.1%), both the parents were ICTC positive. five children had lost their father, while two had lost their mother to AIDS (Table 5).

Out of 31 children for whom people other than the parents are aware of the disease status, grandparents of 23 children and siblings of 12 children knew about the HIV status of the child. Interestingly, out of these 31 children, 80.65% did not face any stigma associated with the disease. The rest of the six children faced stigma from relatives and neighbors (Table 6).

Clinical and laboratory measures of ART adherence
The majority of the study population had the last CD4 count >500/μL (89.80%), and the mean was 679/μL. There was no association between the WHO clinical stage and CD4 count. Amongst the study population who took medication recommended by the ART Centre other than ART (n=11), the majority (81.82%) took tuberculosis prophylactic dose (Isoniazid + Pyridoxine) and 18.18% took Cotrimoxazole (Table 7).

Significant associations of study parameters with adherence to ART
The adherence to ART therapy was found to be significantly associated ($P<0.05$) with the occupation of the caregiver ($P=0.006$) with the number of non-adherent patients being 7/23 and 6/11 when the caregiver was a homemaker and unskilled worker respectively. Significant associations were also found between adherence to therapy and the age of the child at the time of ART initiation ($P=0.001$), death of parents due to AIDS ($P=0.003$), and time taken to reach the ART center from home ($P<0.02$) (Table 8).

Other notable findings
1. All patients had come for medication refills before they ran out of ART
2. HIV transmission was perinatal for all 49 children
3. None of the patients were seropositive for Hepatitis

B and C, or Syphilis
4. None of the patients or caregivers had complaints about the ART center regarding:
   - Instructions about medicine dose and timings
   - Any negative/judgmental attitude of the clinic staff about the medicines
   - Medicines not being available in the pharmacy.

DISCUSSION

Compliance with ART is an important predictor of HIV progression and a major determinant of HIV drug resistance. This gains more importance in the pediatric population since they do not understand the nature of the disease and are dependent on their caregivers.

While the majority (69.38%) of the children in this study were adherent to ART in the preceding month, the major causes for non-adherence (n=15) included ART dosage timings conflicting with school hours or sleeping hours of the child. Several studies reported comparable rates of adherence.[10-12] In the US, Van Dyke et al.,[13] and Martin et al.,[14] reported adherence to ART ranging from 70% to 81%. The major reasons cited by the caregivers were forgetfulness, medication side effects, medications not refilled, other preoccupations, feeling depressed or stigmatized, and substance abuse.[10,11,15-17] We need to probe deeper into the causes of non-adherence and attempt to solve the same, along with conducting motivational counseling to increase medication adherence.

Similar sociodemographic parameters for pediatric HIV populations in India as in this study were reported by Meena et al., and Chauhan et al.,[18,19] However, Guha and Sardar reported in a study in Kolkata, India with 437 children, 81.7% were ≤5 years, and 29.5% were <1 year. The age group 5–10 years had the lowest rate of HIV infection at 6.4%.[20] This difference may be explained when we compare the sample size of the study populations.

The mother or biological parents were the primary caregivers in studies by Chauhan et al.,[21] and Zegeye and Sendo[10] comparable to this study. About 79.6% of the caregivers were HIV positive, accounting for the 100% vertical transmission reported here, similar to Meena et al.,[18] and Chauhan et al.,[19] In this study, out of the nine children who lost their parents, seven deaths were AIDS-related, with the majority (71.43%) being paternal death, similar to results by Chauhan et al.,[19] Barennes et al., reported from a study in Cambodia that 55.2% and 24.6% of HIV positive children had lost at least one and both parents, respectively.[22]

Table 1: Distribution of study participants according to causes of non-adherence to ART regimen (n=15)

Cause of non-adherence to ART	Frequency	Percentage
ART dosage timing conflicting with school hours	4	26.67
Child fell asleep at the time of drug dose	4	26.67
Caregiver preoccupied with other work	3	20.0
Due to illness of the child	2	13.33
Due to family function	2	13.33

ART: Antiretroviral therapy

Table 2: Distribution of study participants according to sociodemographic characteristics

Characteristics	Category	Frequency	Percentage
Age group (in years) (n=49)	2–5	6	12.2
	5–10	26	53.1
	10–15	17	34.7
Gender (n=49)	Male	27	55.1
	Female	22	44.9
Permanent Residence (n=49)	Rural	29	59.2
	Urban	20	40.8
Patient's educational status (n=49)	Preschool children	8	16.3
	Primary School (Class 1–4)	23	46.9
	Middle school (Class 5–8)	12	24.5
	High school (Class 9–12)	3	6.1
	No formal education	3	6.1
Orphan status (n=9)	Maternal Orphan*	2	22.22
	Paternal Orphan*	7	77.78
Type of family (n=49)	Nuclear	28	57.1
	Joint	21	42.9
Per capita monthly family income in INR (n=49)	Class I (upper class)	2	4.1
	Class II (upper middle class)	1	2.0
	Class III (middle class)	25	51.0
	Class IV (lower middle class)	17	34.7
	Class V (lower class)	4	8.2

*Maternal orphan: Children whose mother have expired, Paternal orphan: Children whose father have expired (Both the categories are mutually exclusive)

Only 14 children knew their HIV status, with 10 out of 14 children being >10–15 years old. However, the majority (53.9%) of children >6 years were aware of their disease in studies by Barennes et al.,[22] and Kalembo et al., (64%).[23] Nath reported that in India, the proportion of children without knowledge of HIV status ranged from 59.6% to

Table 3: Distribution of study participants according to caregiver characteristics

Characteristics	Category	Frequency	Percentage
Relation to the patient (n=49)	Mother	38	77.6
	Father	7	14.3
	Grandparents	2	4.1
	Uncle/Aunt	2	4.1
Age (in years) (n=49)	15–20	2	4.1
	>20–30	6	12.2
	>30–40	27	55.1
	>40–50	7	14.3
	>50–60	5	10.2
	>60	2	4.1
Gender (n=49)	Male	9	18.4
	Female	40	81.6
Educational status (n=49)	No formal education	6	12.24
	Primary education	12	24.5
	Secondary education	22	44.9
	Higher secondary education	4	8.2
	Graduation and above	5	10.2
Occupation (n=49)	Homemaker	23	46.9
	Skilled	14	28.5
	Unskilled	11	22.5
	Others	1	2.1
HIV disease status (n=49)	Positive	39	79.6
	Negative	10	20.4

Table 4: Distribution of study participants according to HIV disease history

Characteristics	Category	Frequency	Percentage
WHO clinical stage (n=49)	Stage 1	46	93.88
	Stage 2	3	6.12
	Stage 3	0	0
	Stage 4	0	0
Year of diagnosis (n=49)	2005–2009	6	12.24
	2010–2014	35	71.43
	2014–2021*	8	16.33
Age of child at the time of diagnosis (n=49)	<18 months	21	42.86
	18 months–5 years	21	42.86
	>5–10 years	7	14.28
	10–15 years	0	0
Year of ART initiation (n=49)	2010–2014	22	44.9
	2014–2021*	27	55.1
Age of child at the time of ART initiation (n=49)	<18 months	15	30.61
	18 months–5 years	15	30.61
	>5–10 years	13	26.53
	>10 years	6	12.25
ART combination regimen (n=49)†	Lamivudine +Zidovudine +Efavirenz	11	22.45
	Lamivudine +Zidovudine +Nevirapine	10	20.41
	Lamivudine +Abacavir +Efavirenz	6	12.24
	Lamivudine +Abacavir +Nevirapine	2	4.08
	Lamivudine +Zidovudine +Lopinavir +Ritonavir	8	15.33
	Lamivudine +Abacavir +Lopinavir +Ritonavir	7	14.29
	Tenofovir +Efavirenz	3	5.12
	Lamivudine +Lopinavir +Ritonavir	2	4.08

*Upto 2021 August. †The first four regimens are first line and the rest have at least one second line ART drug mentioned under the NACO guidelines. ART: Antiretroviral therapy

86% in different study settings.[24] Meena et al., reported that only 33.33% of children knew of their HIV status. The majority in the disclosed group were >10 years old (95.83%) and had been taking ART for a longer duration (5.88 ± 3.06 years).[18]

In most studies, the causes for non-disclosure were: Fear of stigma, discrimination, and concerns about the child's inability to cope with the news.[18-22] However, research studies demonstrate that the disclosure of HIV status to infected children influences their compliance with ART and initiative to take responsibility for their health.

In this study, ART was initiated before 5 years mostly (61%). Poudet et al.,[25] reported that in 46.2% of cases, ART was started at a median age of 67 months.[23] These differences may be because of inaccessibility to healthcare facilities, late presentation, and delay in diagnosis in resource-limited settings.

Similar to the present study where we report that ARI was the most prevalent infection, Mwiru et al.,[26] reported that pediatric HIV infection was associated with a 62% increased risk of ARI.[24] Shahapur et al.,[27] reported that opportunistic infections are common, including oral candidiasis (29%), ARI, tubercular lymphadenitis, and

chronic diarrhea.[24] Antwal et al.,[28] reported that fever, breathlessness, cough with expectoration, weight loss, loss of appetite, and generalized weakness were significantly associated (P<0.001) with HIV positivity.[28] Thus, these studies support the finding of the high prevalence of infections in HIV-positive children in the present study.

About 32.43% used reminders like alarms to take medications at the correct times, similar to studies by Mehta et al.,[15] and Zegeye and Sendo[10] 79.6% had medication refills at monthly intervals. The interval of visits for medication refills is important as reported by Mutasa-Apollo et al., from

Table 5: Distribution of study participants according to possible determinants of ART adherence

Characteristics	Category	Frequency	Percentage
Child disclosure status (n=49)	Child has an understanding about the disease	13	28.57
	Child is not aware about the disease	35	71.43
Illness of child in the preceding 4 weeks (n=49)	Yes	16	32.65
	No	33	67.35
Specific illnesses in the preceding 4 weeks (n=16)	Acute Respiratory Infection (Fever with cough and cold)	9	56.25
	Acute gastroenteritis (Fever and diarrhea)	2	12.5
	Others (nausea, vomiting, loss of appetite, and fatigue)	5	31.25
Medication reminder/timing (n=37)	Use of alarms	12	32.43
	ART taken just after meals	20	54.05
	HIV-positive family members take medications together	5	10.2
Frequency of visiting ART center (n=49)	Monthly	39	79.6
	Every 2 months	10	20.4
Time taken to reach ART center from home (n=49)	<1 hour	16	32.65
	1–2 hours	17	34.7
	>2 hours	16	32.65
HIV-positive family members (n=49)	Mother	44	89.80
	Father	27	55.10
	Sibling	2	4.08
Death of parents due to AIDS (n=7)	Mother	2	28.57
	Father	5	71.43

ART: Antiretroviral therapy

Table 6: Distribution of study participants according to possible determinants of ART

Characteristics	Category	Frequency	Percentage
People who are aware of the HIV status of the child, other than parents (n=31)	Siblings	12	38.70
	Grandparents	23	74.19
	Uncles/aunts	19	61.29
	School teachers	4	12.9
	Neighbors	4	12.9
Stigma faced by the child when people other than parents knew about the disease status (n=31)	Yes	6	19.35
	No	25	80.65
Settings of stigma faced by the child (n=6)	From relatives	6	100.0
	Neighbors	2	33.33

ART: Antiretroviral therapy

Table 7: Distribution of study population according to markers for ART adherence

Characteristics	Category	Frequency	Percentage
CD4 count (per µL) (n=49)	<500	5	10.20
	>500	44	89.80
Medications taken for opportunistic infection prophylaxis (n=11)	Tuberculosis prophylactic dose (Isoniazid + Pyridoxine)	9	81.82
	Cotrimoxazole	2	18.18

ART: Antiretroviral therapy

Table 8: Distribution of study parameters significantly associated with adherence to ART

Variables	Categories	Adherent	Non-adherent	P-value
Occupation of the caregiver (n=49)	Homemaker	16	7	0.006
	Skilled	12	2	
	Unskilled	5	6	
	Others	1	0	
Age of child at the time of ART initiation (n=49)	<18 months	13	2	0.001
	18 months –5 years	6	9	
	>5–10 years	13	0	
	>10 years	2	4	
Time taken to reach ART center from home (n=49)	<1 h	12	4	0.02
	1–2 h	15	2	
	>2 h	7	9	
Death of parents due to AIDS (n=7)	Mother	0	2	0.003
	Father	1	4	
	None	9	7	

ART: Antiretroviral therapy

a comparative analysis of eight studies that less frequent clinic visits led to higher odds of being retained in care.[28]

Of the 31 children for whom people other than parents were aware of the diagnosis, only 19.35% faced stigma. These data are in contrast to Barennes et al., who reported that 43.2% of patients experienced stigma, including rejection by others (26.8%), no invitations to social activities (18.6%), and exclusion from games (14.2%). About 3.8% could not go to school due to perceived stigma.[22] The lack of knowledge among the masses about the transmission of HIV and the associated taboo leads to the stigmatization of the disease.

Significant associations with adherence to therapy were reported about the occupation of the caregiver, age of the child at the time of ART initiation (P=0.001), and death of parents due to AIDS (P=0.003). Other studies cite several

factors associated with adherence including increasing age of the child,[10,12] female gender,[12] relationship with the child,[10] Occupational status,[10] disclosure of the child's HIV status to the child,[10,17] and caregiver knowledge of ART[10,17] and occurrence of recent stressful life events.[12]

Further, Williams et al., reported that having an adult other than the biological parent as the primary caregiver, using a buddy system to remember to take ART and higher caregiver education level were associated with improved adherence.[12]

Limitations of the study

1. This is a mono-centric study hence we have been able to study patients from only a particular region.
2. This study was conducted for 2 months. A study of a longer duration would have enabled to check adherence throughout the year.
3. Given that this study was conducted in a tertiary care centre, the people coming from remote areas are fewer where ART availability is limited too.

CONCLUSION

In India, HIV is associated with the lifelong burden of immense social stigma and discrimination. This study explores medication adherence in the especially vulnerable pediatric population. Medication adherence is dependent to a large extent on the caregiver, especially for smaller children. While the majority of the participants in this study were adherent to medications, there is still an area for improvement. Any incidences of non-adherence should be identified and addressed at once, as the effects will be lifelong. In children, the psychiatric and social issues change with their physical and mental development. Thus, it is extremely important to be cognizant of their concerns offer age-appropriate information about the disease, and ensure continued adherence for a healthy life.

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