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Risk Factors for First-line Antiretroviral Treatment Failure in HIV-1 Infected Children Attending Jos University Teaching Hospital, Jos, North Central Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author AOE performed conception, design, data analysis/ results, manuscript writing, revision and patient care. Authors SO, EUE, SEO performed manuscript revision and patient care. Authors OOA, SAS, PO, JAI, PK performed manuscript revision. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: To determine risk factors for first-line antiretroviral treatment failure in HIV-1 infected children attending Jos University Teaching Hospital, Jos.
Study Design: Retrospective cohort study.
Place and Duration of Study: Paediatric HIV clinic at the Jos University Teaching

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Hospital, Jos, between February 2006 and December 2010.
Methodology: Data on demographic, clinical and laboratory variables for 580 HIV-1 infected children aged 2 months to 15 years on antiretroviral therapy (ART) were analysed. A comparison of the data on children with and without treatment failure was made. Variables associated with treatment failure in a univariate analysis were then fit in a multivariate logistic model to determine the factors that were associated with treatment failure.
Results: The rate of treatment failure among the children was 18.8%. Previous antiretroviral drugs (ARV) exposure for treatment, not receiving cotrimoxazole prophylaxis before commencement of ART and having severe immune suppression at HIV diagnosis were the factors independently associated with treatment failure. Children with previous ARV exposure for treatment were 4 times more likely to fail treatment compared to those without previous exposure (AOR=4.20 (1.93-9.15); p <0.001). Children who did not receive cotrimoxazole prophylaxis were twice more likely to develop treatment failure compared to those who did (AOR=2.26 (1.06-4.79); p=0.03) and children with severe immune suppression at HIV diagnosis were twice more likely to develop treatment failure compared to those without severe immune suppression (AOR=2.34 (1.47-3.72); p<0.001).
Conclusion: HIV-infected children with previous ARV exposure for treatment and severe immune suppression should be monitored closely and given frequent adherence counseling to minimize the risk of treatment failure. Cotrimoxazole prophylaxis should be encouraged in HIV-infected children while they await commencement of ART, which may improve ART adherence and thus reduce the risk of treatment failure.

Keywords: HIV-1; antiretroviral; treatment failure; cotrimoxazole prophylaxis; ARV exposure; paediatric ART; Africa.

1. INTRODUCTION

Human immunodeficiency virus (HIV) infection and Acquired immunodeficiency syndrome (AIDS) remain an important health problem in sub-Saharan Africa (SSA) [1] with an estimated 2.9 million children living with HIV/AIDS in 2012; of which only 34% of them were receiving anti-retroviral therapy (ART) [2]. A 2010 estimate indicated that Nigeria had 440,000 children below the age of 15 years living with HIV/AIDS [3] of which 280,000 were eligible for ART, however only 7% were receiving it [4].The benefits of ART in children, which includes reduction in morbidity and mortality, are well documented [5-9]. But these benefits could be greatly compromised by ART failure in children on first-line antiretroviral drugs (ARVs). With more countries scaling-up ART in the sub-region, there is the possibility of more children developing ART failure. In children, first-line ART failure rate was reported as: 2.3% in Burkina Faso (with a mortality rate of 25% in these children) [10]; less than 1% in Rwanda [11] and 5.8% in South Africa [12].

Treatment failure is the suboptimal response or the lack of a sustained response to ART, which can be determined using clinical, immunologic or virologic criteria, either singly or in concert [13,14]. Socio-demographic, clinical, immunologic with virologic factors and poor adherence to treatment have been shown to be associated with ARV treatment failure in children [15-20]. ARV drug resistance is also another factor [21-25].

Though there are a number of published studies on factors associated with first-line ART failure in SSA [15-17,19,20], such data are scarce in Nigeria. In this study we identified the risk factors for first-line ART failure in children at time of HIV diagnosis prior to the start of ART. Identifying such factors before treatment begins could be of potential benefit in reducing the frequency of subsequent treatment failure.

2. METHODOLOGY

2.1 Study Site and Population

The study site was the paediatric HIV clinic at the Jos university teaching hospital (JUTH), Jos. This clinic provides comprehensive HIV care services for the city of Jos, which is located in the Jos North Local Government Area (LGA) of Plateau State and serves as a referral centre for health facilities in other LGAs of the state as well as some neighbouring states. The population of the state was estimated at 3,206,531 in the 2006 census, with the state capital having a population of approximately 900,000 [26].

2.2 Study Subjects

Children aged 2 months -15 years diagnosed with HIV-1 infection at presentation to the HIV clinic that were subsequently commenced on ART.

2.3 Study Design

This was a retrospective cohort study analysing data on 580 children who were consecutively enrolled on ART between February 2006 and December 2010. A written informed consent was obtained from the parents/ guardians of the children for use of the data for research as approved by the Ethics committee of the Jos University Teaching Hospital, AIDS Prevention Initiative in Nigeria (APIN) Ltd, Abuja and Harvard School of Public Health, Boston, USA. The data obtained included baseline data as at the time of HIV diagnosis prior to the commencement of ART including the following variables: demographic (age, sex), clinical (previous use of ARVs, use of cotrimoxazole for opportunistic infection (OI) prophylaxis, WHO HIV clinical stage, and oral thrush) and laboratory (viral load, CD4 absolute cell count and percentage CD4 count).The diagnosis of HIV and the criteria for commencement of ART in children was based on the Nigerian National Guidelines for Paediatric HIV and AIDS Treatment and Care [13]. Data on treatment failure was also obtained. Treatment failure was either virological or immunological or both; with or without clinical failure and defined using the National guidelines for Paediatric HIV and AIDS Treatment and Care [13] as follows:

1. Virological failure is persistent viral load higher than 5,000 RNA copies per ml after at least 24 weeks on ART, in a treatment-adherent child.
2. Immunological failure is the development or return to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:

    - CD4 count of <200 cells/mm3 or %CD4+ <10 for a child ≥2 years to <5 years of age.
    - CD4 count of <100 cells/mm3 for a child 5 years of age or older.

3. Clinical treatment failure was diagnosed when either new or recurrent stage 3 or 4 clinical events developed in a child on ART.

At the time of establishing treatment failure, all the children had been on ART for at least 6 months. HIV infected children and perinatally HIV exposed infants (awaiting DNA PCR confirmation of their HIV status) were placed on daily cotrimoxazole prophylaxis for opportunistic infections (OIs) before and during ART according to the programme protocol [13].

Previous ARV exposure for treatment was defined in this study as previous treatment elsewhere with either Zidovudine (AZT) + Lamivudine (3TC) or AZT + 3TC + Nevirapine (NVP) prior to enrolment into our ART programme. Some of the children were also referred to our facility from other facilities for further evaluation and care. Previous ARV exposure for prevention of mother-to child-transmission (PMTCT) was defined as the use of single dose NVP (sd NVP) intrapartum or AZT + NVP in the neonatal period for 6 weeks.

In this study the interruption of ART was defined as failure to take medications once or more than once during the first one month of commencing ART; for reasons ranging from: forgot to take medication, caregiver travelled and medicine not available or too costly (before August 2005 patients had to buy their ARVs from drug stores outside the hospital).

2.4 Laboratory Methods

All laboratory tests performed were part of the existing HIV treatment programme. For HIV serodiagnosis, two different rapid HIV tests - Uni-Gold (Trinity Biotech Plc Bray Co.; Wicklow, Ireland) and Determine (Determine Alere Medical Co. Ltd.; Matsuhidai, Japan) HIV-1/2 tests were used for children 18 months of age and above. For children under 18 months of age, Amplicor HIV-1 DNA PCR test, version 1.5 (Roche Molecular Systems; Branchburg, NJ, USA) was used to diagnose HIV infection. Flow cytometry (Partec GmbH, Munster Germany) was used to measure the CD4+ lymphocyte count and Roche Cobas Amplicor HIV-1 Monitor, version 1.5 (Roche Diagnostics GmbH, Mannheim, Germany) was used to measure HIV-1 RNA viral load.

2.5 Statistical Methods

The outcome variable, a binary variable, was first-line antiretroviral treatment failure. Children who failed treatment after at least 6 months of ART were compared with those who did not. All other variables were considered as independent variables. The z scores were determined from the weight and height of the children, adjusted for age and sex, using the WHO AnthroPlus software [27] by importing the variables - weight, height, age and sex in the form of a text file into the software. The weight-for-age z scores (WAZ) were then categorized into a binary variable using the WHO cut-off of $Z < -3$ and $WAZ < -3$ was defined as acute severe malnutrition [28]. The immune status of each child was determined from the absolute CD4+ cell count using the Centers for Disease Control and Prevention (CDC) definition [29], where counts of <750/mm3 for children < 1year, <500/mm3 for those 1–5 years and, <200/mm3 for those > 5 years were considered as severe immune suppression – this variable was then used in our analysis as a binary categorical variable.

The association between each independent variable and the outcome was examined using the Chi squared or Fisher's exact test for categorical variables while the Wilcoxon-Mann-

Whitney test was used for comparison of two medians. Univariate logistic regression was also used to examine the association between the independent variables and outcome with the results expressed as odds ratios with their 95% CIs. Variables that were associated with treatment failure in the univariate analyses at p<0.05 were fit in a multivariate logistic regression model. Age and sex were included a *priori* in the multivariate model since these could influence disease processes. A forward stepwise modelling strategy was used in building the final multivariate model. The area under the receiver operating characteristic (ROC) curve was determined to assess the performance of the model. All analyses were performed using Stata software version 10.0 (Stata Corporation, College Station, Texas, USA) and all tests were two-sided with a p-value of <0.05 considered statistically significant.

3. RESULTS

Of the 580 HIV-1 infected children that were placed on first-line ARVs, 109 (18.8%) developed treatment failure over the 5 years period of observation. The median age of the children was 3.5 years (IQR, 1.8 – 6.6 years). Majority were below the age of 6 years (64%) and were not on cotrimoxazole prophylaxis prior to commencing ARVs (82.9%).The proportion of males (50.9%) and females (49.1%) was similar. There were 42.9% children with severe immune suppression, 41.4% with WHO clinical stage 3/4, 23.1% with severe malnutrition, 7.4% with previous ARV exposure for treatment, 9.5% with previous ARV exposure for PMTCT, 4.8% with mild anaemia and 3.4% with oral thrush. Only 4.7% of children interrupted their ART more than once. The most common reasons for interruption were: forgot to take drug, drugs were finished or care giver travelled. The median viral load of the children was 38,597 copies/mL (IQR, 4145-170133 copies/mL) while the median absolute CD4+ cell count was 478 cells/mL (IQR, 267-794 cells/mL) with the median absolute CD4+ cell count of those with treatment failure being lower: 423 (IQR, 194-646 cells/mL) compared to those without treatment failure: 506 (IQR, 288-818 cells/mL), the difference being significant, p=0.006 (Table1). The proportion of children who failed treatment was significantly higher compared to those who did not, prior to 2006 (25.7% vs 12.3%) in contrast to no difference between the two groups, after 2006 (74% vs 87%), P<0.001 (Table 1).

Univariate analysis showed that previous ARV exposure for treatment, not receiving cotrimoxazole prophylaxis and severe immune suppression were significantly associated with treatment failure, p=0.001, p<0.001 and p=0.001 respectively, but not previous ARV exposure for PMTCT (p=0.74) (Table1). Similarly, in the unadjusted logistic regression analyses, the variables significantly associated with treatment failure included: previous ARV exposure (OR=3.06 and p=0.001), not re ceiving cotrimoxazole prophylaxis (OR=9.97 and p=0.002) and having severe immune suppression at HIV diagnosis (OR=2.11 and p=0.001) but previous ARV exposure for PMTCT was not associated with treatment failure (OR=1.12 and P=0.74) (Table 2).

In the multivariate analyses, children with previous ARV exposure were 4 times more likely to develop treatment failure compared to those without previous ARV exposure, (Adjusted Odds Ratio (AOR) = 4.2; 95% confidence interval (95% CI) (1.93-9.15); p <0.001). Children who did not receive cotrimoxazole prophylaxis were about twice more likely to develop treatment failure compared to those who did (AOR= 2.26; 95% CI (1.06-4.79); p=0.03) and children with severe immune suppression at HIV diagnosis were about twice more likely to develop treatment failure compared to those without severe immune suppression (AOR =

2.34; 95% CI (1.47-3.72); p<0.001). (Table 2).The area under the ROC curve for the final model was 0.70.

Table 1. Baseline characteristics of children with first-line antiretroviral treatment failure

Characteristics	Subjects	Treatment failure		
	Total	Yes	No	P value*
	N (%)	N (%)	N (%)	
Age (yrs)				0.69
<1	73 (12.6)	15 (13.8)	58 (12.4)	
1-5	297 (51.4)	58 (53.2)	239 (51.0)	
6-10	147 (25.4)	23 (21.1)	124 (26.4)	
>10	61 (10.6)	13 (11.9)	48 (10.2)	
Median (IQR)	3.5 (1.8-6.6)	2.6 (1.7-7.5)	3.7 (1.8-6.6)	0.49**
Sex				0.11
Male	295 (50.9)	63 (57.8)	232 (49.3)	
Female	285 (49.1)	46 (42.2)	239 (50.7)	
Previous ARV exposure for treatment				0.001
Yes	40 (7.4)	16 (15.2)	24 (5.5)	
No	498 (92.6)	89 (84.8)	409 (94.5)	
Previous ARV exposure for PMTCT				0.74
Yes	53 (9.5)	11 (10.4)	42 (9.3)	
No	503 (90.5)	95 (89.6)	408 (90.7)	
Cotrimoxazole prophylaxis				<0.007
Yes	99 (17.1)	9 (8.3)	90 (19.1)	
No	481 (82.9)	100 (91.7)	381 (80.9)	
WHO clinical stage				0.42
1/2	335 (58.6)	67 (62.0)	268 (57.8)	
3/4	237 (41.4)	41 (38.0)	196 (42.2)	
Oral thrush				0.06
Present	20 (3.4)	7 (6.4)	13 (2.8)	
Absent	559 (96.6)	102 (93.6)	457 (97.2)	
Haemoglobin level				0.65
<8 g/dL	26 (4.8)	4 (4.0)	22 (5.0)	
≥8 g/dL	513 (95.2)	97 (96.0)	416 (95.0)	
WAZ				0.82
≤-3.0	120 (23.1)	23 (24.0)	97 (22.9)	
>-3.0	400 (76.9)	73 (76.0)	327 (77.1)	
Severe immune suppression				0.001
Present	230 (42.9)	59 (57.8)	171 (39.4)	
Absent	306 (57.1)	43 (42.2)	263 (60.6)	
Interruption of ART†				0.11
Once	450 (95.3)	98 (92.5)	352 (96.2)	
More than once	22 (4.7)	8 (7.5)	14 (3.8)	
Year of enrollment in programme				<0.001
2005	86 (14.8)	28 (25.7)	58 (12.3)	
2006-2010	494 (85.2)	81 (74.3)	413 (87.7)	
HIV RNA viral load (copies /ml)				
Median (IQR)	38597 (4145-170133)	50978 (3985-255586)	37547 (4145-156108)	0.52**

Table 1 Continued……

HIV RNA log viral load (copies /ml)				
<10.5				
≥10.5	182 (48.8)	30 (44.8)	152 (49.7)	0.47
Median (IQR)	191 (51.2)	37 (55.2)	154 (50.3)	
	10.56 (8.33-12.04)	10.8 (8.30-12.45)	10.53 (8.23-11.95)	0.52**
Absolute CD4+ cell count (per mm^3)				
Median (IQR)	478 (267-794)	432 (194-646)	506 (288-818)	0.006**
Percentage CD4+ cell count				
Median (IQR)	17 (11-25)	15 (8-21)	17 (12-26)	0.01**

**P value for Chi squared or Fisher's exact test for the association between categorical variables and treatment failure.*

***P value for Wilcoxon rank sum test for comparison of two medians.*

†This was the only non baseline characteristic examined in this study.

WAZ = Weight-for-age z score

Table 2. Risk factors for first-line antiretroviral treatment failure

Risk factor	% ART Treatment Failure	Crude OR (95% CI)	P Value	Adjusted OR* (95% CI)	P Value
Age (yrs)					
Per 1 yr increase in age		1.00 (0.94-1.05)	0.78	0.97 (0.91-1.04)	0.37
Sex					
Female	42.2	1.00 (Ref)		1.00 (Ref)	
Male	57.8	1.41 (0.93-2.15)	1.09	1.49 (0.93-2.47)	0.09
Previous ARV exposure for treatment					
No	84.8	1.00 (Ref)		1.00 (Ref)	
Yes	15.2	3.06 (1.56-6.00)	0.001	4.20 (1.93-9.15)	<0.001
Previous ARV exposure for PMTCT					
No	503 (90.5)	1.00 (Ref)			
Yes	53 (9.5)	1.12 (0.56-2.26)	0.74		
Cotrimoxazole prophylaxis					
Yes	8.3	1.00 (Ref)		1.00 (Ref)	
No	91.7	2.62 (1.28-5.40)	0.009	2.26 (1.06-4.79)	0.03
WHO clinical stage					
1/2	62.0	1.00 (Ref)			
3/4	38.0	0.84 (0.54-1.29)	0.42		
Oral thrush					
Absent	93.6	1.00 (Ref)			
Present	6.4	2.41 (0.94-6.20)	0.07		
Haemoglobin level					
≥8 g/dL	96.0	1.00 (Ref)			
<8 g/dL	4.0	0.78 (0.26-2.31)	0.65		

Table 2 Continued…

WAZ					
≥-3.0					
<-3.0	76.0	1.00 (Ref)			
	24.0	1.06 (0.63-1.79)	0.82		
Severe immune suppression					
Absent	42.2	1.00 (Ref)		1.00 (Ref)	
Present	57.8	2.11 (1.36-3.27)	0.001	2.34 (1.47-3.72)	<0.001
Interruption of ART†**					
Once	92.5	1.00 (Ref)			
More than once	7.5	2.05 (0.84-5.03)	0.12		
Year of enrolment in programme**					
2006 - 2010	74.3	1.00 (Ref)			
2005	25.7	2.50 (1.48-4.10)	0.001		
HIV RNA Log viral load (copies /ml)					
<10.5	44.8	1.00 (Ref)			
≥10.5	55.2	0.82 (0.48-1.40)	0.47		

** Adjusted ORs for risk factors that remained in the final model.*
***These variables were not used in the multivariate modeling.*
†This was the only non baseline characteristic examined in this study.
WAZ = Weight-for-age z score.

4. DISCUSSION

Previous ARV exposure for treatment, not receiving cotrimoxazole prophylaxis before commencement of ART and having severe immune suppression at HIV diagnosis were the risk factors for failing first-line ART.

In our study we found a very strong association between treatment failure and previous ARV exposure for treatment which was similar to the findings of Rath et al. that children exposed to erratic ARV treatment from other facilities without a well established ART programme had a significant risk of developing treatment failure [22]. We found that, the proportion of children who failed treatment was significantly higher compared to those who did not prior to 2006 (25.7% vs 12.3%) in contrast to no difference between the two groups after 2006 (74% vs 87%), P<0.001 (Table 1). Before August 2005, the ARVs for the children were obtained outside the hospital by care givers because the ARVs were not yet provided free by the programme. This implies that the ARVs could have been used erratically since it was expensive buying them at that time, resulting in poor adherence and hence treatment failure. The mechanism of ART treatment failure associated with previous ARV exposure is explained by the development of ARV drug resistance [21-25].

The lack of an association between previous ARV exposure for PMTCT and treatment failure that we noted in our analysis, may be due to the very small proportion (53/503 = 9.5%) of our study subjects having previous ARV exposure for PMTCT. This was in contrast to the well recognized fact that the use of single dose NVP for PMTCT can lead to drug resistance that would compromise first line regimens; one recent study illustrates this [30]. We did not determine the length of time since the exposure and it is known that associated drug resistance mutations will decrease with time [30].

We found that HIV infected children on cotrimoxazole were less likely to have treatment failure and this finding was similar to that of Biadgilign et al. [20].This may be because being on cotrimoxazole prophylaxis had already familiarized the children and caregivers to good adherence to ART which is important in preventing treatment failure. Several studies have shown an association between poor adherence and treatment failure [17,20,23].

The finding of severe immune suppression at HIV diagnosis being a risk factor for subsequent treatment failure was similar to that of Rath et al. who demonstrated that advanced immunosuppression at baseline was a very strong correlate of subsequent treatment failure in Peruvian children [22]. Also, Bacha et al. showed that a CD4+ cell count below 50 cells/mm3 at baseline was an important predictor of treatment failure in a cohort of Ethiopian children [19]. The possible explanation for the increased likelihood of treatment failure with severe or advanced immune suppression is the increased risk of OIs that occur in such children which could further impair good responses to ART.

One of the limitations of our study was our inability to consider ART adherence during follow-up visits since we only used subject characteristics at baseline in our analysis. Thus, treatment adherence which we did not determine could be a potential confounder for treatment failure. But an indirect indicator of treatment adherence that we were able to determine was the number of times ART was interrupted during the first one month of commencing ART. Since we did not find any significant association between treatment failure and interruption of ART in our univariate analysis (Tables 1 and 2) we could assume that adherence was not a potential confounder.

5. CONCLUSION

At the time of HIV diagnosis prior to the commencement of ART, previous ARV exposure for treatment, not receiving cotrimoxazole prophylaxis and severe immune suppression were identified as the risk factors for subsequent development of treatment failure. Children diagnosed with HIV who have had a previous ARV exposure for treatment and have severe immune suppression should be monitored closely and given frequent adherence counseling to minimize the risk of ARV treatment failure. Cotrimoxazole prophylaxis should be encouraged in children diagnosed with HIV while they await commencement of ART as doing so may prime them for a better ARV adherence and thus reduce the risk of treatment failure.

CONSENT

A written informed consent was obtained from the parents/ guardians of the children for use of their data for research.

ETHICAL APPROVAL

The research was approved by the Ethics committee of the Jos University Teaching Hospital, AIDS Prevention Initiative in Nigeria, Abuja and Harvard School of Public Health, Boston, USA.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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