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Immunovirological treatment outcomes after 2 years of antiretroviral therapy in children living with the human immune deficiency virus in Lagos Nigeria

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Abstract: *Background/objective:* The World Health Organization (WHO) recommends routine assessment of antiretroviral treatment outcomes to detect treatment failure early and prevent the development of drug resistance. The aim of this study was to describe treatment outcomes of antiretroviral therapy (ART) over 2 years in children living with the human immune deficiency virus enrolled in the paediatric HIV clinic at the Lagos University Teaching Hospital (LUTH).

Materials and methods: This was a retrospective study of antiretroviral treatment outcomes in 278 children receiving antiretroviral therapy at the paediatric HIV clinic of LUTH. Demographic, clinical and laboratory data were retrospectively collected from clinical records of pediatric patients who received antiretroviral therapy for 2 years (from November 2015 to December 2017) . Virological failure was defined as viral load > 400 copies/ml and immunological failure was defined as a CD4 count <100 cells/ mm^3 or CD4 % <15% after receiving antiretroviral agents for 12 months. Data was analysed using graph pad prism version 5.0.

Results: After 12 months on antiretroviral therapy (ART), 101 (36%) had virological failure while 14 (5%) and 36 (13%) failed immunologically [CD4 count <100 cells/ mn^3 and CD4 <15% respectively]. Virological blips were observed at 24 months in 6.1% of patients while immunovirological discordance occurred in 30% of patients (poor virological clearance despite good immunological recovery) . High baseline viral load (>5000 copies/ml), poor adherence (<95%) and low baseline CD4 counts (101-249 cells/ mn^3) were significantly associated with virological failure, while low baseline CD4 counts (<350 cells/ mn^3) and poor adherence (<95%) were significantly associated with immunologic failure.

Conclusion: The treatment outcomes observed in this study are similar to those reported in earlier studies. At 1 and 2 years of antiretroviral therapy , there was immune restoration however 101 (36%) and 87 (31%) respectively had virological failure despite good adherence to therapy and good Immunological restoration. This calls for early initiation and switch to second and third line drugs .

Key words: Human immunodeficiency virus (HIV), zidovudine, lamivudine, nevirapine, virological blips, immunovirological discordance , children, Nigeria.

Introduction

The introduction of antiretroviral therapy has considerably improved health outcomes of HIV-infected children. Ninety per cent of children living with HIV live in Africa and in 2015 only 49% of children living with HIV globally were estimated to be receiving ART antiretroviral therapy[1]. In the paediatric population in resource limited countries, the combination of zidovudine, lamivudine (nucleoside reverse transcriptase inhibitors) and nevirapine (non nucleoside reverse transcriptase inhibitor) is considered as one of the preferred recommended antiretroviral treatment regimens. The World Health Organization (WHO) advocates a public health approach to antiretroviral therapy and recommends monitoring of treatment outcomes especially in resource-constrained countries such as Nigeria[2, 3] . Response to therapy is monitored by clinical symptoms and signs, quantifying HIV RNA copies (viral load), CD4 T-lymphocyte count and CD4% all of which are important indicators of

therapeutic success or failure [4].

Delayed detection of treatment failure leads to poor treatment outcomes and may increase drug toxicity, cause accumulation of drug resistance associated mutations and may result in increased morbidity and mortality. This makes regular monitoring of children on antiretroviral therapy an important activity to optimize treatments and prevent treatment failure and eventual emergence of HIV drug resistance [5-7].

In Nigeria good ART outcomes have been reported from paediatric HIV/AIDs programs, comparable to those in high-income countries. Some of these studies consisted of different designs with varying sample sizes and data on patient characteristics, adherence and treatment outcomes in adults and children [8-11]. This study assessed and described the treatment outcomes in children aged 2-14 years living with human immune deficiency virus (HIV) and receiving antiretroviral drugs for 2 years in Lagos, Nigeria.

Methods

The study was done at the paediatric HIV clinic of the Lagos University Teaching Hospital (LUTH), Lagos, Nigeria. The study population comprised of paediatric patients living with HIV, aged 2 years to 14 years and receiving a combination of zidovudine, lamivudine and nevirapine for a period of two years from November 2015 to December 2017. In this observational study all patients were included into this study as they consecutively attended the clinic. Diagnosis and confirmation of HIV status, choice and initiation of 1st line ARV therapy were already decided by the HIV treatment Program team before the study according to the National guidelines [12].

Standardized data collection forms were used to document demographic, clinical and laboratory data including anthropometric measurements, viral load, CD4 count, CD4 %, haematological and biochemical parameters. Virological and immunological outcomes were assessed. Virological failure (VF) was defined as a HIV RNA level of equal or more than 400 copies/ml at the 1 year visit after initiation of antiretrovirals in line with local laboratory assay detection limits at the time of study. Virological suppression was defined as VL<400 cps/µl[13,14].

Immunological failure was defined according to the WHO guidelines as having a CD4 T lymphocytes count of less than 100 cells/mm^3 or CD4% < 15% at twelve months post ART. Immune recovery was defined as CD4% ≥25% after one year of ART [15]. Adherence was assessed by refill visit report for picking up medications from the pharmacy on the appointment day. Refill adherence was calculated based on the cumulative sum of days that a patient was late for ART pick-up appointments, divided by the total number of days over all such periods. Each refill period was identified as the interval between the last pharmacy visit date and the schedule refill date. Refill adherence was 100% if all pills during the schedule refill period were picked up on time. Good adherence and poor adherence was defined using a threshold of > 95% and <95% respectively [16].

Ethics approval

Ethical approval was received from the Lagos University Teaching Hospital Health Research Ethics Committee (ADM/DCST/HERC/2259) and the permission to collect data was granted by the Director of LUTH HIV clinic. Informed consent for participation in the study was obtained from children's parent/caregivers, next of kin, caretakers, or guardians on behalf of the minors/ children who participated. The names of the patients and their unique antiretroviral treatment numbers were not included during data collection to protect patient identity

Statistical analysis

Data for continuous variables were expressed as mean and standard deviation (SD) if normal distributed or median and inter-quartile range (IQR) if not normally distributed. Categorical data were reported as counts and percentages. Analysis was conducted using Graph Pad Prism version 5 for windows (Graph Pad Software, San Diego California USA.. In comparative analyses, the Chi-square test was used to investigate the association between categorical covariates and outcomes. Parameters associated with virological or immunological failure, according to the univariate analysis, were entered into a linear regression model to determine the respective contribution of each patient characteristics predicting virological or immunological failure. The association was measured by adjusted odds ratio (AOR). Factors with P-value 0.2 or less at bivariate analysis were selected for further multivariate analysis.

Results

Study population

A total of 278 children were enrolled in this study, comprising one hundred and forty two (51%) females and one hundred and thirty six (49%) males. The median age at treatment initiation was 8 years (IQR 4.6-14.0). Table 1 shows patient characteristics. The patients received combination antiretroviral therapy with body weight based dosing. At antiretroviral initiation and 2 years two hundred and fifty six patients (92.1%) and one hundred ninety five 195(70%) respectively received fixed dose combination of zidovudine, lamivudine and nevirapine. Patients in whom first line therapy failed or were not tolerated received second line drugs. Some patients were switched to protease inhibitors or efavirenz containing regimens if they were on treatment for tuberculosis with rifampicin containing regimens. Table 2 shows antiretroviral first line regimens (initial and at 2 years).

Table 1: Baseline patient characteristics

Patient characteristics at baseline	Number	Percentage
Age		
2-5 Years	51	18%
6-10 Years	119	43%
11-14 Years	108	39%
Gender		
Male	136	49%
Female	142	51%
WHO clinical stage classification		
Stage1	98	35%
Stage2	44	16%
Stage3	127	46%
Stage4	9	3%
Mean CD4 + Cells/mm^3		
<50	8	3%
50-100	7	2%
101-249	22	8%
250-349	16	6%
>350	225	81%
Mean CD4 %		
>25%	172	62%
15-25%	56	20%
<15%	50	18%
Mean viral load (copies/ml)		
>5000	145	52%
1000-5000	25	9%
>400-1000	88	32%
<400	20	7%

Table 2: Antiretroviral therapy at baseline and at two years of antiretroviral therapy

Antiretroviral regimen at ARV initiation	No(%)	Antiretroviral regimen at 2 years of ARV	No (%)
Zidovudine/ lamivudine/nevirapine	256(92%)	Zidovudine/ lamivudine/ nevirapine	190(70%)
Zidovudine/ lamivudine/efavirenz	6(2%)	Zidovudine/ lamivudine/ efavirenz	25(9%)
Zidovudine/ lamivudine/lopinavir/r	2(2%)	Zidovudine/ lamivudine/ lopinavir/r	8(3%)
Abacavir/lamivudine/ nevirapine	6(2%)	Abacavir/ lamivudine/ nevirapine	5(2%)
Abacavir/lamivudine/ efavirenz	5(2%)	Abacavir/ lamivudine/ efavirenz	30(11%)
Abacavir/lamivudine/ lopinavir/r	3(1%)	Abacavir/ lamivudine/ lopinavir/r	15(15%)
Total	278(100%)	Total	278(100%)

Adherence characteristics

The mean cumulative percentage adherence to drug-refill visits was 100± 12.44. In the 1st years, 75(27%) had poor adherence (<95%) while 203(73%) had good adherence (>95%) while in the 2nd year we had <95% 52(19%) and >95% 226(81%) respectively. Poor adherence (<95%)to drug refill visits (adjusted OR [AOR] 1.51; 95% CI: 1.20–3.01).(p<001) was significantly associated with virologic failure . Also poor adherence to drug refill (95%) was significantly associated with immunological failure (CD4 count <100 cells/mm^3) .

Immunovirological response

The viral loads at 6, 12, 18 and 24 months are significantly different from baseline counts (Table 3). There was therefore a decrease in the proportion of patients with virological failure as treatment progressed. After 12 months on antiretroviral therapy, 101(36 %) had failed virological (viral load > 400 copies/ml). One hundred and seventy seven patients (64%) achieved viral suppresion (viral load > 400 copies/ml) at 12 months.
However at 2 years (24 months) 17 patients (6.1%) who had been viral suppressed at 18 months had a viral blip at 24 months (VL ≥500 copies/ml). Table 3 also shows mean CD4 count, percentages, gain, immunological failure and recovery over time from baseline to 24 months. Discordant immunovirological responses following ART initiation occurred in 30% of patients at 2 years and was associated with baseline CD4 cell count <500, vl > 1000 and adherence <95 % . At 2 years, the median CD4 count was 826 cells/mm^3, and the median CD4 count was 29%. 10(4%) patients had CD4 <100cells , 38(14%) had CD4 <15% while 87 (31%) had VL/mm^3 >400copies/ml. Virologic response lagged behind Immunological response .

Viral blips were commoner in patients with low adherence (Table 4). After 12 months on antiretroviral therapy, 14(5%) of patients and 36(13%) failed immunologically (CD4 count <100cells/mm^3 and CD4%, 15% respectively). Tables 5, 6 and 7 show factors associated with virological and immunological failure. On multivariate analysis factors significantly associated with virological failure were baseline viral load >500 copies/ml (AOR 7.476; 95% CI 2.34-10.050) p=0.001, baseline CD4 count 101-249 cells/mm^3 (advanced immunosuppression) (adjusted OR [AOR] 0.215; 95% CI: 0.064-0.727). p-value (0.013) and poor adherence (<95%) (Adjusted OR [AOR] 1.51; 955 CI: 1.20-3.01) (p<001).
Low baseline CD4 counts (<350 cells/mm^3) and poor adherence to drug refill (95%) were significantly associated with immunological failure (CD4 count <100 cells/ml) while pre-initiation CD4 count 50-100mm^3 (severe immunosuppression) was significantly associated with immunological failure (CD4 <15%) at 1 year.

Table 3: Immunovirological responses at baseline and after 6, 12, 18 and 24months of antiretroviral therapy

Viral load (VL) (copies/ml	baseline	6 months*	12 months*	18 months*	24 months*
Mean viral load	130709±428	54268±155	38268±126	30040±105	52376±34
Proportion of children with viral load <400	87(31%)	160(58%)	177(64%)	186(67%)	191(69%)
Proportion of children with viral load >400	191(69%)	118(42%)	101(36%)	93(33%)	87(31%)
P-value		P<0.0001*	P<0.0001*	P<0.0001*	P<0.0001*
Immunological parameters					
Mean CD4+ cells/mm^3	902±652	953±692	1028±686	1070±722	1000±28
Mean CD4%	35.8±20	34.4±19	35±19	36±19	34±19
Mean CD4+ cells gain after ARV		52(5%)	126(14%)	168(19%)	98(11%)
Proportion of children with CD4 cells <100/mm^3	14(5%)	15(5%)	14(5%)	9(3%)	10(4%)
Proportion of children with CD4% <15%	48(17%)	47(17%)	36(13%)	38(14%)	38(14%)
Proportion of children with CD4% <25%	172(62%)	179(64%)	192(69%)	188(68%)	177(64%)

*P value $\leq$ 0.05 is statistically significant

Table 4: Factors associated with virologic blips at 24 months of antiretroviral therapy

Characteristics	Viral Blip No (%)	Viral Blip No (%)	X^2	P-value
Age Group			0.447	0.801
2-9 years	6(5)	136(95)		
10-14 years	8(7)	128(93)		
Gender			0.097	0.755
Male	9(7)	128(93)		
Female	8(6)	133(94)		
Weight (kg)			0.039	0.843
≤25kg	12(6)	190(94)		
≤25kg	5(7)	71(93)		
Adherence			2.284	0.131
≤95%	6(10)	52(90)		
≤95%	11(15)	209(95)		

Virologic Blips is higher among subjects with adherence <95%

Table 5 : Factors associated with virological failure(VL>400 copies/ml) at one year of antiretroviral therapy

Baseline characteristics	Number (%) 278(100%)	Virological failure	Adjusted odds ratio (95%, Confidence interval)	P-Value
Age				
2-5 Years	51(18%)	14(27%)	1.802(0.634-5.127)	0.269
6-9 Years	119(43%)	36(30%)	1.033(0.462-2.307)	0.937
Gender				
Female	146(53%)	42(29%)	1.614(0.776-3.356)	0.202
Male	132(47%)	46(35%)	0.170(0.11-2.568)	0.201
Baseline CD4 cells/mm^3				
<50	8(3%)	2(25%)	0.185(0.28-5.1225)	0.81
50-100	7(3%)	3(43%)	4.007(0.399-4.273)	0.24
101-249	22(8%)	4(18%)	0.215(0.064-0.727)	0.013*
250-349	16(6%)	6(38%)	1.046(0.250-4.525)	0.933
CD4 percentage				
>25	172(62%)	50(29%)	1.390(0.459-4.212)	0.561
15-25	56(20%)	23(14%)	1.420(0.571-3.528)	0.451
Baseline VL copies/ml				
>5000	145(52%)	66(46%)	7.476(2.34-19.050)	0.001*
1000-5000	25(9%)	6(24%)	2.646(0.653-10.721)	0.173
>400 - <1000	21(8%)	12(57%)	2.375(0.674-8.368)	0.178
Who stage				
Stage 1	98(35%)	23(23%)	0.934(0.131-6.638)	0.946
Stage 2	44(16%)	28964%)	1.014(0.137-7.500)	0.989
Stage 3	127(46%)	57(45%)	0.612(0.88-4.256)	0.621
TB at baseline				
Yes	8(3%)	5(63%)	0.392(0.125-1231)	0.109
Haemoglobin g/dl				
≤10	123(44.2%)	37(30%)	1.202(0.578-2.503)	0.622
WBC count				
≤400 x109/L	28(10%)	8(29%)	0.691(0.204-2.339)	0.622
Weight for age (WAZ)				
Malnourished	171(62%)	51(30%)	1.295(410-4.092)	0.661
Normal	74(27%)	23(8.2%)	0.998(0.274-3.633)	0.997
Adherence at one year				
<95%	75(27%)	25(38%)	151(1.20-3.01)	0.001*
Caretaker education				
No education	20(7%)	9(45%)	1.25(0.44-70.12)	0.79
Primary	170(61%)	30(18%)	1.80(1.06-3.01)	0.19
Secondary	58(21%)	35(60%)	2.40(1.32-4.20)	0.06
Disclosure (yes)	38(14%)	18(47%)	1.90(0.30-9.78)	0.703

Table 6: Factors associated with immunological failure(CD4<100cells/mm^3) at one year of antiretroviral therapy

Baseline patient Characteristics	Number (%)	Immunological failure Cd4 <100 cells/mm^3 at one year	Adjusted odds ratio (95%, confidence interval)	P-value
Age	278(100%)			
2-5 years	51(18%)	1(2%)	1.161(0.71-19.109)	0.917
6-9 years	119(43%)	8(8%)	5.393(0.842-34.534)	0.075
Gender				
Female	146(53%)	7(5%)	0.803(0.172-3.751	0.781
Baseline CD4 cells/mm^3				
<50	8(3%)	2(25%)	79.966(4.157-1499.987)	0.004*
50-100	7(3%)	3(43%)	166.569(11.865-2338.352)	0.001*
101-249	22(8%)	4(21%)	17.256(2.055-1455.388)	0.009*
250-349	16(6%)	2(13%)	22.228(1.814-272.418)	0.016*
CD4 percentage				
>25	172(62%)	9(5%)	0.284(0.41-1.973)	0.284
15-25	56(20%)	2(4%)	0.239(0.23-2.520)	0.239
Baseline VL copies/mm^3				
>5000	145(52%)	11(8%)	0.317(0.26-904)	0.369
1000-5000	25(9%)	1(4%)	0.527(0.33-8.338	0.649
>400 - <1000	21(8%)	19(90%)	1.327(0.77-22.833)	0.846
Who stage				
Stage 1	98(35%)	8(8%)	0.98(0.003-3.626)	0.207
Stage 2	44(16%)	1(2%)	0.280(0.008-9.566)	0.481
Stage 3	127(46%)	5(4%)	0.277(0.008-9.452)	0.476
TB at Baseline				
Yes	8(3%)	4(50%)	0.415 90.54-3.178	0.397
Haemoglobin g/dl				
≤10	123(44.2%)	7(6%)	1.201(0.234-6.154)	0.826
WBC count				
≤4.00 x 109/L	28(10%)	3(11%)	0.392(0.016-9.767	0.568
Adherence				
<95%	75(27%)	24(32%)	1.96(1.09-3.51)	0.004*
Weight for age (WAZ)				
Malnourished	171(62%)	9(5%)	0.545(0.62-4.796)	0.584
Normal	74(27%)	3(4%)	0.385(0.36-4.126)	0.43

*p ≤ 0.05 is statistically significant

Table 7: Factors associated with immunological failure (CD4 <15%) at one year of antiretroviral therapy

Baseline patient Characteristics	Number (%) 278(100%)	Immunological failure CD4 %<15%	Adjusted odds ratio (95%, Confidence interval)	P-value
Age				
2-5 years	51(18%)	6(12%)	1.269(0.356-4.525)	0.713
6-9 years	119(43%)	17(14%)	1.459(0.560-3.801)	0.439
Gender				
Female	146(53%)	15(10%)	0.579(0.241-1.392)	0.222
Male	132(47%)	21(16%)	1.321(0.880-19.787	0.841
Baseline CD4 cells/mm^3				
<50	8(3%)	2(25%)	4.022(0.491-33.009)	0.194
50-100	7(3%)	3(43%)	15.962(1.696-150.255)	0.015*
101-249	22(8%)	4(18%)	1.849(0.397-8.608)	0.434
250-349	16(6%)	3919%)	2.227(0.0101-1.569)	0.356
CD4 percentage				
>25	172(62%)	20(12%)	0.397(0.0101-1.569)	0.188
15-25	56(20%)	10(18%)	0.743(0.272-2.027)	0.562
Baseline VL copies/ml				
>5000	145(52%)	24(17%)	0.42(0.134-1.310)	0.135
1000-5000	25(9%)	2(8%)	1.963(0.46-9.480)	0.401
>400 - <1000	21(8%)	19(90%)	0.547(0.88-3.403)	0.517
Who stage				
Stage 1	98(35%)	1(1%)	0.019(0.001-0.268)	0.003
Stage 2	44(16%)	8(18%)	0.673(0.101-4.483)	0.693
Stage 3	127(46%)	7(6%)	0.677(0.104-4.421)	0.684
TB AT baseline				
YES	8(3%)	7(88%)	0.331(0.097-1.124)	0.076
Haemoglobin g/dl				
≤10	123(44.2%)	14(11%)	0.792(0.307-2.046)	0.631
WBC count				
≤4. 00 x 10 9/L	28(10%)	4(14%)	0.672(0.139-3.263)	0.622
Weight for age (WAZ)				
Malnourished	171(62%)	23(13%)	1.381(0.324-5.887)	0.662
Normal	74(27%)	10(14%)	1.800(0.353-9.169)	0.479

*p ≤ 0.05 is statistically significant

Discussion

The use of a potent combination of antiretroviral drugs has led to reductions in the morbidity and mortality associated with human immunodeficiency virus (HIV)-1 infection. Antiretroviral therapy can reverse HIV-related growth failure with a significant reduction in HIV-related morbidity and mortality [17,]

In this retrospective study we report immune-virological outcomes in paediatric patients receiving antiretroviral agents for 2 years. The median age at antiretroviral therapy initiation in this study was 8 years. Early antiretroviral initiation is recommended in all children aged <5 years before growth failure and severe immunosuppression sets in and this prevents growth failure and opportunistic infections[18,19]

After one year of antiretroviral therapy, 36% of the children had virological failure (viral load > 400 copies/ mL). Five percent (CD4count <100 cells/ mm^3) and thirteen percent (CD4 count < 100 cell /mm^3) of the children failed immunologically. Previous reports indicate that within two years of first-line ART initiation, 33-38% of children experience virological failure and those on NNRTI-based regimens, have shown lower (19-20%) rates of virological failure at 12 months[20,21]. These findings are also similar to results of a meta-analyses on VL suppression on NNRTI-based first-line ART in children (60%–70%) in low- and middle-income countries [22]. Different limits of quantification and variations in definitions of virological failure as a VL of 400, 1000 or 5000 copies/ml at one or two repeated visits in different studies may be responsible for different rates observed in literature[23-25]. Failure to achieve virological suppression may be due to the presence of HIV species resistant to antiretroviral drugs including maternally transmitted resistant strains or inadequate adherence, amongst other factors [26]

Virological failure was significantly more common in patients with baseline viral load >5000 copies/ml, low baseline CD4 count and poor adherence. This finding is consistent with earlier observations which suggest that infants and young children often present high viral load and that it will take longer to fully suppress viral replication[27.] Surprisingly, non-disclosure of the child's status was not associated with virological failure. Disclosure of the child's HIV status should be done when the child is old enough to understand the information and this should be accompanied by appropriate health education and counselling to ensure a positive impact on adherence to therapy and treatment outcomes. Other factors such as weight and gender were not significant in this study. Limited paediatric data suggest that underlying malnutrition may not adversely affect immunologic and virologic response to antiretroviral therapy. In addition to sustained adherence which results in optimal therapeutic drug levels, several factors including gender of the child, lower CD4 counts, longer duration on antiretroviral therapy, genetic variants, co-infection with tuberculosis and lower baseline weight have all been demonstrated to affect virological suppression [28] .

Viral blips (temporary , detectable increase in the amount of HIV in the blood (viral load) that occurs after antiretroviral therapy (ART) has effectively suppressed the virus to an undetectable level) and rebound (persistent , detectable levels of HIV in the blood after a period of undetectable levels) has been associated with a poorer clinical outcome [29]. In this study, 6.1% of patients had virologic blips at 24 months. Several retrospective and prospective studies have demonstrated that blips are common, with the percentage of patients who experience a blip over time ranging from 10% to 40%. Previous reports show that among patients who reach an undetectable viral load in the early course of therapy 20 to 53% have a subsequent virological rebound, i.e. an increase in viral load above the detection. The cause of viral blips and rebound is likely multi-factorial and several contributing factors have been proposed to explain detection of intermittent low-level viral loads. These include emergence of mutant resistant viruses, with detection of persistent or intermittent low-level releases of virus from existing reservoirs, random laboratory variation, laboratory test and operator error, poor and decreased adherence to antiretroviral therapy, immunization or intercurrent illness, and insufficient antiretroviral drugs threshold.[30-32]

In the present study, virologic blips were higher among subjects with adherence <95%(although not statistically significant), however the association between viral blips and either age, weight, or gender was not significant. There are concerns that measurable virologic blips and rebound viremia may represent an increased risk for subsequent drug resistance and treatment failure. Viral rebound has been associated with increased drug resistance and has been shown to occur more often in patients with high baseline HIV RNA and low baseline CD4 cell count (less than 350 cells/mm^3).[33]

Despite an adequate immunological response, about 30% of patients in this study did not achieve an adequate virologic response. In previous studies, discordant response to therapy occural in 20 to 40% of treated patients, with isolated immunological response being slightly more common than isolated virologic response. The mechanisms by which CD4 cell counts are maintained in the face of ongoing viral replication are not known, but they may include decreased viral replication capacity, impaired viral replication in thymic tissue, decreased cell death by activation-induced apoptosis, or regeneration of HIV-specific immune responses[34-36].

The CD4 absolute count is the most important laboratory indicator of immune function in patients with HIV and is highly variable. CD4 percentage remains stable and may be more appropriate parameters to assess a child's immune function. The follow up of patients on antiretroviral therapy in various countries without uniform guidelines on clinical, immunological and virological criteria had resulted in early or late switching for second line drugs [24] .

Progression of HIV is faster in children than in adults. Differences between absolute CD4 lymphocyte count and CD4 lymphocyte percentage may represent a type of

immune discordance. A relatively high absolute CD4 lymphocyte count and a low CD4 lymphocyte percentage may occur in 8%-10% of untreated HIV-infected patients. This has potentially important clinical implications. Therefore, some investigators have argued that since the CD4 lymphocyte percentage is directly measured and is less variable over time, it may be a better marker for monitoring patients than the absolute CD4 lymphocyte count [37-39].

In this study, in all age groups there was an improvement in CD4 t-lymphocyte cell indices and during the first year on antiretroviral therapy. The patients had high baseline CD4 counts. Previous studies suggest that HIV patient with high CD4 cell count at the time of ART initiation may be at greater risk of treatment attrition. Patient education and healthcare provider training on the importance of ART adherence in patients with high pre-initiation CD4 counts should be enhanced [40,41]. The finding that low baseline CD4 counts and poor adherence were significantly associated with immunological failure is supported by several other studies. HIV-infected children who start antiretroviral therapy at lower CD4% reach lower peak CD4 levels perhaps from persistent effects of chronic immune activation. Antiretroviral therapy initiation at younger ages is associated with better immunologic recovery[42-44]
It is estimated that 90% of these children would have experienced CD4% recovery to normal within 4 years, and 80% would have had a normal CD4% at 4 years. Biologically, it is expected that relationships between CD4% recovery and age plateau because the thymic potential stabilizes as children approach adult immune maturity. Early diagnosis and treatment for HIV-infected children before they reach a stage of profound immunodeficiency is very important and this finding will guide clinicians in assessing immunologic response to non-nucleoside reverse transcriptase inhibitor-based antiretroviral in HIV infected children [45,46].

Conclusion

The treatment outcomes observed in this study were similar to those reported in earlier studies. Immunological restoration and viral suppression can be achieved and sustained after two years of antiretroviral among children in resource-constrained settings. The high rates of virological failure observed despite good adherence to therapy calls for early introduction and switch to 2nd and third line drugs. The clinical relevance of the observed virological blips, discordant immunovirological responses, needs further investigations in larger studies. Good adherence and caregiver training needs to be sustained .

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