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Profile of Pediatric HIV Patients on Second line ART (Anti-Retroviral Therapy)

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Abstract

Background: HIV (human immunodeficiency virus) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS) by infecting helper T cells of the immune system.

The greatest impact of HIV/AIDS is seen in resource-limited settings (RLS). As the access to and time on ART (Anti-retroviral treatment) increases in RLS, patients increasingly experience first-line treatment failure or other events that necessitate a switch to protease inhibitor (PI)-based second-line treatment.

So far, there is limited knowledge about the clinical characteristics and treatment outcomes of pediatric patients receiving second-line therapy. Hence the present study was done at our tertiary care centre to **define the** clinical, immunological, and virological profile of pediatric HIV patients on Second-line ART.

Aim: To describe the profile of children and adolescents living with HIV, and receiving second-line ART.

Methods: The study was conducted prospectively at a tertiary care center after due permission from the Institutional Ethics Committee and Review Board and after obtaining Written Informed Consent/assent from the parents/patients**.** It was conducted from Jan 2018 to June 2019(1.5 years).

Details of 70 HIV-infected children and adolescents on 2nd line ART <18 years of age were noted in the predesigned proforma, and their clinical profile was studied.

Results: Seventy HIV-positive children (42 males and 28 females; M: F = 1.5:1) were enrolled. 51 children (72.9%) were from the age group of 12-18 years. 48 (68.5%) were completely immunized, while 11(15.7%) were unimmunized. Clinical features at presentationin

30(42.85%) cases included fever > 1 month (42.9%), 16 cases of persistent cough (22.8%), 14 cases of lymphadenopathy (20%) followed by 10 cases with gastrointestinal symptoms (14.3%).

The age at initiation of first-line ART for 25 (35.7%) and 28 (40%) children was 6-12 years and 12-18 years respectively, while the age at initiation of second-line ART for 19 (27.1%) and 44 (62.9%) children was 6-12 years and 12-18 years respectively.

The cause of the switch to 2nd line ART was clinical in 37 (52.9%) children while it was immunological and virological in 17 (24.3%) and 16 (22.8%) children, respectively.

Tuberculosis was the most common opportunistic infection present in 45 children (64.28%), followed by candidiasis (10%), PCP (Pneumocystis jirovecii) pneumonia (7.1%) and 1(1.4%) patient had CMV infection. 12 (17.1 %) children did not have any opportunistic infection.

The mean Viral Load values of children on enrolment were 40422.872±2149.21copies/ml that decreased significantly to 22282.50±5997.55copies/ml at 6 months. ($p<0.05$).

Conclusion: Optimal second-line HIV treatment approaches should critically consider immediate and aggressive viral load suppression, rapid immune recovery, and excellent adherence to the therapy. More frequent clinical follow-ups and viral load monitoring are recommended for HIV-infected children that help in the rapid identification and intervention of failure cases. Comprehensive care of children affected by HIV/AIDS is important, with focus also being given to the overall development including nutritional status and counselling with moral support.

Keywords: Pediatric HIV, Second line ART, CD4 count, Viral load, opportunistic infections

Introduction

HIV infection includes a spectrum of clinical manifestations, the extreme end of which is the most severe form of the disease-acquired immunodeficiency syndrome (AIDS). [1-5] As per the report in 2021, globally, around 1.7 million children were living with HIV, with 1.6 lakh children being newly affected per year. Children accounted for 15% of all AIDS-related deaths, although only 4% of the total number of people living with HIV are children. Only half (52%) of children living with HIV(CLHIV) are on life-saving treatment, far behind adults of whom three-quarters (76%) are receiving antiretrovirals. Around the world, one child dies from AIDS-related causes every five minutes. [1]

In the absence of antiretroviral therapy (ART), the median time to progress from HIV infection to AIDS is nine to ten years, and the median survival of AIDS is 9.2 months. Treatments for HIV can slow the course of the disease; however, there is no cure. [1] The greatest impact of HIV/AIDS is seen in resource-limited settings (RLS). [3]

Patients increasingly experience first-line treatment failure or other events that necessitate a switch to protease inhibitor (PI)-based second-line treatment. [6,7] Unfortunately, in RLS, the rate of switching for patients experiencing treatment failure is lower, for several reasons. The challenges faced include limited access to viral load monitoring, low sensitivity of immunological/clinical definitions of treatment failure, the limited availability and high cost ofsecond-line drugs, co-morbidities, and high pill burden. [3,4] The prevalence of first-line ART failure differssignificantly

acrosscountries depending on the criteria (clinical,immunological, or virological) used for its diagnosis. Also, second-line ART has more toxicity profile. [7-11]

To ensure adequate long-term treatment for children and adolescents, evaluation of current second-line treatment is essential. Data, however, is scarce. In adults, many studies regarding second-line ART have been conducted [12-20], but such analyses are missing for children. We performed the present study at the PCOE (Pediatric Centre of Excellence) for HIV-infected children and adolescents to assess the clinical profile of pediatric HIV patients on second-line treatment and their outcomes.

Aim

To describe the profile of children and adolescents living with HIV, and receiving second-line ART.

Objectives

1. To study the various clinical features of patients on second-line anti-retroviral therapy.
2. To study the virological profile of these patients.
3. To study the immunological profile of these patients.

Material and methods

This prospective observational study was conducted at the Pediatric Center of Excellence for HIV at a tertiary care center in India from January 2018 to June 2019. Due permission from the Institutional Ethics Committee and Review Board was taken. Informed consent/assent was obtained from the parent/guardian and children (when applicable) for all 70 patients enrolled. All children and adolescents (< 18 years) on second-line ART were included in the study.

A special proforma was designed to record the demographic data, history and clinical findings at presentation, nutritional status, history of opportunistic infections etc. Baseline investigations included a complete blood count, absolute CD4lymphocyte count, Aspartate Transaminase/Alanine Transaminase (AST/ALT), blood urea nitrogen (BUN)/Creatinine, erythrocyte sedimentation rate (ESR), chest radiograph, tuberculin test and ultrasonography of the abdomen.

All children were confirmed to have failed first-line ART as per NACO (National AIDS Control Organization) guidelines.[1] Side effects of Second-line ART, if any were documented.

Data was analyzed using SPSS V15.0 (Statistical Package for Social Sciences, Version 15.0).

Definition of Clinical Treatment Failure. [1,21,22]

The detection of new or recurrent WHO clinical stage 3 or 4 events may reflect the progression of the disease. Treatment failure should be considered if the child has been on therapy for at least 24 weeks and is adequately adherent to treatment.

Immunological criteria for recognizing treatment failure: [1,21,22]

Drop in the CD4, after the initial immune recovery following ART initiation:

* To values at or below the age-related CD4 threshold for treatment initiation OR

* 50% drop of CD4% or value from peak post-therapy levels

Virological failure is recognized as persistent plasma viral load (VL) above 5000 copies/ml, after at least 24 weeks on ART, in a fully treatment-adherent child.

Second line treatment [1]

Selecting a Second-line Regimen for Children with Treatment Failure on First-line Regimen

SITUATION	Preferred First line Regimen	Preferred Second line Regimen
INFANTS		
Infant not exposed to ARV	NVP + 2 NRTIs	LPV/r + 2 new NRTIs
Infant exposed to NVP	LPV/r + 2 NRTIs	NNRTI + 2 new NRTIs
Infant with unknown ARV exposure	NVP + 2 NRTIs	LPV/r + 2 new NRTIs

Recommended Second Line Regimens in Infants and Children in the event of First Line Treatment Failure			
	Preferred Second Line Regimens		
First Line Regimen at Failure	Second Line RTI Components (NRTI/NNRTI)	Plus	PI Component
2 NRTIs + NNRTI: AZT or d4T containing	ABC + 3TC Or ABC + ddI		LPV/r

In case of any other regimens being given as first line, refer to pSACEP or SACEP for further management.

The NACO standard pediatric second line regimen (ABC/3TC + LPV/r) aims to achieve viral suppression for as long as possible, so that survival can be prolonged.

Results

Seventy children and adolescents living with HIV on second-line ART (42 males and 28 females) were enrolled in the study. Table 1 shows the demographic profile of study subjects. The mean age of the children was 14.03 ± 3.66 years, with male to female ratio being 1.5: 1.

The majority of the children, 51 (72.9%) were from the age group of 12-18 years followed by 16(22.8%) from the age group of 6-12 years. Most of the (54.3%) children belonged to lower socioeconomic status, followed by upper-lower (24.3%) and lower-middle (21.4).

The immunization status of 48 (68.6%) and 7 (10%) children was complete and incomplete respectively while 11 (15.7%) children were unimmunized. The immunization status of 4 (5.7%) children was not known. Nutrition-wise, 30 (43%) children were Severely Thin, 27 (38.5%) were Thin and 13 (18.6%) children were normal according to anthropometry. Only 7 (10%) children received nevirapine at birth while 63 (90%) children did not receive nevirapine at birth.

The most common complaint at presentation was prolonged fever of more than 1 month (42.9%) followed by persistent cough (22.8%), lymphadenopathy (20%), and gastrointestinal symptoms (14.3%). Tuberculosis was the most common opportunistic infection present in 45 children (64.28%), followed by candidiasis (10%), PCP (Pneumocystis jirovecii) pneumonia (7.1%) and 1(1.4%) patient had CMV infection. 12 (17.1 %) children did not have any opportunistic infection.

Out of 70 children, 26 (37.1%) patients had 76-100% adherence while 29 (41.5%) patients had 50-75% adherence. 14 patients (20%) had poor adherence of 26-50% and 1 had < 25 % adherence. Regarding side effects and intolerance to medications, 28 (40%) children had anaemia while 10 (14.3%) and 7 (10%) children had transaminitis and AKI respectively. 6 (8.6%) children had drug rash.

Table 1: Demographic Details of Patients

Variables	Number of Patients(n=70)
Age	
0-6 years	3(4.3%)
6-12 years	16(22.8%)
12-18 years	51(72.9%)
Gender	
Male	42(60%)
Female	28(40%)
Socioeconomic Status	
Lower middle	15(21.4%)
Upper lower	17(24.3%)
Lower	38(54.3%)
Immunization Status	
Complete	48(68.6%)
Incomplete	7(10%)
Unimmunized	11(15.7%)
Not Known	4(5.7%)
Nutritional Status	
Severe Thinness	30 (43%)
Thin	27 (38.5%)

Normal	13(18.6%)
Mode of Delivery	
FTNVD (Institution delivery)	50(71.5%)
LSCS	9(12.8%)
Home Delivery	11(15.7%)
Nevirapine at birth	
Yes	7(10%)
No	63(90%)
Clinical Features	
Prolonged Fever	30(42.9%)
Persistent Cough	16(22.8%)
Lymphadenopathy	14(20%)
Gastrointestinal Symptoms	10(14.3%).
Opportunistic Infections (OI)	
Tuberculosis	45(64.28%)
Candidiasis	7(10%)
PCP Pneumonia	5(7.1%)
CMV Retinitis	1(1.4%)
NO OIs	12(17.1%)
Adherence toTreatment	
0-25%	1(1.4%)
26-50%	14(20%)
51-75%	29(41.5%)
76-100%	26(37.1%)

Was not known.38 (54.4%) mothers were on art while the ICP status of 5 (7.1%) and 20 (28.6%) mothers were positive and negative respectively. The ICP status of 7 (10%) mothers was not known.

Table 2: ICP status of parents.

ICP Status	Father	Mother	Both Parents
On ART	35(50%)	38(54.4%)	20(28.57%)
Positive (ART status unknown)	17(24.4%)	5(7.1%)	0
Negative	9(12.8%)	20(28.6%)	2(2.85%)
Not known	9(12.8%)	7(10%)	1(1.42%)

The mean age of the children at diagnosis and start of 1st line ART was 10.01 ± 4.46 years & 10.09 ± 4.43 years, respectively. The mean age of the children at initiation of 2nd Line ART was 12.76 ± 3.82 years.

Table 3 shows age group distributions of CLHIV at diagnosis, at the start of 1st line of ART & age at the start of 2nd line of ART. The majority of patients were diagnosed after 6 years of age (74.2%), started 1st line of ART after 6 years of age and 90 % of patients started second-line ART after 6 years of age.

Table 3: Total number of patients based on age at diagnosis, initiation of treatment of 1st and 2nd line ART.

Age in years	Age at Diagnosis (Total Number)	Age at Initiation of 1st line ART (Total Number)	Age at Initiation of 2nd line ART (Total Number)
0-6 years	18 (25.8%)	17 (24.3%)	7 (10%)
6-12years	23 (32.8%)	25 (35.7%)	19 (27.1%)
12-18years	29 (41.4%)	28 (40%)	44 (62.9%)
Total	70	70	70

Age in years	Age at Diagnosis (Total Number)	Age at Initiation of 1st line ART (Total Number)	Age at Initiation of 2nd line ART (Total Number)
number			
Mean ± SD	10.01 ± 4.46	10.09 ± 4.43	12.76 ± 3.82

As observed in Table 4, the cause of the switch to 2nd line ART was clinical in 37 (52.9%) children while it was immunological and virological in 17 (24.3%) and 16 (22.8%) children respectively.

Table 4: Cause of switch to 2nd line ART

Cause of switch to 2nd line ART	Total Number
Clinical treatment failure	37(52.9%)
Immunological failure	17(24.3%)
Virological failure	16(22.8%)

Table 5: Comparison of Complete Blood Count (CBC) and CD4 Count

Parameters	On Enrolment	6 Months	P-Value
	Mean ± SD	Mean ± SD	
Hb (g/dL)	7.89 ± 2.35	8.30 ± 1.98	<0.05
TLC (/mm3)	8025.06 ± 2050.12	4972.14 ± 2215.27	<0.05
Platelet (×106/L)	309441.43 ±194634.33	295710.43 ±188053.81	<0.05
BUN (mg/dL)	6.51 ± 3.31	8.67 ± 4.45	<0.05
Creatinine (mg/dL)	0.50 ± 0.17	0.66 ± 0.38	<0.05
CD4 COUNT(/mm^3)	454.47 ± 283.40	715.96 ± 400.11	<0.05
VIRAL LOAD(copies/ml)	40422.87 ± 22149.21	22282.50 ± 5997.55	<0.05

As shown in Table 5, the mean Hemoglobin values of children on enrolment were 7.89±2.35g/dL which increased significantly to 8.30±1.98g/dL at 6 months ($p<0.05$). The mean TLC values on enrolment were 8025.06±2050.12cell/mm3 which decreased significantly to 4972.14±2215.27cell/mm3 at 6 months ($p<0.05$). The mean Platelet values on enrolment were 309441.43±194634.33×106/L that decreased significantly to 295710.43±188053.81×106/L at 6 months ($p<0.05$). The mean BUN values of children on enrolment were 6.51±3.31mg/dl which increased significantly to 8.67±4.45mg/dl at 6 months as per Student t-test ($p<0.05$). The mean Creatinine value on enrolment was 0.50±0.17mg/dl which increased significantly to 0.66±0.38mg/dl at 6 months.

The mean CD4 count values of children on enrolment were 454.47±283.40/mm3 which increased significantly to 715.96±400.11/mm3 at 6 months. The mean Viral Load values of children on enrolment were 40422.8722149.21 copies/ml which decreased significantly to 22282.50±5997.55copies/ml at 6 months. ($p<0.05$)

Discussion

The present hospital-based prospective study aimed to describe the profile and outcomes of children and adolescents living with HIV receiving second-line antiretroviral therapy (ART). The study included 70 children and examined various demographic, clinical, and treatment-related factors. The findings of this study have been extensively discussed in the context of existing literature.

The study showcased a male preponderance. This gender distribution was analogous to previous studies conducted by Shah et al, [23] Sidemo et al, [24] and Nsheha et al. [25]

There was a predominance of children aged 12-18 years (72.9%), followed by those aged 6-12 years (22.8%), and 0-6 years (4.3%). The mean age of the children was 14.03 ± 3.66 years. This distribution was in line with studies by Shah et al, [23] Sidemo et al, [24] and Nsheha et al. [25]. which also reported higher proportions of adolescents in their respective study populations. These findings underscore the ongoing challenge of HIV transmission to adolescents.

The mean age at diagnosis was 10.01 ± 4.46 years. [26]. Likewise, the age at initiation of first-line ART showed a pattern, with 35.7% starting between 6-12 years and 40% between 12-18 years. These findings align with studies by Boerma et al [27, 28] and Suaysod et al, [29] indicating comparable trends in age at diagnosis and ART initiation.

The socioeconomic status analysis revealed that a significant proportion of children came from lower-middle and lower-class families. This socioeconomic distribution was consistent with Nsheha et al's study. [25]

Parental factors, including ICP status and access to ART and interventions like hospital delivery and nevirapine prophylaxis, played a role in the vertical transmission of HIV. The study demonstrated the challenges of implementing nevirapine prophylaxis, especially among home deliveries. Comparable observations were made by Boerma et al. [27, 28]

The study highlighted a concerning nutritional status, with 43% of children classified as severely thin and 38.5% as thin. This corroborated findings from Sidemo et al [24] and Boerma et al, [27, 28] indicating the adverse impact of malnutrition on HIV-infected children's outcomes.

In the present study, tuberculosis was found to be the most common opportunistic infection in 64.28% of children (including all forms of TB). A similar observation was noted by Sidemo NH et al [24] and Merchant et al. [30]

The most common reason for switching to second-line ART was clinical failure (52.9%). Immunological and virological failures were also significant contributors. As our study was conducted at a tertiary care center, which is the referral centre, there may be a delay in the referral of children for a switch to 2nd line ART. Delayed referral to a tertiary care center was noted as a reason for clinical failure, emphasizing the importance of timely management transitions. [30-33]

Adherence to ART is critical for successful HIV management. In this study, the majority of children reported adherence between 51-100%, with some reporting lower adherence levels. This pattern of adherence was congruous with findings from other studies, [29, 34, 35] highlighting the need for continued efforts to improve treatment adherence among pediatric HIV patients.

The study revealed significant improvements in immunological and virological outcomes, on second-line treatment. CD4 counts increased over the study period, and viral load decreased substantially, indicating the effectiveness of second-line ART. These findings were consistent with studies by Krogstad et al [36] and Mutwa et al. [34]

The study identified changes in clinical parameters and laboratory values. While certain parameters like hemoglobin and CD4 counts improved, others such as liver enzymes and renal function showed variations. These trends in laboratory values mirrored the studies of Bhaisara et al [37] and Boerma et al. [27, 28]

The study has some limitations, including its single-center nature and the relatively small sample size. The findings might not be entirely generalizable to broader populations due to regional variations in healthcare access and practices.

Conclusion

Optimal second-line HIV treatment approaches should critically consider immediate and aggressive viral load suppression, rapid immune recovery, and excellent adherence to the therapy.

The aim should be early diagnosis and early treatment along with appropriate ART to the mother in the peripartum period to reduce mother-to-child transmission. More frequent clinical follow-ups and viral load monitoring are recommended for HIV-infected children that help in the rapid identification and intervention of failure cases.

Comprehensive care of children affected by HIV/AIDS is important, with focus also being given to the overall development including nutritional status and counselling with moral support. Proper treatment of side effects of drugs and opportunistic infections is of paramount importance.

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