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RESEARCH

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Adherence, safety and efficacy of antiretroviral therapy among children at a tertiary hospital in India

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Abstract

Background: Successful response to treatment of HIV infection is largely determined by adherence to antiretroviral therapy (ART) and manifests as an improvement in CD4 counts. Certain challenges to attaining high rates of adherence are specific to the paediatric population since children are dependent on a caregiver and are not often disclosed with the status of being infected. Analysing the factors affecting adherence, monitoring the side effects related to therapy and the progress of CD4 counts will help identify challenges to treatment and improve quality of life in these children.

Results: 89.6% of children ($n = 86$) showed optimal adherence to ART. The relationship of the caregiver to the child (biological parents) and the rise in CD4 count were the only factors found to be significantly associated with adherence to ART. The most reported side effect following ART was a skin rash, associated with the use of Nevirapine.

Conclusions: Adherence to ART in the paediatric age group can be improved by facilitating counselling services and regular monitoring of therapy in children who are not under direct care of their biological parents. Monitoring the safety profile of ART along with the CD4 count is necessary to limit adverse effects and monitor efficacy to treatment.

Keywords: Antiretroviral therapy, HIV, CD4 count, Adherence

Background

In 2019, the National Aids Control Organization (NACO) estimated 23.49 lakh (17.98 lakh–30.98 lakh) people to be living with HIV (PLHIV) (NACO 2019). This included around 79 thousand children living with HIV accounting for 3.4% of the total PLHIV estimates.

With recent advances in treatment of HIV infection in children, there has been a significant decrease in morbidity and progression to AIDS. The AIDS-related mortality has shown a steady decline since 2004–2005 and was at 4.43 per 100,000 population in the year 2019 (NACO 2019). Success of ART is determined by adherence to therapy and is characterised by a decrease in viral load or an improvement in CD4 count (Duarte et al. 2015). In vertically transmitted HIV infection, early initiation of ART has been associated with a stronger immune response (Haberer and Mellins 2009). Non-adherence in the form of missed doses can lead to high levels of antiviral drug resistance and can render therapy ineffective (Nachega et al. 2011).

While adherence to ART translates to better long-term quality of life in children, there are challenges in attaining high rates of adherence. Factors affecting adherence to ART can be broadly classified into four groups regarding the child, their caregiver, the regimen of ART and social/cultural factors (Rinaldi et al. 2020). Children often lack knowledge regarding the nature of the disease and its long-term complications and hence fail to understand why they are put on such complex regimens while their peers aren't. The caregiver's role is of importance since children are unable to procure and administer medication

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independently. Caregivers who are HIV positive or suffering from a chronic illness themselves may understand the importance of long-term adherence. However, suffering from a chronic illness may also affect the caregiver's ability to care for the child. Other factors influencing the caregiver's involvement in promoting adherence to ART in their wards could be their educational status and monthly income. Regimen characteristics include aversion to taste and complexity of the regimen. Social and cultural characteristics include challenges faced due to traditional practices that favour alternative medicine over antiretroviral therapy.

Methods

We performed a cross-sectional study of 96 children aged between 6 months and 12 years who were attending out-patient clinics at a tertiary care centre in Mumbai between January 2014 and May 2015. Sample size was determined using a type 1 error of 5% against precision of 10% with an estimated adherence of 70% based on previous studies in the Indian population (Mhaskar et al. 2012; Charan and Biswas 2013). Prior to enrolling participants in the study, we obtained approval from the Institutional Ethics Committee (IEC) at Seth G.S Medical College and King Edward Memorial Hospital, Mumbai, India. Following this, written informed consent for publication was obtained from caregivers. Children who were receiving ART at our clinic for a minimum of six months were included in our study. Data regarding demographics of the child and the caregiver, educational status and monthly income of the caregiver, presence of chronic illness in the caregiver, disclosure of HIV status to the child, regimen characteristics (duration and complexity) were collected. Clinical staging of HIV was reported in accordance with the World Health Organisation (WHO) guidelines (Adapted from WHO 2005) (Table 1). Laboratory values of complete blood count, renal and liver function tests were noted to determine side effects and safety of ART. Efficacy was determined by CD4 count and clinical staging of the disease at enrolment.

Adherence was determined by the pill count and by the caregiver recall method. A balance pill count of less than five percent of the total number of pills on a monthly visit was considered good adherence while greater than five percent was considered poor adherence. Caregivers were interviewed and asked to report the number of missed doses over the past 30 days. Children were then grouped into good adherence (> 95% of monthly doses taken) and poor adherence (< 95% of monthly doses taken). Categorical analyses of factors thought to affect adherence was carried out.

Microsoft Excel 2017 (Microsoft Corporation, Redmond, WA, USA) and SPSS ver. 17.0 (IBM, Armonk, NY, USA) were used in analysis of data. Quantitative data was represented as mean and standard deviation. Categorial analyses was performed using the chi-square test.

Results

Demographic characteristics

Of 96 children who visited the out-patient clinic between January 2014 and May 2015, 57 were male (59.4%) and 39 (40.6%) were female (Table 2). The mean age was 10 years with a standard deviation (SD) of 2.5. HIV was initially diagnosed at an average age of 4.6 years. Most children ($n=70$, 72.9%) presented with symptoms consistent with stage 1 infection (WHO) (Table 2). Good adherence to treatment, as estimated by the pill-count method was observed in 89.6% ($n=86$) children and poor adherence in 10.4% ($n=10$) children. Female (66.6%, $n=64$) were more common than male caregivers. 83.3% ($n=80$), primary caregivers were biological parents.

Factors affecting adherence to ART

Age and sex of the child

Good adherence was noted in approximately 90% children. All children below the age of 5 years showed good adherence. The proportion of children showing good adherence was similar across both genders (about 89%). Age of the child and gender were not statistically significant with adherence to ART.

Clinical stage of HIV infection and disclosure of status to the child

Most children were in stage I of HIV infection during initiation of ART. 88.6% ($n=62$) children in stage I of the disease showed good adherence to ART. Maximal adherence (100%) was noted in stages II and IV of the infection. Most children (73.9%, $n=71$) were not disclosed with the status of an HIV infection by their caregiver. 84% of children who were disclosed with a positive status of HIV infection had good adherence to ART. There was no statistically significant association between clinical stage of HIV infection or disclosure of HIV status to the child and adherence ($p>0.05$).

Caregiver demographics, monthly income and HIV status

The mean age (standard deviation (SD)) of the caregiver in children showing poor adherence was 42.8 years (8.1) and in children showing good adherence was 39.9 years (6.1). 64 children (66.6%) had female caregivers and 32 children had male caregivers. Adherence was slightly higher in children with female caregivers as compared to children with male caregivers (Table 3). There was no statistically significant association between age/ sex of the caregiver and adherence to ART. Children whose primary caregiver

Table 1 Table showing the clinical staging of HIV infection in children according to the World Health Organisation (WHO) (Adapted from WHO 2005)

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2
Unexplained persistent hepatosplenomegaly
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Herpes zoster
Lineal gingival erythema, recurrent oral ulceration, papular pruritic eruption, fungal nail infections
Extensive wart virus infection, extensive molluscum contagiosum
Unexplained persistent parotid enlargement
Clinical stage 3
Unexplained moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhea (14 days or more)
Unexplained persistent fever (above 37.5 °C, intermittent or constant, for longer than one 1 month)
Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia
Lymph node tuberculosis Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Acute necrotizing ulcerative gingivitis or periodontitis
Unexplained anemia (< 8 g/dl), neutropenia (< 0.5 × 109 /l) or chronic thrombocytopenia (< 50 × 109 /l)
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis (jirovecii) pneumonia
Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)
Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month)
Central nervous system toxoplasmosis (after the neonatal period)
HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial
Infection
Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
Cerebral or B-cell non-Hodgkin lymphoma
HIV-associated nephropathy or cardiomyopathy

was a biological parent showed 92.5% adherence to ART. Adherence to ART was significantly lower (75%) in children who were not under direct parental care ($p < 0.05$).

The average monthly family income (SD) among children who showed good and poor adherence to ART was Indian Rupee (INR) 18,018 (4561.3) and 19,000 (4216.4) respectively. Monthly income and adherence were not statistically significant.

Duration of ART and type of regimen

92.3% of children on treatment for 1–5 years and 83.3% children on treatment for more than 5 years showed good adherence. 72 children (75%) were on the Zidovudine, Lamivudine, Nevirapine (ZLN) regimen. The rate of adherence was highest in children receiving Efavirenz (EFV) based therapy and Stavudine, Lamivudine, Nevirapine (SLN) based therapy. Children receiving Abacavir (ABC)-based regimens showed low

Table 2 Table showing demographics of children and caregivers involved in the study

Age group (patient) (yrs.)	*n* (%)
Demographic characteristics	
Below 5	8 (8.3%)
5–10	35 (36.5%)
11–15	53 (55.2%)
Sex	
Male	57 (59.4%)
Female	39 (40.6%)
Adherence	
Good adherence	86 (89.6%)
Poor adherence	10 (10.4%)
Relationship of caregiver to the child	
Parent	80 (83.3%)
Extended relative/ guardian	16 (16.7%)
Sex of caregiver	
Male	32 (33.3%)
Female	64 (66.6%)

adherence (85.7%). The association between duration or regimen of ART was not statistically significant to the adherence to ART.

Reasons for non-adherence

Non-adherence was reported in 10 of 96 children. 60% of children were outside their hometown and did not carry medication with them during this period. 40% were not administered ART due to forgetfulness, either by the caregiver or by the child themselves.

Efficacy of ART

An increase in CD4 count was noted in 90 children (93.75%). The CD4 count showed a decreasing trend in six children. The clinical stage of the disease decreased to a less severe stage in 88 children (91.6%) while 8 children remained in the same clinical stage despite receiving ART.

Relationship between CD4 count and adherence

Of the 96 children on ART, 90 showed an increase in the CD4 count over time and 6 children showed a decrease in CD4 count (Table 4). All children who had a decrease in CD4 count over time had poor adherence to ART. The relationship between adherence and efficacy as measured by CD4 count was found to be statistically significant ($p < 0.05$).

Side-effects of ART

Myelosuppression was found in 6 out of 64 (9.3%) of children on the ZLN regimen of ART. These children required change in regimen to SLN. Eight children (8.3%) who were found to have skin rashes were receiving Nevirapine-based therapy (Table 5).

Table 3 Table showing the adherence to ART in association with different factors

Age Group (years)	Adherence		*p* value
	Good	Poor	
Below 5	8 (100%)	0	> 0.05
6 to 10	31 (88.6%)	4 (11.4%)	
10 to 15	47 (88.7%)	6 (11.3%)	
Sex of the child			
Female	35 (89.7%)	4 (10.3%)	> 0.05
Male	51 (89.5%)	6 (10.5%)	
Sex of caregiver			
Female	58 (90.6%)	6 (9.4%)	> 0.05
Male	28 (87.5%)	4 (12.5%)	
Relationship of caregiver with child			
Parent	74 (92.5%)	6 (7.5%)	< 0.05
Other	12 (75%)	4 (25%)	
Duration of ART (years)			
< 1	10 (100%)	0 (0%)	> 0.05
1–5	48 (92.3%)	4 (7.7%)	
> 5	30 (83.3%)	6 (16.7%)	
ART regimen*			
ABC-based	12 (85.7%)	2 (14.3%)	> 0.05
EFV	2 (100%)	0 (0%)	
SLN	8 (100%)	0 (0%)	
ZLN	64 (88.9%)	8 (11.1%)	
Disclosure of HIV status to the child			
Yes	4 (16%)	21 (84%)	> 0.05
No	6 (8.4%)	65 (91.6%)	
WHO staging of HIV at initiation			
1	62 (88.6%)	8 (11.4%)	> 0.05
2	4 (100%)	0 (0%)	
3	6 (75%)	2 (25%)	
4	14 (100%)	0 (0%)	

Legend: *ABC = Abacavir, SLN = Stavudine, Lamivudine, Nevirapine, EFV = Efavirenz, ZLN = Zidovudine, Lamivudine, Nevirapine

Table 4 Table showing the relationship between CD4 count and adherence

CD4 count	Good adherence	Poor adherence	Total
Increasing trend	86 (95.6%)	4 (4.4%)	90
Decreasing trend	0 (0%)	6 (100%)	6

Table 5 Table showing the frequency of side-effects and their percentage (of the total cohort) reported in children who were on different regimens of ART

Side-effects	*n* (% of total cohort)
Myelosuppression	6 (6.25%)
Skin rash	8 (8.3%)
GI distress	6 (6.25%)
CNS side effects	2 (2.1%)

Discussion

In 2019, the National AIDS Control Organisation (NACO) estimated about 20.52 thousand pregnant women to be infected with HIV annually (NACO 2019). The Prevention of Parent to Child Transmission (PPTCT) intervention aims to limit perinatal transmission by initiating ART during the antenatal period. Despite this, 3.98 thousand new infections in children aged below 15 were reported (NACO 2019). Vertical transmission is the most dominant mode of acquiring HIV infection in children and early initiation of antiretroviral therapy is vital in limiting the progression to AIDS (Haberer and Mellins 2009).

This cross-sectional study of 96 children on antiretroviral therapy was performed to analyse the adherence, safety and efficacy among children at a tertiary hospital in Mumbai. We used two methods to assess adherence to ART since there is no gold standard for the same. 89.6% of children ($n=86$) enrolled in our study were found to have good adherence (>95%) by the pill count method. On determining adherence by the caregiver recall method, we found >95% adherence in all children. This difference in adherence obtained by two methods could suggest inaccuracies while using the caregiver recall method. Although the caregiver recall method is very commonly used, it has been known to be associated with recall bias (Vreeman et al. 2008). This could result in incorrect interpretation of the adherence unless combined with one of the more accurate methods of determining adherence. The adherence determined by the pill-count was taken as a closer approximate to the actual value of adherence. Rates of adherence can vary across centres due to different policies on provision of ART, availability of pre-ART counselling services and the access to an ART clinic. Our centre is in an easily accessible location, provides free ART and has a skilled team involved in counselling the patient prior to initiation of ART. This could explain the high levels of adherence in our study.

All children aged below 5 reported good adherence to ART. These children are completely dependent on their caregiver for regular intake of medication and a 100% rate of good adherence (>95% of prescribed pills taken) reflects active participation of the caregiver and their understanding of the importance of early treatment. However, the association between age group and adherence to ART was not statistically significant in our study. Results from a similar study in Ethiopia showed statistically significant decrease in adherence as children grew older. This was explained by the fact that older children are often entrusted with the responsibility of taking their own medication and this may come at an age where they are not yet able to comprehend the value of adherence to long-term therapy (Dachew et al. 2014). This contrasts with a study in Kenya which reported higher adherence in older children (Wadunde et al. 2018). Higher adherence was attributed to an increased awareness among these children once they were disclosed with the status of being HIV positive. Bhattacharya et al., reported a significantly higher adherence in male children perhaps due to prevalent cultural norms that favoured the male child (Bhattacharya and Dubey 2011). We did not find a similar association between sex of the child and adherence to ART.

Children who were under direct care of a biological parent showed significantly higher rates of adherence. This emphasises the need for counselling services and regular monitoring of children who are not under direct care by their biological parents. Non-biologically related caregivers may often neglect the wellbeing of their children, and this could explain the poor levels of adherence.

Most children were diagnosed at stage 1 of HIV infection perhaps due to more awareness and early detection of HIV infection. The clinical stage of the infection is predictive of the CD4 count during recovery and children with a less severe clinical stage of HIV have been reported to have higher CD4 counts on follow-up (Barry et al. 2013). 91% of children in our study showed a decrease in clinical stage of the disease on follow-up, while the remaining did not show a change in the clinical stage of their disease.

Regarding a particular regimen of ART, adherence depends on the frequency of dosage, palatability, side-effects and dietary restrictions (Chesney 2003). Certain regimens that require a high frequency of dosage require the caregiver's effort in ensuring doses are administered on time. However, side-effects and taste of a particular regimen play a part in how the child reacts to the regimen and such factors are not under the caregiver's control. Syrups are the easiest form of medication to administer to children (Goode et al. 2003). ART medication in children should be in a form that is easy to administer or can be mixed with food without much aversion to taste. All children on EFV and SLN regimens showed >95%

adherence. This contrasts with the ZLN regimen which was associated with myelosuppression and resulted in > 95% adherence in only 88.9%. Zidovudine-associated myelosuppression requires close monitoring to facilitate transfusion in case of anaemia and to regulate dosage in case of neutropenia (Morales-Pérez 2021). Children who developed myelosuppression were switched to the SLN regimen. 8.3% of our cohort developed a skin rash due to nevirapine and were withdrawn from the drug immediately. Prompt discontinuation following development of cutaneous rashes is necessary to prevent the risk of progression to Stevens Johnson's syndrome or toxic epidermal necrolysis (Fagot et al. 2001). Offering the caregiver medication-specific advice prior to initiation of ART and at regular intervals, either over a phone call or during their visit to the ART clinic can help address issues faced by them.

Unintentional non-adherence has been described as a lack of understanding of the importance of adhering to therapy (Iacob et al. 2017). Forgetfulness was the cause of poor adherence in four children. Caregivers of the other six children who were found to have poor adherence attributed this to being out of their hometown. Our ART clinic provides the necessary amount of medication for the month and these drugs can be administered at home under parental guidance. Thus, devising ways to tackle the problem of unintentional adherence can lead to significant improvement in adherence rates.

An optimum level of adherence at 95% was shown to be associated with significant virological death (Kim et al. 2018). In a similar study, 90.9% of children had an optimal adherence of > 95%. However, 15.4% of these optimally adherent children did not achieve viral suppression, possibly due to resistance to ART (Mehta and Ekstrand 2016). All children who had a decrease in CD4 count in our study were poorly adherent to ART. Apart from optimum adherence, an improved CD4 count following ART depends on the child's age and the clinical stage of the infection at initiation of treatment wherein early diagnosis and initiation of treatment corelates to an increase in CD4 count (Birhan et al. 2020). This increase was found to be maximum during the first 3 months of therapy (Birhan et al. 2020). Thus, offering regular counselling services to caregivers at the initial phase of treatment can improve the overall outcome. Support services offered to caregivers in the form of text messages have been shown to increase the rate of adherence to ART (Kaufmann et al. 2003).

Our study is limited due to its cross-sectional design, wherein children underwent a single assessment to determine their adherence to ART. This could be inaccurate since adherence to a chronic illness like AIDS is a process that may change over time and a better estimate could have been obtained by assessing adherence at regular monthly intervals. In addition to this, we did not account for the children who were lost to follow-up and only included children who visited the ART clinic during the study period. We also did not study the relationship between adherence and side- effects of a particular regimen of ART. Analysing specific factors pertaining to each regimen that affect adherence could help identify problems and implement strategies to improve adherence.

Conclusions

Adherence to ART in the paediatric age group can be improved by facilitating counselling services and regular monitoring of therapy in children who are not under direct care of their biological parents. Further research on the side effects of various ART regimens could guide clinicians in prescribing the appropriate regimen and help counsel caregivers prior to initiation of ART. Monitoring the safety profile of ART along with the CD4 count is necessary to limit adverse effects and monitor efficacy to treatment.

Abbreviations

ART: Antiretroviral therapy; NACO: National AIDS Control Organisation; WHO: World Health Organisation; ABC: Abacavir; SLN: Stavudine, Lamivudine, Nevirapine; EFV: Efavirenz; ZLN: Zidovudine, Lamivudine, Nevirapine.

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Author contributions

KR and JMR prepared the manuscript, SC analysed and interpreted data, VDS performed critical revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Permission from the Institutional Ethics Committee (IEC) at Seth G.S Medical College and King Edward Memorial Hospital, Mumbai, India and informed consent was obtained from caregivers prior to enrolment in the study.

Consent for publication

Written informed consent for publication was obtained from caregivers.

Competing interests

The authors declare that they have no competing interests.

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