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Immunological outcomes of neverapin (NVP) versus efafrenz (EFV) based antiretroviral therapy (ART) regimen among children on ART: A study from Black Lion Hospital, Addis Ababa, Ethiopia

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Antiretroviral therapy has reduced HIV-related morbidity and mortality substantially. WHO recommends the use of Nevirapine or Efavirenz as first line combined with two from nucleoside reverse transcriptase inhibitors. In this study the immunological outcomes of Neverapin versus Efafrenz based ART was assessed. Medical records of patients were retrieved and important variables were captured to standard questionnaire. Medical records of 120 patients from NVP-based regimen and 60 patients from EFV groups were revised. The CD4 cell count at the start of HAART ranged from 3-2003 cell/ml with an inter quartile range (IQR) of 231-317 cell/ml among NVP group. And among patients taking EFV based ART regimen, baseline CD4 count ranged 13-2095 cell/ml with an IQR range of 250-345 cell/ml. After six months of HAART, the CD4 cell count of NVP based regimen range from 71-2300 c/ml with IQR of 458-612 c/ml, and mean CD4 cell count difference of 215, 95% CI (175.414-245.613). From EFV based group, CD4 count ranged from 65-2100 c/ml with IQR of 435-605 c/ml, and the mean CD4 cell count difference of 205, 95% CI (155.404-235.623). The immunological recovery was found to be comparable among the two groups. Advanced clinical stage of the disease, severe immune suppression, presence of anemia, presence of chronic diarrhea , poor weight gain during first six months of ART were adversely affected the trends of CD4 recovery. This research report demonstrated that immunological outcomes were comparable among patient taking NVP vs EFV based ART regimen.

Key words: Immunologic outcomes, HIV/AIDS; HAART/ART, nevirapine (NVP), efavirenz (EFV).

INTRODUCTION

Antiretroviral therapy (ART) reduces HIV-related mortality and morbidity substantially among HIV infected patients. If HAART is not started timely, a third of children infected prenatally will not survive to their first birthday, and more than half will succumb to death by their second birthday (Abebe, 2017). The advent of highly active antiretroviral therapy (ART) has brought a paradigm shift in the survival of HIV infected patient. The standard therapy consists of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase

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inhibitor (NNRTI). In resource-limited countries, World Health Organization (WHO) recommends the use of either nevirapine (NVP) or efavirenz (EFV) as first line NNRTI (Tadesse et al., 2017). The controversy over which of the two drug dNNRTI should be started in combination with NRTI for the treatment of HIV infection has been growing recently (Tadesse et al., 2017; Kate et al., 2014). Previous studies comparing NVP-based and EFV-based regimens in adult patients have shown comparable effectiveness. However, some studies have shown the superiority of EFV. There are limited data comparing NVP to EFV in HIV-infected children (Lapphra et al., 2008). A study from the United States also found an increased risk of virologic failure for patients on NVP as compared to EFV based regimen (Tadesse et al., 2017; Brian et al., 2012). However, study from Nepal showed that patient taking NVP based regimen had superior clinical outcomes than EFV based regimen (Theophilus et al., 2015).

Children's immune response to ART differs based on age at ART initiation and degree of viral level. As shown in recent adult studies, there are likely other baseline factors contributing to differential immunologic responses (Ojha et al., 2016). Studies are, however, scarce in assessing the potential difference based on type of ART regimen.

This study focuses on assessing immunologic outcomes of the two first lines (NVP versus EFV) NNRTI which could contribute some inputs for the scarce and conflicting data so far reported.

Objective

The objective of this study was to compare immunological outcomes of NVP versus EFV based regimen among HIV infected children.

METHODOLOGY

A comparative cross sectional study was conducted by evaluating ART documents of children infected with HIV who were taking ART at Pediatric Infectious Disease clinic (PIDC), Black Lion Hospital (BLH). The hospital is a teaching specialized and national tertiary hospital. Pediatric and child health department is one of the major departments delivering patient caring service, teaching and research activities under different unit categories. Pediatric infectious clinic (PIDC) is one of the well-organized subspecialty unit of the hospital giving care for patients with infectious disease with major focus of delivering pediatric HIV/AIDS care and treatment.

Sample

At the time of data collection, about 1145 children with HIV infection were on follow up at pediatric infectious disease clinic. A total of 503 patients have already been on HAART and 405 patients have been on ART for at least six months duration at the time of the study. The sampling procedure was determined by patients' ART regimen and patients and to minimize sampling error and to have proportional representation from each groups; the number of patients taking 30 patients were taking d4T/3TC/EFV regimen which represent the least proportion of patients' ART regimen and the base for requirement of other patient from other regimen. Patients from the other regimens were selected based on the aforementioned figure to make the NVP to EFV group ratio 2:1. Accordingly, systematic cross matching was made among the four group of patients based on the ART regimen, and they were taken so as to recruit total of 180 study participants, with 120 patients from NVP arm and 60 from EFV arm (Figure 1). A simple random sampling technique was used to select patient charts from each regimens using computer generated random number. For one patient from EFV based regimen selected; two patients from NVP based regimen were selected, yielding a total of EFV group (n1=60) and NVP group (n2 = 120).

Data collection and analysis

Data were collected from the patients' ART documents (medical records, ART log books, HMIS books) using standardized format. Data entry was made to EPI info software for cleanup and analysis; exported to SPSS version 17 for further analysis. The factors considered to affect the immunologic recovery in both groups include: baseline CD4%/count, WHO clinical staging, presence of chronic diarrhea, anemia, and baseline weight. The patients were grouped into two based on the age of the patients: under 5 years and 5 to 14 years old. Independent t-test was used to assess the difference in CD4 cell count recovery among the two groups' patients. Binary and multiple logistic regressions were used to assess factors affecting CD4 cell recovery in both groups of patient. 95% CI with p value of less than 0.05 was considered statistically significant.

RESULTS

ART documents of 120 patients from NVP based groups and 60 patients from EFV based regimen were reviewed. Important clinical and laboratory data were captured to standardized questionnaires. Males constitute 51% (61/120), while females were 49% (59/120) from NVP based regimen. From EFV-based regimen, male comprised of 52.6% (32/60) and female 47.4% (28/60).

The youngest age at the initiation of ART was 4 months from NVP-based regimen and 37 months from EFV-based groups with the highest being 144 and 168 months (IQR age 74-104 and 95-130 months), respectively.

Baseline anthropometry showed that 20.4 and 1.5% from NVP-based regimen and 22 and 2.5% from EFV based regimen were having moderate and severe wasting, respectively. Anemia was observed in 15% (18/120) of patients from NVP-arm regimen and 20% (12/60) of EFV-arm at the initiation of ART with the majority of the cases were having mild anemia.

With regards to non-nucleoside reverse transcriptase inhibitors (NNRTIs) as backbone about 66.7% (120/180) were taking NVP containing regimen, while 33.3% (60/180) were on EFV-containing regimen. With regards to NRTI, about 102 (57.1%) of patients were started on AZT-based Nucleos, while 78 (43%) patients were taking

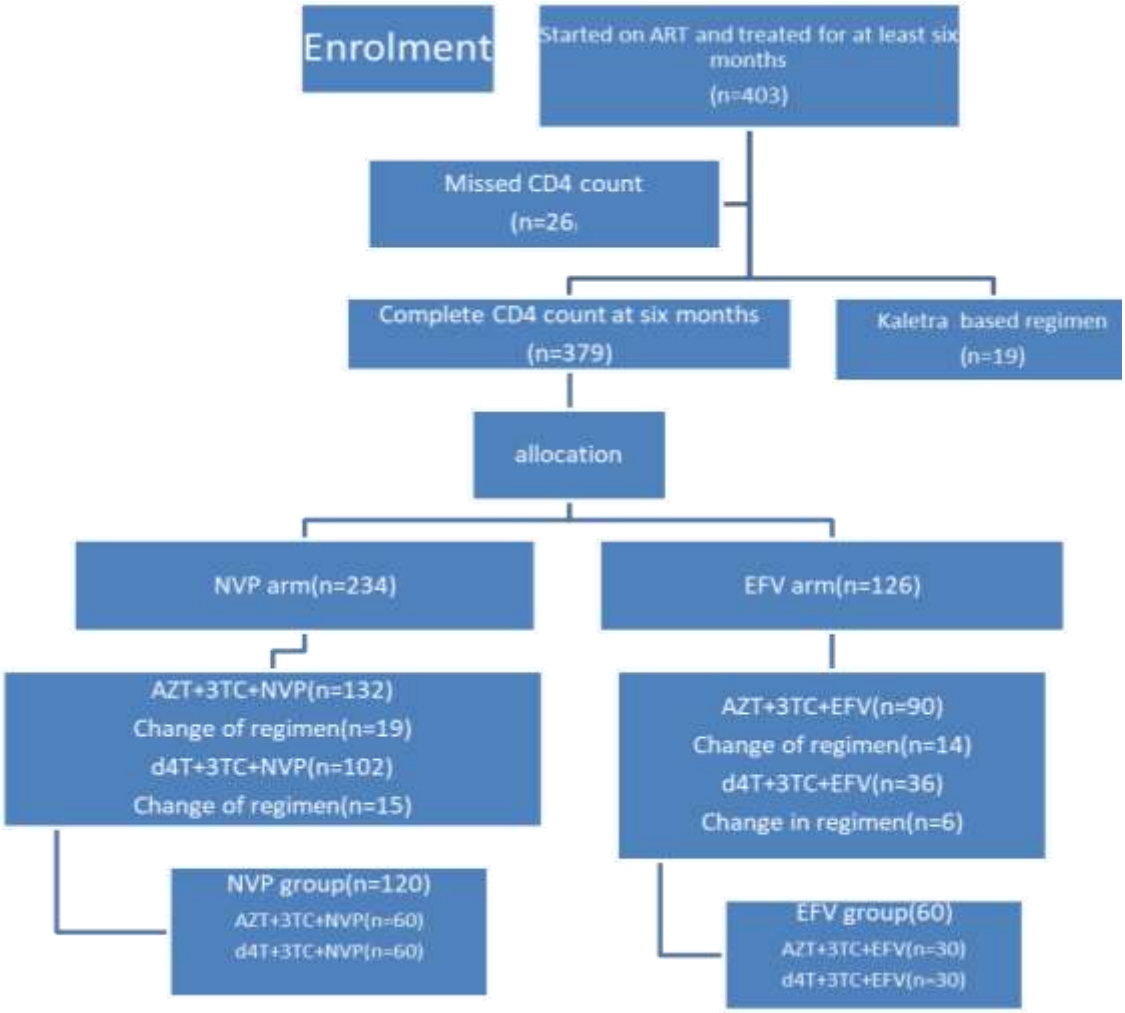

Figure 1. Schematic flow chart demonstrating sampling method at BLH of patients attending pediatric infectious clinic, August 10 to October 10, 2014.

d4T based regimen.

Most patients were having 52.9% (64/120) moderate immune suppression (CD4 cell count of 200-500 or CD4 cell percent 15-25%), while 38.9% (47/120) of patients were having severe immune suppression (CD4 cell count < 200 or <15%) at start of NVP-based ART. From EFV-arm ART regimen, 50.2% (31/60) were having moderate immune suppression (CD4 cell count of 200 to 500 or CD4 cell percent 15-25%), while 42.4% (25/60) of cases were having severe immune suppression (CD4 cell count < 200 or <15%) (Figure 2). With regards to WHO AIDS clinical staging; stages II, III, and IV were 27.6, 51 and 18.8%, respectively among NVP based group and 23.7, 52.3, and 20.8%, respectively among EFV based groups (Table 2).

The CD4 cell count at the start of HAART ranged from 3 to 2003 cell/ml with an inter quartile range (IQR) of 231 to 317 cell/ml among NVP group. And among patients taking EFV based ART regimen, baseline CD4 count ranged from 13 to 2095 cell/ml with an IQR range of 250 to 345 cell/ml.

After six months of HAART, the mean CD4 cell count of pre and post-HAART were compared among the two groups; from NVP based ART regimen, the CD4 cell count range from 71 to 2300 c/ml with IQR of 458 to 612 c/ml, and mean CD4 cell count difference of 215, 95% CI (175.414 to 245.613). From EFV based group, CD4 count ranged from 65 to 2100 c/ml with IQR of 435 to 605 c/ml, and the mean CD4 cell count difference of 205, 95% CI (155.404-235.623). About 85% (102/120) of patients from NVP-based regimen and 82.5% (50/60) from EFV-based regimen showed CD4 cell increment of greater than 20% or 50 cell/ml of baseline value. There is no difference in degree of CD4 recovery among patient taking the two regimen (p value is 0.34).

By taking weight gain into consideration, patients who have been on NVP-based regimen gained mean weight of 0.77 and 1.80 kg with 95% CI (0.588 - 0.957 and 1.60 -

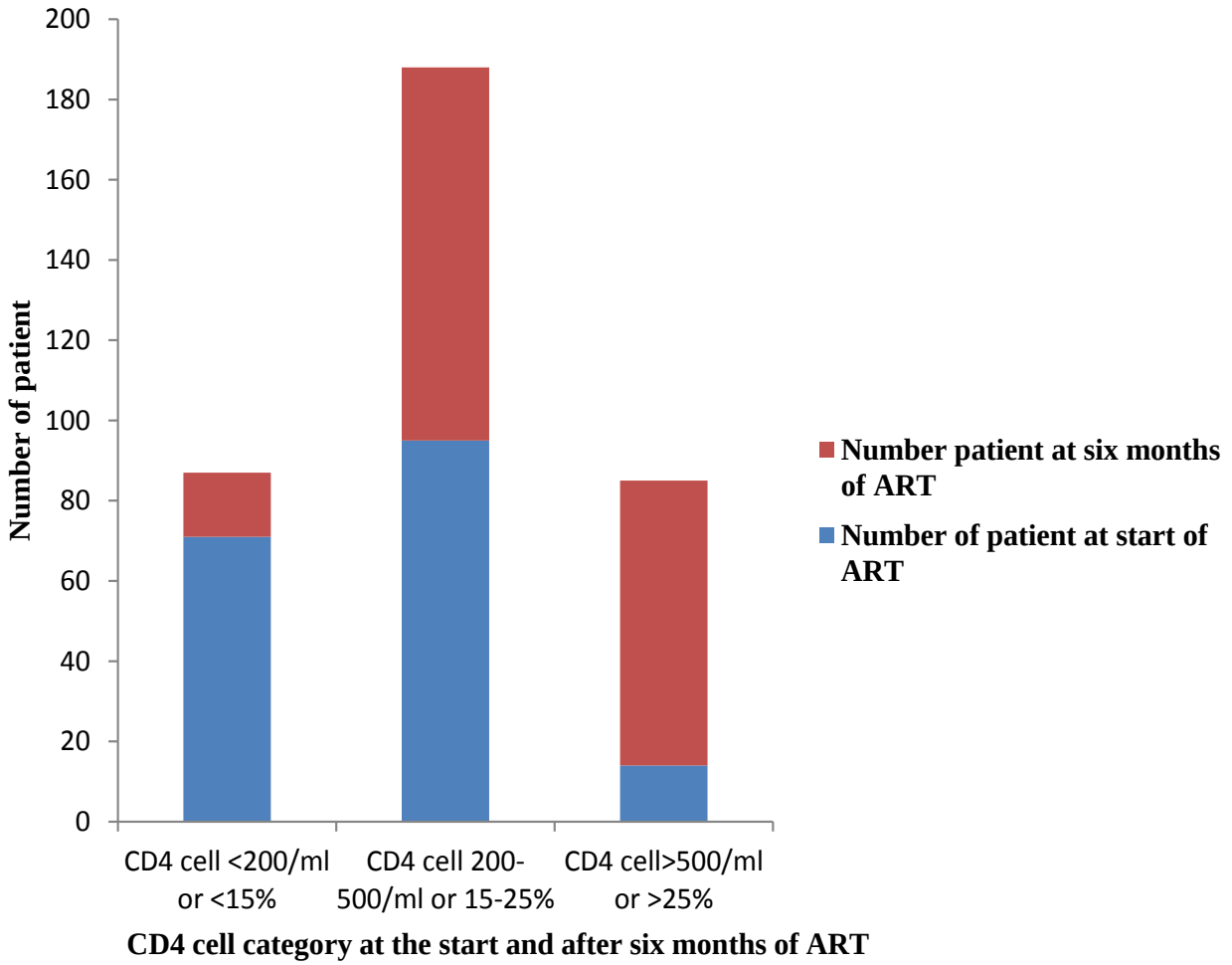

Figure 2. showing CD4 cout/percent distribution at the start and after six months of ART; Pediatric Infection Clinic, BLH, 2014.

2.2, respectively) at three and six months of HAART. Similarly, the mean weight gain at three and six months of EFV-based ART were 0.75 and 1.70 kg with CI (0.588 - 0.954) and 1.70 kg, 95% CI (1.50 - 1.95). Still there is no significant difference in weight gain among the two groups (Table 1).

Advanced WHO clinical staging and severe immune suppression at start of ART negatively affected the degree of CD4 recovery among the two groups of patients (Table 3). Similarly, low baseline weight, presence of, presence of chronic diarrhea, and poor weight gain at three and six months of ART was found to have detrimental impact to CD4 cell recovery (Table 3).

DISCUSSION

In this study, after six months of NVP based ART regimen, the CD4 cell count increased to the level of 75 to 2400 c/ml with IQR of 468 to 632 c/ml with the mean CD4 cell count difference of 215, 95% CI (175.414-245.613) from baseline value. From EFV based group, CD4 count ranged from 65 to 2100 c/ml with IQR of 435 to 605 c/ml, and the mean CD4 cell count difference is 205, 95% CI (155.404-235.623) with comparable finding between two wings of treatment, P-0.34. Similar reports from central China disclosed that ART (AZT/3TC/NVP) comparably effective in achieving an adequate response in HIV- infected children (Junwen, 2014), which is also This is in accordance with the study from Thailand children which showed comparable CD4 cell count gains between the NVP and EFV groups (Hai-Yin et al., 2014). Likewise, a Cochrane review of seven randomized clinical trials demonstrated that the two drugs provided comparable levels of viral suppression in non-TB patients infected with HIV when combined with two nucleoside reverse transcriptase inhibitors (Hai-Yin et al., 2014). However, in a meta-analysis, patients in the EFV treatment group achieved statistically higher rates of virological response, likely due to the effects of rifampin

Table 1. Demographic, anthropometry, CD4 category and hemoglobin at start of ART, Black Lion Hospital (BLH), Addis Ababa Ethiopia, 2014.

Variable		NVP group	EFV group	P value
Gender	Male	61 (50.1)	31 (51.7)	0.605
	Female	59 (49.9)	29 (48.3)	
Age category	Under 5 years	44 (36.7)	10 (16.7)	0.021
	5 - 14 years	76 (63.3)	50 (83.3)	
Weight-for-age	<3rd centile	62 (51.7)	32 (53.3)	0.056
	3rd - 97th centile	58 (48.3)	28 (46.7)	
Weight-for-height	<3rd centile	58 (48.3)	25 (41.7)	0.085
	3rd - 97th centile	62 (51.7)	35 (58.3)	
WHO Clinical Staging of AIDS	I & II	58 (48.3)	24 (40)	0.123
	III &IV	62 (51.7)	36 (60)	
CD4 cell category	>25% or >500	9 (7.5)	5 (8.3)	0.115
	15-25% or 200 - 500	45 (37.5)	30 (50)	
	<15% or <200	66 (55)	25 (40.7)	
Base anemia	-	22 (18.3)	8 (13.3)	0.095

Table 2. Proportion of weight increment and CD4 cell recovery at three and six month of ART, BLH, Addis Ababa Ethiopia, 2014.

Profile after HAART	Category	NVP group	EFV group	P value
Rate of weight increment at three months of HAART	<5%	70 (58.3)	36 (60)	0.524
	6-10%	24 (20)	13 (21.7)	
	>10%	26 (21.7)	11 (18.3)	
Rate of weight increment at six months of HAART	< 5%	41 (34)	20 (33.3)	0.105
	5-10%	27 (22)	14 (23.3)	
	>10%	52 (44)	26 (43.4)	
CD4 cell count or percent at six month of HAART	>25% or >500	48 (40)	24 (40)	0.315
	15-25% or 200 - 500	62 (52)	30 (50)	
	<15% or <200	10 (8)	6 (10)	

on drug metabolism (Hai-Yin et al., 2014). Another cohort study in ARV Thai adult patients with advanced HIV infection showed that NVP- and EFV-based HAART regimens were equally effective in terms of virological and immunological responses (Lapphra et al., 2008).

The positive association between younger age groups and better immune recovery demonstrated comparably among the two groups in this study which is in congruence with other previous pediatric and adult reports (de Castilla et al., 2008; Reda et al., 2013; Gezie, 2016; Asfaw et al., 2015; Eshun-Wilson et al., 2012). This might be justified by high reserve of lymphocytes cell and early initiation of ART among younger age groups. On the other hand, in the present study, there is no relationship between gender of the patient and immunologic recovery from both NVP and EFV based regimen though other studies were with discordant results; some reported female gender is associated with better immune recovery others showed no gender difference (Crum-Cianflone et al., 2011; Mihiretu et al.,

Table 3. Displaying predictors CD4 cell recovery of >20% baseline increment among patient at six months of ART, Pediatric infectious clinic; BLH, Addis Ababa Ethiopia, 2014.

Variable		CD4 cell recovery (above >15% or >200 cell/ml)	
		N=180, Adjusted Odds Ratio (95% CI)	P-value
Weight category	<3rd centile	3.22 (1.09-6.56)	0.018
Sex	Male	1.02 (0.9-1.5)	0.073
WHO clinical Staging	II	0.21 (0.05-1.4)	0.014
	II I &IV	0.58 (0.10-1.65)	0.006
Base line CD4 count category	<10%	0.23 (0.089-1.2)	0.025
	10-15%	0.56 (0.16-2.11)	0.015
Age category	5-14 years	0.47 (0.11-1.23)	0.017
Base line hemoglobin level	<10g/dl	0.34 (0.14-0.98)	0.014
Percent of weight gain at three month of ART	>10%	2.5 (1.3-4.9)	0.012
Percent of weight gain at six month of ART	>10%	4.23 (2.12-7.2)	0.002
Chronic diarrhea	yes	0.39 (0.05-1.45)	0.007
ART regimen	NVP based	1.05 (1.045-2.5)	0.086

2014). Presence of chronic diarrhea during ART treatment is associated with poor CD4 cell recovery independent of nutritional status of the patient which is in agreement with most previous studies. The reason is not clearly identified so far but could be because of associated mal-absorption and poor adherence during the illness. Our study also showed that the presence of anemia at baseline (Hgb<10 g/dl) is related with poor immune system regeneration which is in concordant with similar studies from other sites (Puthanakit et al., 2009; Ethiopia Ministry of Health, 2012; Bacha et al., 2012). For instance, the report from South Africa demonstrated that children living with HIV who started on ART with lower hemoglobin level at the start of ART had significant risk of adverse CD4 cell recovery (OR = 0.87 for each 1 g/dl decrease in hemoglobin; 95% CI: 0.75-0.99) (Doris et al., 2015; Brian et al., 2012). Such relationship is apparently reasonable as there are evidences from other literature supporting the contribution elemental irons in immune restoration system. This research findings of lower baseline CD4 cell value predicting poor six month CD4 cell recovery in both groups of patients is supported with a large cohort study involving 861 adult patients living with HIV in Spain which showed that patients with baseline CD4 count of 200 and of 201 to 350 cells/mm^3 had a significantly lower chance of achieving CD4 count of 500 cells/mm^3 when compared with patients with baseline CD4 350 cells/mm^3 and above (Mihiretu et al., 2014; Third International Work Shop on HIV in Pediatrics, 2011; Zanoni et al., 2012).

This research finding also disclosed comparable weight recovery between the two wings of treatment category at three and six months of ART which is also in compatible with other research findings (Abebe, 2017). Weight gain of greater than 10% at six months of ART was demonstrated in 44% of the patients in our study which was in consistence with the study from Brazil which showed mean weight-for-age z scores increment from -1.62 (±1.32) at baseline to -1.14 (±1.12) weight-for-age z scores at week 24 (Diniz, 2011).

The suboptimal weight recovery after initiation of ART could imply poor adherence, an advancing disease stage or associated opportunistic infection signaling that the patient should undergo extensive clinical and blood test assessment. Likewise study in South Africa and elaborated lower percentiles of weight gain after six months of ART were associated with poor subsequent treatment outcomes and higher risk of mortality independent of other baseline characteristics (Kaufmann et al., 2005; Chiappini et al., 2009; Ahoua et al., 2009; Madec et al., 2009; Yotebieng et al., 2010). Likewise, underweight at start of ART was an independent prognosticator of poor CD4 outcome in both wings of the study, which is in line with other observational studies where patients who were underweight had a two-fold increased risk of dying (Madec et al., 2009).

Conclusion

This research finding demonstrated that there is no difference in immunological outcomes among patients taking NVP versus EFV. Higher WHO clinical stage of the disease, severe degree of immunosuppression, lower hemoglobin level at start of ART and presence of chronic diarrhea, and suboptimal weight increment at first six months of ART were factors that negatively affected the patterns of CD4 recovery.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Abbreviations: AIDS, Acquired immunodeficiency syndrome; **ART,** antiretroviral treatment; **HAART,** highly active antiretroviral therapy; **HIV,** human immune-virus; **MTCT,** mother to child transmission; **NNRTI,** non-nucleoside reverse transcriptase inhibitors; **NRTI,** nucleoside reverse transcriptase inhibitors; **PMTCT,** prevention of mother to child transmission; **SD,** standard deviation; **TB,** tuberculosis; **WHO,** World Health Organization.

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