ORIGINAL ARTICLE

Factors associated with antiretroviral treatment interruption in human immunodeficiency virus (HIV)-1-infected children attending the Jos University Teaching Hospital, Jos, Nigeria

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ABSTRACT

Background: Interrupting anti-retroviral therapy (ART) for any number of reasons is an indication of a compromised adherence to ART. Several factors, including the pill burden from other drugs used in treating co-infections in children with human immunodeficiency virus (HIV), may influence ART adherence. The aim of this study was to identify the factors associated with ART interruption in HIV-1-infected children. **Materials and Methods:** A retrospective cohort study analysing data on 580 children consecutively enrolled on ART between February 2006 and December 2010 at the paediatric HIV clinic of Jos University Teaching Hospital (JUTH), Jos. Subjects were children aged 2 months — 15 years diagnosed with HIV-1 infection and on first-line ART. Cotrimoxazole prophylaxis was usually commenced at diagnosis while awaiting ART commencement. Children diagnosed with tuberculosis (TB) were also placed on multiple individual anti-TB drugs. **Statistical analysis used:** A comparison of the data on children with and without ART interruption was made. Variables associated with ART interruption in a univariate analysis were fit in a multivariate logistic model to determine the factors that were associated with ART interruption. **Results:** Children on anti-TB drugs were twice more likely to interrupt ART compared to those who were not, (adjusted odds ratio, AOR = 1.84 (1.03-3.28); *P* = 0.04). But children on cotrimoxazole prophylaxis had a 57% reduction in the odds of interrupting ART compared to those who were not, (AOR = 0.43 (0.20-0.93); *P* = 0.03). **Conclusion:** Children on ART and also taking multiple individual anti-TB drugs should be monitored closely for ART adherence. Cotrimoxazole prophylaxis should be encouraged in children diagnosed with HIV while awaiting ART commencement as this may prime them for a better ART adherence.

Key words: ART interruption, anti-TB drugs, ART adherence, cotrimoxazole prophylaxis, HIV-1, Pill burden.

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INTRODUCTION

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) continues to constitute a major health problem in sub-Saharan Africa (SSA) where it is estimated that 2.9 million children were currently living with HIV/AIDS in 2012.[1] Only 34% of these children are currently on anti-retroviral therapy (ART).[2] In 2010, Nigeria had about 440,000 children below the age of 15 years living with HIV/AIDS[3] of which 280,000 were eligible for ART but only 7% were receiving ART.[4] In children, the benefits of ART include the reduction in morbidity and mortality.[5-9]

Interrupting ART for any reason, which could lead to poor ART adherence, may encourage the development of resistance to antiretroviral drugs (ARVs).[10] Poor adherence[11-13] and drug resistance[13,14] are known to be associated with ART failure which could compromise the benefits of ART in children.

Access this article online

Quick Response Code:

Website: www.nigeriamedj.com

DOI: 10.4103/0300-1652.149170

Interrupting ART is an indication of a compromised adherence to ARVs. Socio-economic, cultural, behavioural and clinical[12,15-20] factors have been reported to be associated with poor ART adherence in children. Few studies[12] have looked at the influence of other medications taken along with ARVs, on adherence to ART. Also, pill burden may affect adherence to ART[16]; with one study showing that, the rate of adherence improves when the pill burden is low.[21] Drugs, such as cotrimoxazole, used for prophylaxis against opportunistic infections (OIs) and anti-tuberculosis (anti-TB) drugs, are commonly used in children with HIV/AIDS and these may affect ART adherence. In this study, we determined the factors associated with ART interruption in HIV-1 infected children attending the HIV clinic at the Jos University Teaching Hospital, Jos.

MATERIALS AND METHODS

This was a retrospective cohort study which analysed data on 580 children who were consecutively enrolled on ART between February 2006 and December 2010. Study subjects were children aged 2 months — 15 years diagnosed with HIV-1 infection at presentation to the AIDS Prevention Initiative in Nigeria (APIN)-supported paediatric HIV clinic at the Jos university teaching hospital (JUTH), Jos, Nigeria and who were subsequently commenced on first-line ART. 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.

The data obtained included the following: Demographic (age and sex); clinical (the use of cotrimoxazole for opportunistic infections prophylaxis, treatment with anti-TB drugs, treatment with ARVs, World Health Organisation (WHO) HIV clinical stage, oral thrush and weight-for-age z score (WAZ)) and laboratory (haemoglobin (Hb) level, viral load, absolute cluster of differentiation 4 (CD4) cell count). In this study, ART interruption was defined as failure to take medications (missed more than 2 doses or missed more than 1 day of ART) during any 4 weeks follow-up period. Each child had a total of seven follow-up visits over a period of 8 months since starting ARVs. And the common reasons for interrupting treatment include: Forgot to take medication, caregiver travelled and medicine not available.

The diagnosis of HIV and the criteria for commencement of ART in children was based on the Nigeria's National Guidelines for Paediatric HIV and AIDS Treatment and Care.[22] 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 Nigeria national guidelines for paediatric HIV and AIDS treatment and care.[22] The diagnosis of TB was based on WHO guidelines for the management of TB in children.[23]

Medications used by study subjects: At diagnosis of HIV infection, prior to starting ART, all children were usually commenced on cotrimoxazole for prophylaxis against OIs. Children diagnosed with HIV were placed on first-line ART which could be any one of the following combinations: Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) or AZT + 3TC + Efervirenz (EFV); and the dosing regimen were twice a day for AZT, 3TC & NVP or once a day for EFV.[22] HIV-positive children diagnosed with TB were placed on a multiple individual anti-TB drugs at the time of this study (2005-2010) and not fixed dose combination (FDC) drugs which were only recently introduced in 2012. These individual anti-TB drugs, which were taken separately, include: Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E). For the treatment of pulmonary TB (PTB), the children received all four of the single drugs for 2 months in the intensive phase and two of the single drugs (R and H) for 4 months in the continuation phase; the dosing regimen being once a day. The duration of treatment varies with the other forms of TB.[23]

Laboratory investigations done were part of the existing HIV treatment programme. HIV serodiagnosis, was done using two different rapid HIV test — 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. Amplicor HIV-1 deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) test, version 1.5 (Roche Molecular Systems; Branchburg, NJ, USA) was used to diagnose HIV infection in children under 18 months of age. 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 ribonucleic acid (RNA) viral load.

Statistical analyses

ART interruption was the outcome variable (a binary variable). Children who had ART interruption were compared with those who did not. All other variables were regarded as independent variables. The weight-for-age z score (WAZ) was determined from the weight of the children, adjusted for age and sex, using the WHO AnthroPlus software[24] by importing the variables — weight, age and sex in the form of a text file into the software. The WAZ was then categorised into a binary variable using the WHO cut-off of Z < –3 with WAZ < –3 defined as severe malnutrition.[25] WHO clinical stage was stratified into stage 3 or 4 versus stages 1 or 2 and HIV RNA viral load categorised into <10.5 $\log_{10}$ versus ≥10.5 $\log_{10}$ copies/mL using the median cut-off value.

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. The association between the independent variables and outcome was examined using univariate logistic regression. Variables that were associated with treatment failure in the univariate analyses at P <0.02 were considered for inclusion in the multivariate model. Age and sex were included *a priori* in the multivariate model since these could influence disease processes. A backward 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. Results of the logistic regression analyses were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs). 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.

RESULTS

The frequency of antiretroviral treatment interruption was 20.2% among the 580 children enrolled to receive ART. Among the study subjects, majority were: Children aged 1-5 years (49.6%), females (51.5%), on anti-TB drugs (64.4%), not on cotrimoxazole prophylaxis before commencement of ART (82.4%). Only a few had oral thrush (3.2%), anaemia (5.4%), severe malnutrition (24.5%), failed first-line ART (22.5%) or were in WHO clinical stage 3 or 4 (58.1%). The median CD4 cell count was 478 cells/mL (interquartile range (IQR), 267-794 cells/mL), median viral load 38,597 copies/mL (IQR, 4,145-170,133 copies/mL) [Table 1].

In the unadjusted logistic regression analysis, the odds of ART interruption was about twice more in children on anti-TB drugs compared to those who were not (OR = 1.95) and this was significant (P = 0.005). The odds of ART interruption was reduced by about half in those who were on cotrimoxazole prophylaxis compared to those who were not (OR = 0.56) but not significant (P = 0.06). Though the odds of ART interruption was more: In those who failed first-line ART compared to those who did not (OR = 1.52), in those with HIV RNA viral load ≥10.5 $\log_{10}$ copies/mL compared to those with less (OR = 1.53) and in those with Hb <8.0 g/dL compared to those with higher levels (OR = 1.51), these findings were not significant (p = 0.09, p = 0.10 & 0.35 respectively). Also, despite a reduced odds of ART interruption in males compared to females (OR = 0.66) this was not significant (P = 0.05) [Table 2].

In the multivariate analysis, only the use of anti-TB drugs and cotrimoxazole for prophylaxis were significantly associated with ART interruption. Children on anti-TB drugs were twice more likely to interrupt ART compared to those who were not, Adjusted Odds Ratio (AOR) = 1.84; 95% CI (1.03-3.28); P = 0.04). But children on cotrimoxazole prophylaxis had a 57% reduction in the

Table 1: Characteristics of HIV-1 infected children interrupting antiretroviral therapy

Characteristics	Subjects	Treatment interruption		*P* value*
	Total *n* (%)	Yes *n* (%)	No *n* (%)	
Age (yrs)				
<1	61 (13.0)	14 (12.0)	47 (13.3)	0.72
1-5	233 (49.6)	54 (46.1)	179 (50.7)	0.38†
6-10	124 (26.4)	34 (29.1)	90 (25.5)	
>10	52 (11.0)	15 (12.8)	37 (10.5)	
Median (IQR)	3.5 (1.8-6.6)	3.8 (1.9-7)	3.5 (1.7-6.6)	
Sex				
Male	243 (51.5)	51 (43.6)	192 (54.1)	0.05
Female	229 (48.5)	66 (56.4)	163 (45.9)	
Oral thrush				
Present	15 (3.2)	4 (3.4)	11 (3.1)	0.77
Absent	456 (96.8)	113 (96.6)	343 (96.9)	
WHO clinical stage				
1/2	270 (58.1)	71 (61.2)	199 (57.0)	0.43
3/4	195 (41.9)	45 (38.8)	150 (43.0)	
Cotrimoxazole prophylaxis				
Yes	83 (17.6)	14 (12.0)	69 (19.4)	0.06
No	389 (82.4)	103 (88.0)	286 (80.6)	
Anti-TB medications				
Yes	304 (64.4)	88 (75.2)	216 (60.9)	0.005
No	168 (35.6)	29 (24.8)	139 (39.1)	
Haemoglobin level				
≤8 g/dL	24 (5.4)	8 (7.1)	16 (4.8)	0.34
>8 g/dL	419 (94.6)	104 (92.9)	315 (95.2)	
Median (IQR)	10 (9-11)	10.5 (9-11.5)	10 (9-11)	0.10†
WAZ				
≤–3	103 (24.5)	28 (27.2)	75 (23.7)	0.47
>–3	317 (75.5)	7 (72.8)	242 (76.3)	
Median (IQR)	–1.8 (–2.9–0.8)	–2.0 (–3.3–0.7)	–1.8 (–2.9–0.9)	0.62†
Failed first line ART				
Yes	106 (22.5)	33 (28.2)	73 (20.6)	0.09
No	366 (77.5)	84 (71.8)	282 (79.4)	
Absolute CD_4 count (per mm^3)				
Median (IQR)	478 (267-794)	454 (211-713)	439 (228-749)	0.94†
HIV RNA viral load (copies /ml)				
Median (IQR)	38597 (4145-170133)	21860 (2635-155371)	45206(4103-170805)	0.48†
HIV RNA Log viral load (copies /ml)				
<10.5	157 (51.0)	35 (43.2)	122 (53.7)	0.10
≥10.5	151 (49.0)	46 (56.8)	105 (46.3)	
Median (IQR)	10.6 (8.3-12.0)	10.0 (7.9-12.0)	10.7 (8.3-12.0)	0.48†

**P* value for Chi squared or Fisher's exact test for the association between categorical variables and treatment failure; †P value Wilcoxon rank sum test for comparison of two medians; Abbreviation – HIV – Human immunodeficiency virus; WHO – World health organisation; TB – Tuberculosis; ART – Antiretroviral therapy; RNA – Ribonucleic acid; WAZ – Weight-for-age z score;

Table 2: Factors associated with antiretroviral treatment failure in HIV-1 infected children

Risk factor	Crude OR (95% CI)	*P* value	Adjusted OR*(95% CI)	*P* value
Age (yrs)				
Per 1 yr increase in age	1.03 (097-1.09)	0.32	1.00 (Ref) 0.97 (0.91-1.05)	0.50
Sex				
Female	1.00 (Ref)		1.00 (Ref)	
Male	0.66 (0.43-0.99)	0.05	0.71 (0.42-1.20)	0.20
Oral thrush				
Absent	1.00 (Ref)	0.87		
Present	1.10 (0.34-3.5)			
WHO clinical stage				
1/2	1.00 (Ref)	0.43		
3/4	0.84 (0.54-1.29)			
Cotrimoxazole prophylaxis				
No	1.00 (Ref)		1.00 (Ref)	
Yes	0.56 (0.30-1.04)	0.06	0.43 (0.20-0.93)	0.03
Anti-TB medications				
No	1.00 (Ref)		1.00 (Ref)	
Yes	1.95 (1.22-3.12)	0.005	1.84 (1.03-3.28)	0.04
Haemoglobin level				
>8 g/dL	1.00 (Ref)	0.35		
≤8 g/dL	1.51 (0.63-3.64)			
WAZ				
> −3	1.00 (Ref)	0.47		
≤ −3	1.20 (0.73-2.00)			
Failed first line ART				
No	1.00 (Ref)	0.09		
Yes	1.52 (0.94-2.44)			
HIV RNA Log viral load (copies /ml)				
<10.5	1.00 (Ref)		1.00 (Ref)	
≥10.5	1.53 (0.92-2.55)	0.10	1.40 (0.82-2.37)	0.21

*Adjusted ORs for factors that remained in the final model. HIV – Human immunodeficiency virus; WHO – World health organsation; TB – Tuberculosis; ART – Antiretroviral therapy; RNA – Ribonucleic acid; OR – Odds ratio; CI – Confidence interval; WAZ – Weight-for-age z score.

odds of interrupting ART compared to those who were not, (AOR = 0.43; 95% CI (0.20-0.93); *P* = 0.03). The area under the ROC curve for the final model was 0.62.

DISCUSSION

Being on anti-TB drugs and on cotrimoxazole where the factors independently associated with ART interruption.

In our study, we found a strong association between taking multiple single anti-TB drugs along with ARVs and ART interruption which is an indicator of compromised ART adherence. Taking multiple individual anti-TB drugs as in our study as against taking FDC anti-TB drugs increased the pill burden. To support our finding, one meta-analysis study involving patients with various chronic diseases including tuberculosis and HIV infection, showed that adherence was better in those who took fewer pills in the form of FDCs.[26] Another study by O'Connor *et al.* in patients on ART also showed an association between a greater pill burden and suboptimal adherence.[21]

Our observation of a reduction in ART interruption in children on cotrimoxazole is supported by the findings of Biadgilign *et al.*[17] and Ebonyi *et al.*[27] that children on ART who also took cotrimoxazole, were more likely to adhere to ART. This may be so because being on cotrimoxazole prophylaxis even prior to commencing ART had already familiarised the children and caregivers to good adherence.

One of the limitations of our study was that we did not assess the influence of the adverse effects of ARVs or anti-TB drugs on ART adherence which could be confounding factors in the association between anti-TB drugs and ART treatment interruption. It is well documented that the side effects of these drugs could interfere with ART adherence.[28,29] Another limitation was our inability to measure the potential confounding effects of socio-economic, cultural or behavioural factors[12,15-20] on the association between our identified independent variables and ART interruption.

CONCLUSION

Being on anti-TB drugs and cotrimoxazole prophylaxis were the factors identified to be associated with ART interruption. Children on ART and also taking anti-TB drugs should be monitored closely for ART adherence. Cotrimoxazole prophylaxis should be encouraged in children diagnosed with HIV while awaiting ART commencement as this would prime them for a better ART adherence.

ACKNOWLEDGMENT

This publication was facilitated in part, by the US Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) which funded HIV/AIDS treatment and care services at APIN, JUTH, Jos. We are grateful to APIN, JUTH, JOS for permission to use the data and we thank Placid Ugoagwu for data management.

AUTHOR CONTRIBUTIONS

AOE: Concept, Design, Literature search, Data acquisition, Data analysis, Manuscript preparation/editing/review. SO, EUE, SEO, DDS, ESY, MOO: Data acquisition, Manuscript editing/review.

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How to cite this article: Ebonyi AO, Ejeliogu EU, Okpe SE, Shwe DD, Yiltok ES, Ochoga MO, Oguche S. Factors associated with antiretroviral treatment interruption in human immunodeficiency virus (HIV)-1-infected children attending the Jos University Teaching Hospital, Jos, Nigeria. Niger Med J 2015;56:43-7.

Source of Support: Nil, **Conflict of Interest:** None declared.