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High prevalence of late presentation of ART-naïve perinatally infected children for care in Pune, India

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Abstract

Delayed presentation to care of perinatally infected children in India is a hindrance to achieving the “*end pediatric HIV by 2020*” goal. We describe the prevalence, risk factors and temporal trends of delayed presentation to care among them.

Programmatic data of perinatally infected antiretroviral therapy (ART) - naïve children of Byramjee Jeejeebhoy Government Medical College (BJGMC) and Sassoon General Hospitals’ (SGH) ART center, Pune, India from 2006 to 2016 was used. Children with WHO categories for moderate and severe immunodeficiency were classified as delayed presenters. Multivariable logistic regression was used to identify risk factors for delayed presentation.

Of 269 children with available CD4 count registered for care, median age at presentation was 4 years (IQR: 3 – 6 years), 53% were male and 76% registered for care after 2009. Prevalence of delayed presentation was 52% (95% Confidence Interval 46% – 58%). In multivariable models adjusted for age, sex and domicile distance, unit increase in age was inversely associated with delayed presentation (OR: 0.8, 95% CI: 0.7 – 0.9). Domicile distance 20km from the ART center was also associated with delayed presentation (OR: 2.2, 95% CI: 1.02 – 4.7). Median age at presentation increased over time ($p < 0.001$), but proportion of children with delayed presentation remained unchanged ($p = 0.36$).

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Authors’ Contribution: IPM, SN, VM conceived the study idea. AK, IPM, VM, framed the research question and provided scientific input on methodology. AC, SN helped in data acquisition, IPM, AC, analysed and interpreted the data. BR, AK, provided technical expertise on the functioning of the national AIDS program, IPM, VM, AG, provided clinical scientific input to contextualise the study findings. SN, AK drafted preliminary manuscript. IPM, VM, revised the manuscript critically for important intellectual content. All authors approve of the final revised version submitted for publication.

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More than half of the children in our cohort presented late into care, with the age of delayed presentation increasing over time. Initiatives to improve linkage of these children at the earliest into the Indian HIV pediatric care continuum need to be identified.

Keywords

Delayed presentation; perinatal HIV infection; pediatrics; India

Introduction

With an estimated 145,000 Indian children (0 to 15 years) living with HIV and approximately 22,000 new infections each year, India has the highest global pediatric HIV burden outside sub-Saharan Africa (Nath, 2017; Avert, 2017). Recognizing early on that perinatal transmission causes most pediatric HIV cases in India, the National AIDS Control Programme (NACP) launched the Prevention of Parent to Child (HIV) Transmission (PPTCT) strategy in 2002 (NACO, 2016), and subsequent expansion of services for HIV-infected women and their children has been commendable (Tanwar, 2016). However, delayed presentation to care among a subset of HIV-infected children remains one of India's biggest challenges to attaining the UNAIDS goal of ending pediatric AIDS by 2020 (UNAIDS, 2014). Data are needed to inform targeted interventions.

Since its inception, India's PPTCT program has gained steady momentum. Testing services for pregnant women at publicly funded health centers have expanded from 0.8 million in 2004 to 8.83 million in 2013, and the World Health Organization (WHO) B+ recommendations were implemented as national PPTCT guidelines, in 2014. The revised guidelines made provisions for free antiretroviral drugs for HIV-infected pregnant mothers irrespective of CD4 count and extended treatment to 6 weeks for their babies (NACO, 2014). Despite these gains, anecdotal awareness exists that delayed linkage to care is a problem among perinatally HIV-infected children. Empirical data, however, is lacking. We found only one study from south India that discusses the issue, albeit after a diagnosis of HIV had been made (Alvarez-Uria, 2013).

The dearth of empirical evidence impedes the planning of suitable interventions designed to improve linkage to care among children living with HIV. We aimed to describe the prevalence and risk factors for delayed presentation to care among perinatally HIV-infected children using 10 years of programmatic data from a large, public antiretroviral treatment (ART) center in Pune, India. Secondly, we explored the temporal trend of delayed presentation to care.

Methods

Study design and population

We conducted a retrospective analysis of routinely collected programmatic data among all ART-naïve children (age < 12) registered at the Byramjee Jeejeebhoy Government Medical College (BJGMC) and Sassoon General Hospital (SGH) antiretroviral treatment (ART) center between January 2006 and December 2016. The BJGMC-SGH ART center in Pune is

one of the largest centers for HIV care in western India with approximately 450 children in active follow-up as of December 2018. Since the ART center was instituted late in 2004, we included only those children who were born in and after 2005, as children born prior to 2005 would not have had an ART center to be linked to.

The BJGMC and Johns Hopkins University ethics committees approved the project.

Data variables and definitions

Pediatric data collected routinely under the Indian national HIV program include demographic and clinical characteristics at scheduled visits following voluntary registration by an adult caretaker (> 18 years). Presentation was defined as the first contact with the health system, and registration was defined as the first enrollment in HIV care. However, the terms are used interchangeably throughout the manuscript since drop out and time delay between the two events were negligible in our cohort. We abstracted the following variables from the BJGMC-SGH ART center electronic database: age at registration; sex; CD4 at registration; year of registration; and domicile at registration.

Immunological status served as a proxy for time to presentation to HIV care and was categorized as non-significant, mild, moderate or severe based on CD4 count (proportion or absolute counts depending on age) at registration according to the WHO criteria for children (WHO, 2014); delayed presentation to HIV care was defined as moderate or severe immunodeficiency upon first presentation to clinical care, and non-delayed presentation to HIV care was defined as non-significant or mild immunodeficiency upon first presentation to clinical care. As our outcome of interest was based on CD4 counts at presentation, we included only those children with non-missing CD4 count values. Distance was quantified using Google maps and calculated between the BJGMC-SGH ART center and the domicile at registration approximated to the closest street.

Statistical Analysis

The two study groups, delayed and non-delayed presentation to HIV care, were described using medians and proportions and compared using Wilcoxon rank-sum and Fisher's exact tests for continuous and categorical variables, respectively. Risk factor analysis for delayed presentation to HIV care was performed using logistic regression. Multivariable models included covariates that were identified *a priori* or were statistically significant in univariate analysis. As a sensitivity analysis to test the robustness of our estimates produced as a result of only including those with non-missing CD4 values, we reran our logistic regression model after imputing for missing values using multiple imputation by chained equations. All p-values were two-sided with statistical significance evaluated at an alpha of 0.05. All statistical analyses were performed using Stata version 14 (StataCorp, College Station, Texas).

Results

Between January 2006 and December 2016, a total of 583 ART-naïve children born after 2004 registered for care at the BJGMC-SGH ART center. Of these, only 269 (46%) had available CD4 counts and were included in the analyses. Of the 269, 142 (53%) were male,

median age at registration was 4 years (Interquartile range [IQR], 3–6), 75 (28%) lived 20 km from the ART center at registration, and the majority (75%) registered for care after 2009. Overall, prevalence of delayed presentation (moderate or severe HIV disease at presentation) was 52% (95% Confidence Interval [CI] 46–58). A one-unit increase in age was significantly associated with decreased odds of delayed presentation to care in both univariate analysis (Odds ratio [OR], 0.8; 95% CI, 0.7 – 0.9) and multivariate models adjusted for age, sex and distance of domicile from the ART center (adjusted OR, 0.8; 95% CI, 0.7 – 0.9). Domicile distance 20km from the ART center was significantly associated with increased odds of delayed presentation (OR, 2.2; 95% CI, 1.02 – 4.7) (Table 1). There was a significant increase in median age at presentation to HIV care over the analysis period ($p<0.001$) (Figure 1), but no significant difference in prevalence of delayed presentation to HIV care was observed over time. ($p=0.36$) (Figure 2).

The results we present in this manuscript are based on estimates obtained from listwise deletion. Coefficients and their interpretation obtained thus, were not different from those obtained in our sensitivity analyses using imputed datasets (supplementary file).

Discussion

This retrospective study among ART-naïve perinatally HIV-infected children registered at a large public ART center in western India found >50% prevalence of delayed presentation to HIV care (moderate or severe HIV disease at first presentation) with a median time to presentation of 4 years post infection. Increasing age and distance 20km from domicile to ART center were associated with decreased and increased odds of delayed presentation to HIV care, respectively. Our analysis provides new data on pediatric HIV disease presentation in India. Despite the expansion of HIV services through India's national PPTCT program, our findings suggest potential shortcomings in early HIV detection and linkage to care. Future studies are needed so that targeted interventions may be designed, implemented, and evaluated.

To date, empirical data on timing of presentation to HIV care is lacking in Indian pediatric populations. The 52% prevalence of delayed presentation to HIV care among children in our setting could be explained by a combination of delays in HIV diagnosis (synonymous with unknown HIV status) and/or linkage to HIV care. Although national guidelines recommend initial HIV testing within 4–6 weeks of birth, one study from south India reported that it took up to one year for 85% of HIV-exposed babies to undergo HIV testing, and 33% were lost to follow-up before the second, confirmatory test (Hanna, 2015). Such delays in HIV diagnosis may be particularly relevant among infants born in publicly funded hospitals, as we would expect these children to be linked earlier to care than what we observed. Further, certain attitudes/beliefs among adult caregivers, such as denial of HIV status and/or lack of perceived need for medical care, may delay linkage to HIV care even after HIV diagnosis (Jenness, 2012; Horter, 2017). Specific to our context, non-institutional delivery or death of adult caretakers could delay both HIV diagnosis and linkage to care. Overall, our study highlights the need for greater understanding and potential improvement in both these aspects under the Indian HIV pediatric response program.

Our risk factor analysis indicates an inverse association between age and delayed presentation to HIV care. This finding correlates with what is already known about the natural history of HIV disease among untreated children (Unknown,1991). In contrast to our findings, previous studies conducted in adults have associated older age with advanced HIV disease at presentation and have identified male sex as a risk factor (van der Kop & Jeong, 2016). We found no association between biological sex and delayed presentation to care in our pediatric cohort, which could be a reflection of gender norms in India where the wellbeing of male children is traditionally prioritized (Ganatra,1994).

Interestingly, our analysis suggests that age at presentation to HIV care has increased over time. This finding could be explained by our study population, as we exclusively included children that had conditionally survived earlier time periods. Alternatively, this finding could also reflect the success of the national HIV program in preventing new perinatally transmitted infections in later time periods. Superimposing our findings with current knowledge concerning the course of HIV disease among untreated children, a supposition can be made that 15 –25% of children (i.e. those with a rapid disease course) are being missed by the national program. Correspondingly, strategies promoting concurrent early identification and HIV-service delivery need to be identified for the slow progressors or long-term survivors that most likely comprise our cohort in the later registration periods (some of whom have reached adolescence). (Kliegman,2016).

This study has several limitations. First, our analysis was limited to the variables contained in programmatic datasets. We could not, for example, assess the effect of socioeconomic status or stigma, both of which affect outcomes in adults. (Johnson,2015; AVAC,2017; Orza,2017) We also could not differentiate among the reasons for delayed presentation to care. To better understand factors driving delayed presentation, we did attempt to contact all participants by telephone, but only 34% were traceable (of these, 71% were born in a hospital setting). We also had >50% missingness for our outcome of interest, which reduced the analytical sample size. However, our sensitivity analyses using multiple imputations did not show our results or their interpretation to be different when using only non-missing values. Lastly, we studied a selected sample, as children that either died or did not seek care at the hospital were excluded. Notwithstanding these limitations, our analysis highlights a number of issues affecting the pediatric HIV care continuum in India.

In conclusion, more than half of perinatally HIV-infected children presenting to a large public ART center in India from 2006 to 2016 had delayed presentation to HIV care with either moderate or severe HIV disease. Significantly, this trend remained unchanged over the 10-year analysis period despite concurrent expansion of PPTCT services. Our findings reinforce the importance of linking HIV-infected children to care at the earliest. To this end, methods beyond the scope of the current HIV treatment program are needed. Future studies to understand the independent contributions of delayed diagnosis and delayed linkage to care and would inform specific recommendations for policymakers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Median age of perinatally infected ART naïve children at registration at the ART center of Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Pune, India

Figure 2:

Proportion of perinatally infected ART-naïve children with delayed presentation at the ART center of Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Pune, India

Characteristics of ART naïve children registered at the ART center of Byramjee Jeejeebhoy Government Medical College & Sassoon General Hospitals and risk factors for delayed presentation

Table 1:

Characteristic	Total Number N (%)	Delayed presentation N (%)	Non-delayed presentation N (%)	OR (95% CI)	p-value	aOR* (95% CI)	p-value
Total	269	139 (51.7)	130 (48.3)	-	-	-	-
Age							
Median (IQR)	4 (3 – 6)	3 (2 – 5)	4 (3 – 7)	0.8 (0.7 – 0.9)	0.001	0.8 (0.7 – 0.9)	0.001
Sex							
Male	142 (52.8)	71 (51.1)	71 (54.6)	Ref	-	-	-
Female	127 (47.2)	68 (49.9)	59 (45.4)	1.2 (0.7 – 1.9)	0.56	1.3 (0.8 – 2.2)	0.32
Distance (km)^f							
< 5	48 (17.8)	21 (15.1)	27 (20.8)	Ref	-	-	-
5 – 9.9	84 (31.2)	37 (26.6)	47 (16.2)	1.1 (0.5 – 2.1)	0.95	1.1 (0.5 – 2.2)	0.88
10 – 19.9	62 (23.1)	35 (25.2)	27 (20.8)	1.7 (0.8 – 3.6)	0.19	1.7 (0.8 – 2.2)	0.18
20	75 (27.9)	46 (34.1)	29 (22.3)	2.0 (0.9 – 4.3)	0.06	2.2 (1.02 – 4.7)	0.04
Registration Year							
2006 – 2009	65 (24.2)	38 (27.3)	27 (10.8)	Ref	-	-	-
2010 – 2013	122 (45.3)	63 (45.3)	59 (45.4)	0.8 (0.4 – 1.4)	0.37	-	-
2014 – 2016	82 (30.5)	38 (27.3)	44 (33.8)	0.6 (0.3 – 1.2)	0.15	-	-

* adjusted for age, sex and distance of domicile from the ART center at registration

^f distance calculated as the distance between the ART center and domicile at registration