DIA DEVELOP INNOVATE ADVANCE

Therapeutic Innovation & Regulatory Science
2015, Vol. 49(3) 443-449

DOI: 10.1177/2168479014565472
tirs.sagepub.com

Treatment Outcomes of Nevirapine- Versus Efavirenz-Based Highly Active Antiretroviral Therapy Regimens Among Antiretroviral-Naive Adult Patients in Ethiopia: A Cohort Study

Muktar Sano Kedir, MSc, BPharm[1], Desta Hiko Gemeda, MPHE[2], and Sultan Suleman, MSc, BPharm, PhD[3]

Abstract

Background: Despite wide use of nevirapine- and efavirenz-based highly active antiretroviral therapy regimens in Ethiopia, their treatment outcome has not been well studied. The objective of this study was to compare treatment outcome of nevirapine- and efavirenz-based regimens. *Methods:* This retrospective cohort study was conducted on antiretroviral-naive adult patients with human immunodeficiency virus (HIV) who had started antiretroviral therapy. Study participants were excluded after treatment failure, regimen change, loss to follow-up, or transfer to other health facility. The outcomes of interest included immunologic recovery, immunologic failure, clinical failure, and treatment failure. *Results:* There were 1064 HIV patients in the study; an equal proportion (1:1) from both efavirenz- and nevirapine-based regimens was included. Patients in both regimens had similar baseline CD4 cells count ($P = .876$). In multivariate analysis, efavirenz-based regimens showed more likelihood of immunologic recovery, whether defined as a CD4 cell count of >200 cells/mm^3 (hazard ratio [HR] = 1.31 [95% CI, 1.05-1.59]), >350 cells/mm^3 (HR = 1.26 [95% CI, 1.08-1.47]), or >500 cells/mm^3 (HR = 1.95 [95% CI, 1.57-2.41]). Moreover, efavirenz-based regimens showed a lower hazard of treatment failure (HR = 0.66 [95% CI, 0.49-0.88]). *Conclusion:* Although the finding of retrospective study should be interpreted with caution, efavirenz-based regimens were associated with superior treatment outcome.

Keywords

Ethiopia, HIV, treatment outcome, naive adult patient

Introduction

The emergence of the human immunodeficiency virus (HIV) epidemic is one of the worst public health challenges the world has faced in history. Globally, it is estimated that 2.7 million people were newly infected with HIV in 2010. Of those newly infected individuals, about 1.9 million are living in sub-Saharan Africa, and they represent 70% of all people who acquired the HIV infection globally. Globally, about half of the HIV-positive cases have been women, whereas in sub-Saharan Africa, women make up 60% of the HIV-positive population.[1,2]

Ethiopia is a country in sub-Saharan Africa with one of the highest HIV epidemic rates. In Ethiopia, the first case of AIDS was reported in 1986, and an antiretroviral therapy (ART) program was launched in 2003. The ART service has been universally available in Ethiopia since 2005 for free and has been shown to prolong survival.[1,3] A total of 333,434 people have started ART, and 249,174 adults and 16,000 children were receiving treatment at the end of 2011.[3]

Highly active antiretroviral therapy (HAART) has led to a major reduction of AIDS-related morbidity and mortality both

[1] Department of Pharmacy, College of Health Sciences, Mizan-Tepi University, Mizan Teferi, Ethiopia
[2] Department of Epidemiology, College of Public Health and Medical Science, Jimma University, Jimma, Ethiopia
[3] Department of Pharmacy, College of Public Health and Medical Science, Jimma University, Jimma, Ethiopia

Submitted 21-Aug-2014; accepted 21-Nov-2014

Corresponding Author:
Muktar Sano Kedir, Department of Pharmacy, College of Health Sciences, Mizan-Tepi University, Mizan Teferi, Ethiopia.
Email: muktarsano@yahoo.com

in developed and developing countries.[4,5] In order to maintain long-term virologic suppression and immunologic recovery at a level that significantly reduces the risk of AIDS-defining illness and mortality due to HIV, an evidence-based selection of regimens from the existing alternatives is essential.

World Health Organization (WHO) guidelines[6-8] recommend either of the nonnucleotide reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine as a component of first-line HAART regimens for resource-limited countries. In contrast, the International AIDS Society–United States guidelines,[9-11] the United States Department of Health and Human Services,[11] and the British HIV Association guidelines[12] prefer efavirenz-based first-line HAART regimens over nevirapine-based ones.

Although clinical trials and previous Cochrane reviews of clinical trials[13-15] have shown noninferiority of nevirapine-based HAART regimens to efavirenz-based ones, the findings of many observational studies and recent systematic reviews and meta-analyses contradict those studies. In these observational studies and systematic reviews, patients treated with efavirenz-based HAART regimens showed better immunologic recovery,[16-18] better virologic outcomes,[16-21] better adherence,[21] less probability of developing treatment failure,[16-21] longer time to treatment failure,[21,22] and lower chance of AIDS-defining illness[16] than patients treated with nevirapine-based regimens.

In sub-Saharan Africa, despite the wide use of efavirenz- and nevirapine-based HAART regimens, studies on the long-term effectiveness of these 2 NNRTI regimens are limited.[21,23,24] Similarly, in Ethiopia, despite the wide use of first-line HAART regimens containing efavirenz and nevirapine for a decade, no study has directly compared their treatment outcomes. Due to the limited accessibility of HIV viral load assays and scarce availability of second-line drugs, evidence regarding the comparative efficacy of these 2 NNRTI-based first-line HAART regimens is highly valuable to determine the most effective treatment options for future use.

This study compared treatment outcomes of nevirapine- and efavirenz-based HAART regimens in terms of likelihood of immunologic recovery using CD4 cell counts of 200 cells/mm^3, 350 cells/mm^3, and 500 cells/mm^3 as cutoff points; hazard of immunologic failure; clinical failure; treatment failure; and time to occurrence of immunologic recovery.

Materials and Methods

Patients and Study Setting

Since 2005, Adama Referral Hospital, located 100 km southeast from the Ethiopian capital of Addis Ababa, has been providing a free ART service as part of the National AIDS Control Program in the country. This hospital provides clinical care, including laboratory and pharmacy services. Before January 2008, first-line HAART regimens containing either nevirapine or efavirenz in combination with lamivudine plus stavudine or lamivudine plus zidovudine were used. After January 2008, in addition to lamivudine plus stavudine or lamivudine plus zidovudine, tenofovir plus lamivudine was started as a component of first-line HAART regimens. The doses of specific drugs in HAART regimens were as follows: stavudine 30 mg twice daily; zidovudine 300 mg twice daily; lamivudine 150 mg twice daily; nevirapine 200 mg once daily for first 14 days, then 200 mg twice daily; tenofovir 300 mg once daily; and efavirenz 600 mg once daily. In this study, in order to minimize the heterogeneity of HAART regimens, data were extracted from the medical records of patients started on nevirapine- and efavirenz-based HAART regimens from after January 2008 up to August 2012.

Study inclusion criteria were treatment-naive adult HIV patients (age >18 years), patients receiving treatment follow-up at least for 6 months, and patients with a pretreatment CD4 cell count of <350 cells/mm^3; exclusion criteria involved patients whose ART intake record and/or follow-up format was lost and patients who transferred out, whose regimen was changed, or who were lost to follow-up before the first CD4 cell count measurement.

During extraction of the medical records, initially the medical records of antiretroviral-naive adult patients started on nevirapine- and efavirenz-based HAART regimens were isolated. Then, those patients fulfilling inclusion criteria were arranged in ascending order by their card number for both nevirapine- and efavirenz-based regimens separately. Finally, a systematic sampling technique was used to identify specific patients included in this study.

Study Design

This was a hospital-based retrospective cohort study. See Table 1 for definitions of terms used.

Study Variables

The primary study outcome was treatment failure, while the secondary outcomes included immunologic recovery, immunologic failure, and clinical failure. Patients who developed treatment failure, regimen change, loss to follow-up, or transfer out were censored, while those who developed secondary outcomes were followed up to the occurrence of a primary outcome or end of the study (April 10, 2013).

Time to the first occurrence of any of these outcomes was calculated by subtracting the date of the HAART regimen initiation from the date the event occurred. Predictor variables were coded into discrete categories: NNRTI (efavirenz vs nevirapine), HAART backbone (zidovudine + lamivudine vs stavudine + lamivudine and tenofovir + lamivudine vs stavudine + lamivudine), CD4 count category (<200 vs ≥200 cells/mm^3, <350 vs ≥350 cells/mm^3, and <500 vs ≥500 cells/mm^3),

Table 1. Definition of Terms Used.

Advanced disease: Refers to the group of opportunistic infections categorized under World Health Organization (WHO) clinical stage III or IV.
Antiretroviral-naive patient: A patient with no previous history of taking a highly active antiretroviral therapy (HAART) regimen.
Clinical failure: The occurrence of new or recurrence of advanced disease.
Functional status: Categorized as *working* (patients able to perform usual work in or out of the house), *ambulatory* (patients able to perform activities of daily living but not able to work), or *bedridden* (patients not able to perform activities of daily living).
Immunological failure: A drop in the CD4 count value below baseline (pretreatment value) or a drop of more than half from treatment peak value.
Lost to follow-up: A patient who has missed any drug pick-up appointment.
Regimen change: A switch from first-line regimen containing nevirapine and efavirenz to another regimen not containing nevirapine or efavirenz, respectively.
Treatment failure: The occurrence of clinical failure or immunologic failure or confirmed virologic failure.

sex (male vs female), age (≥40 vs <40 years), WHO clinical stage (3 or 4 vs 1 or 2), and functional status (working vs bedridden or ambulatory).

Data Analysis

The baseline characteristics of patients were compared by using the χ^2 test for categorical variables and 2-sample *t* test for continuous variables. The proportional hazards assumption was checked by Schoenfeld residuals. Cox proportional hazards regression was used to model the individual and simultaneous effect of NNRTI, HAART backbone, sex, age, baseline clinical stage, and functional status. Any predictor having significant association with treatment outcomes at the 25% level in unadjusted analysis and fulfilled proportional hazards assumption was included in adjusted analysis. Cox proportional hazards regression analysis was used to compare NNRTI difference in the likelihood of immunologic recovery and hazard of immunologic failure, clinical failure, and treatment failure after adjusting for other potential determinants. The time to immunologic recovery and treatment failure was estimated by Kaplan-Meier plot and compared with the log-rank test. In multivariate analysis and log-rank test, statistical significance was attained if $P < .05$. All *P* values were 2-tailed. Analysis was performed using STATA version 11.0 software (StataCorp LP, College Station, Texas).

Results

Patient Characteristics

A total of 1064 patients (532 each for nevirapine-based and efavirenz-based regimen) were retrospectively followed for a total of 5 years and achieved a mean of 2.55 years and 2.32 years respectively. At the time of enrollment, 594 (55.83%) of patients were female, 229 (21.52%) had advanced WHO clinical disease (stage 3 or 4), 733 (68.89%) were enrolled with a CD4 count less than 200 cells/mm^3, and 331 (31.11%) were enrolled in the upper CD4 count stratum (CD4 cell count value between 201 and 350 cells/mm^3). Baseline CD4 cell count and sex distribution of patients exposed to both nevirapine- and efavirenz-based regimens were similar at the beginning of follow-up, while the other baseline characteristics (age, WHO stage, and functional status) were not uniformly distributed (Table 2).

Immunologic Recovery

After adjusting for other potential predictors, efavirenz-based regimens showed more likelihood of immunologic recovery, whether defined as a CD4 cell count of >200 cells/mm^3 ($P = .002$), >350 cells/mm^3 ($P = 0.003$), or >500 cells/mm^3 ($P = 0.001$) (Table 3).

The comparison of time to reach CD4 cell count >200 cells/mm^3 by Kaplan-Meier plot showed overlap between the 2 regimens, indicating a similar time for both regimens to reach a CD4 cell count >200 cells/mm^3 (Figure 1). However, this difference was statistically significant (log rank, $P = .021$). In the Kaplan-Meier plot of time to achieve CD4 cell counts >350 cells/mm^3 and >500 cells/mm^3, the curve representing efavirenz-based regimens was completely above the curve for nevirapine-based regimes for most of follow-up period, indicating a significant difference in time to immunologic recovery (log rank, $P = .001$ and .0001, respectively) (Figures 2 and 3). At all these CD4 cell count cutoff points, efavirenz-based regimens showed faster immunologic recovery compared with nevirapine-based regimens.

Treatment Failure

In nevirapine-based regimens, there were 128 cases of treatment failure (112 immunologic failures, 29 cases of clinical failure, and 13 cases of both immunologic and clinical failure). Of all cases of treatment failure in nevirapine-based regimens, 3 were confirmed as virologic failure besides immunologic and clinical failure. On the other hand, there were 93 cases of treatment failure (72 immunologic failures, 23 cases of clinical failure, and 2 cases of both immunologic and clinical failure) in efavirenz-based regimens.

The incidence of treatment failure in nevirapine- and efavirenz-based regimens was 10.96 per 100 person-years and 6.96 per 100 person-years, respectively. Compared with nevirapine-based regimens, in efavirenz-based regimens, the hazard ratio (HR) of treatment failure was lower (adjusted HR = 0.66 [95% CI, 0.49-0.88], $P = .005$), as displayed in Table 3. Moreover, in the Kaplan-Meier plot of time to

Table 2. Baseline Characteristics of Patients at the Initiation of Nevirapine- and Efavirenz-Based Highly Active Antiretroviral Therapy Regimens.

Characteristic	Nevirapine Group (n = 532)	Efavirenz Group (n = 532)	*P* Value[a]
Sex			.902
Female	298 (56.02)	296 (55.64)	
Male	234 (43.98)	236 (44.36)	
Age, mean, y	34.77	36.12	.017
Baseline CD4 count, mean	152.89	152.06	.876
Initial NRTI backbone			.001
Stavudine-lamivudine	283 (53.19)	264 (49.62)	
Zidovudine-lamivudine	174 (32.71)	55 (10.34)	
Tenofovir-lamivudine	75 (14.10)	213 (40.04)	
Functional status			.001
Working	478 (89.85)	375 (70.49)	
Bedridden or ambulatory	54 (10.15)	157 (29.51)	
WHO stage			.001
I or II	384 (71.18)	451 (84.77)	
III or IV	148 (27.82)	81 (15.23)	

Values are presented as number (%) unless otherwise indicated. NRTI, nucleotide reverse transcriptase inhibitor; WHO, World Health Organization.
[a]Pearson χ^2 test was used for categorical variables and the 2-sample *t* test was used for continuous variables.

Table 3. Cox Proportional Hazards Regression of Factors Associated With Treatment Outcomes Measured by NNRTI Component of First-Line Highly Active Antiretroviral Therapy Regimens.

Treatment Outcome	NNRTI	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value[a]
CD4 count >200 cells/mm^3	Nevirapine	1		1	
	Efavirenz	1.20 (1.02-1.41)	.027	1.31 (1.05-1.59)	.002
CD4 count >350 cells/mm^3	Nevirapine	1		1	
	Efavirenz	1.29 (1.10-1.50)	.001	1.26 (1.08-1.47)	.003
CD4 count >500 cells/mm^3	Nevirapine	1		1	
	Efavirenz	1.53 (1.25-1.87)	.001	1.95 (1.57-2.41)	.001
Immunologic failure	Nevirapine	1		1	
	Efavirenz	0.70 (0.52-0.95)	.020	0.62 (0.45-0.86)	.004
Clinical failure	Nevirapine	1			
	Efavirenz	1.15 (0.66-2.01)		[b]	—
Treatment failure	Nevirapine	1		1	
	Efavirenz	0.72 (0.03-0.74)	.019	0.66 (0.49-0.88)	.005

CI, confidence interval; HR, hazard ratio; NNRTI, nonnucleotide reverse transcriptase inhibitor; —, Not Applicable.
[a]Adjusted HRs included adjustments for sex, age, baseline CD4 counts, baseline World Health Organization clinical stage, and baseline functional status.
[b]No adjusted HR was calculated because NNRTI was not associated with the outcome variable to the specified 25% level in unadjusted analysis.

treatment failure, the curve representing nevirapine-based regimens was above the curve of efavirenz-based regimens, indicating a significant difference in time to treatment failure (log rank, $P = .019$) (Figure 4).

Discussion

The study compared the treatment outcomes of nevirapine- and efavirenz-based regimens among antiretroviral-naive adult HIV patients who started HAART regimens at Adama Referral Hospital from January 2008 to August 2012. A total of 532 HIV patients from both nevirapine- and efavirenz-based regimens were retrospectively followed for a total of 5 years and attained 1358.75 person-years and 1235.17 person-years, respectively. At the time of HAART initiation, patients in both groups had similar sex distribution and average baseline CD4 cell count.

Nevirapine-based regimens showed a lower likelihood of immunologic recovery at all CD4 cell count cutoff points of 200 cells/mm^3, 350 cells/mm^3, and 500 cells/mm^3. This finding was consistent with the HIV-CAUSAL Collaboration study,[16] which identified an 11-cell/mL smaller increase in CD4 cell in nevirapine-based regimens (HR = –11.49 [95% CI, –18.13 to –4.86). Similarly, the Italian Cohort Naïve Antiretroviral Study[18] and study of Veterans Affairs patients[17] also identified more immunologic recovery in efavirenz-based regimens, although their result was less robust ($P = .05$ and .09,

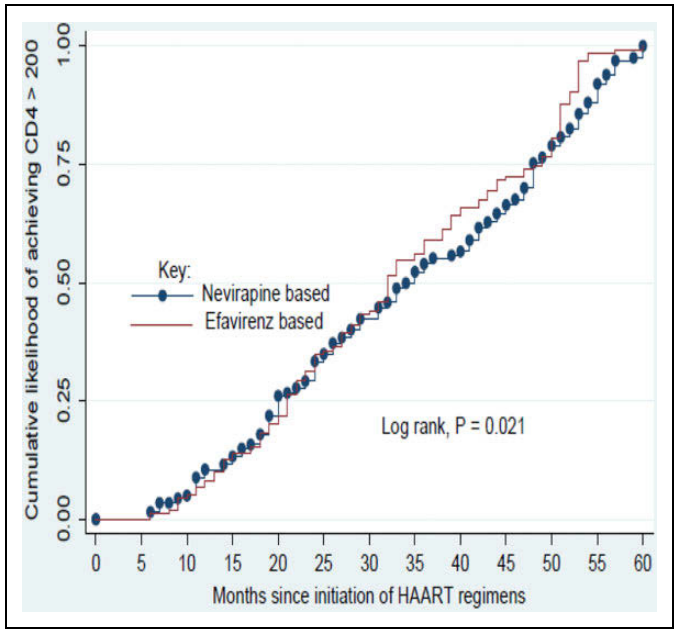

Figure 1. Kaplan-Meier estimates of time to achieve CD4 count >200 cells/mm^3 among nevirapine- and efavirenz-based highly active antiretroviral therapy (HAART) regimens.

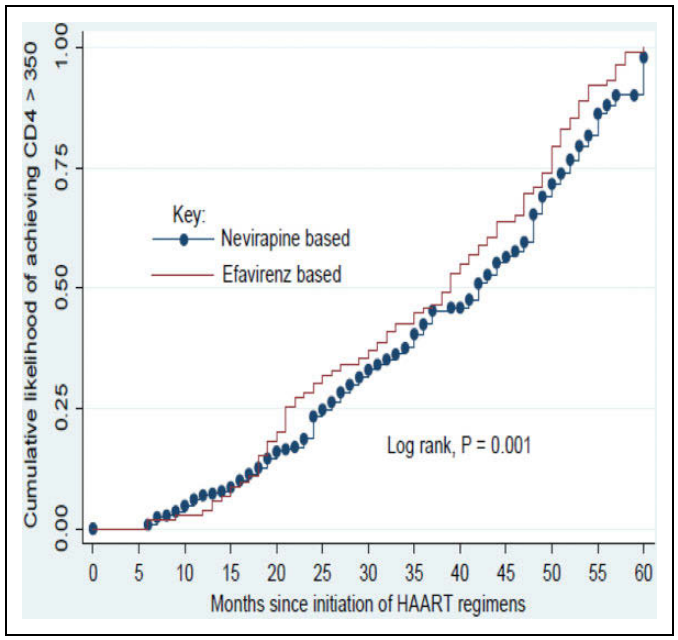

Figure 2. Kaplan-Meier estimates of time to achieve CD4 count >350 cells/mm^3 among nevirapine- and efavirenz-based highly active antiretroviral therapy (HAART) regimens.

respectively). However, other studies[14,23] reported similar immunologic recovery in both efavirenz- and nevirapine-based regimens. The possible reason for this inconsistency may be related to shorter follow-up period or smaller sample size of antiretroviral-naive participants in those studies.

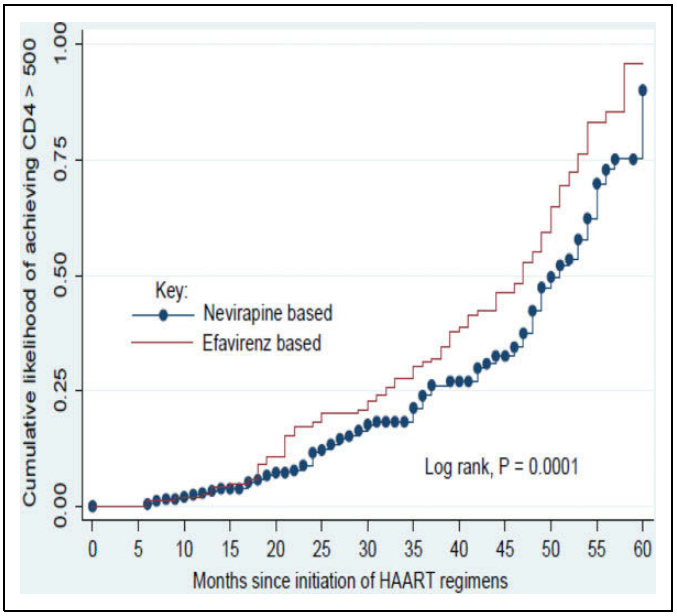

Figure 3. Kaplan-Meier estimates of time to achieve CD4 count >500 cells/mm^3 among nevirapine- and efavirenz-based highly active antiretroviral therapy (HAART) regimens.

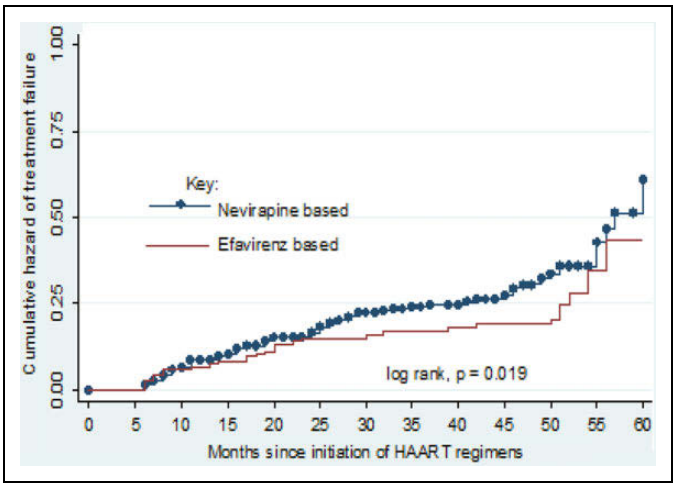

Figure 4. Kaplan-Meier estimates of time to treatment failure among nevirapine- and efavirenz-based highly active antiretroviral therapy (HAART) regimens.

During the follow-up period, the hazard ratio of clinical failure (HR = 1.15 [95% CI, 0.66-2.01]) was similar in both efavirenz- and nevirapine-based regimens. This finding is consistent with the results reported in a study conducted in Senegal (HR = 1.25 [95% CI, 0.61-2.58]).[23] However, the HIV-CAUSAL Collaboration study[16] identified more AIDS-defining illness in nevirapine-based regimens (HR = 1.28 [95% CI, 1.09-1.50]). This inconsistency may be related to study design; in the latter case, the occurrence of AIDS-defining illness was prospectively followed, while in a

retrospective record review (in the case of this study), these illnesses may not have been recorded or even diagnosed.

The overall incidence rate of treatment failure in this study was very low (0.09 events/person-years) compared with the Italian Cohort Naïve Antiretrovirals Study (0.33 events/person-years).[18] The most likely explanation for this difference may be related to the poor sensitivity of WHO treatment failure criteria used in this study, since most treatment failures in the Italian Cohort Naïve Antiretrovirals Study were not confirmed with viral load determination or the presence of drug-experienced patients at initiation of NNRTI-based regimens, which may have increased the rate of treatment failure.

In this study, efavirenz-based regimens showed a lower risk of treatment failure (HR = 0.66 [95% CI, 0.49-0.88]). This finding is consistent with those studies that defined treatment failure using virological load determination.[18,21,22] Moreover, nevirapine-based regimens showed shorter time to the occurrence of treatment failure ($P = .019$); this is also consistent with other studies.[21,22]

Compared with previous studies, this study used a sufficient number of antiretroviral-naive HIV participants. The limitations of this study included the absence of viral load measurement for confirmation of suspected immunologic failure or clinical failure, which may underestimate the rate of treatment failure and individual variations in the diagnosis of AIDS-defining illness.

Conclusion

Although the results of this retrospective study should be interpreted with caution, initial efavirenz-based HAART regimens were associated with superior immunologic recovery and lower hazard of treatment failures compared with nevirapine-based regimens. Therefore, further longitudinal study, ideally a prospective cohort study, should be conducted at the national level for the determination of a preferred NNRTI component of HAART regimens in Ethiopia.

Acknowledgments

The authors express their appreciation to Adama Referral Hospital, particularly ART clinic staff, for their kind cooperation during data collection.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by Jimma University.

References

1. World Health Organization, UNICEF. *Global HIV/AIDS Response: Epidemic Update and Health Sector Progress Towards Universal Access*. Geneva, Swizerland: WHO; 2012.
2. World Health Organization and UNAIDS unveil plan to get 3 million AIDS patients on treatment by 2005. *Ann Saudi Med*. 2004; 24(1):71-72.
3. HAPCO. *Progress Report on HIV/AIDS Response*. Addis Ababa, Ethiopia: HAPCO; 2012.
4. Zaragoza-Macias E, Cosco D, Nguyen ML, Del Rio C, Lennox J. Predictors of success with highly active antiretroviral therapy in an antiretroviral-naive urban population. *AIDS Res Hum Retroviruses*. 2010;26(2):133-138.
5. Vo TT, Ledergerber B, Keiser O, et al. Durability and outcome of initial antiretroviral treatments received during 2000-2005 by patients in the Swiss HIV Cohort Study. *J Infect Dis*. 2008; 197(12):1685-1694.
6. Gilks CF, Crowley S, Ekpini R, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet*. 2006;368(9534):505-510.
7. World Health Organization. *Rapid Advice: Antiretroviral Therapy for HIV Infection in Adult and Adolescent*. Geneva, Switzerland: WHO; 2009.
8. World Health Organization. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach: 2010 Revision*. Geneva, Switzerland: WHO; 2010.
9. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society–USA panel. *JAMA*. 2010;304(3):321-333.
10. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2012;308(4):387-402.
11. US Department of Health and Human Services. What to start: initial combination regimens for the antiretroviral-naive patient | adult and adolescent ARV guidelines | AIDSinfo. http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/11/what-to-start. Accessed February 12, 2013.
12. Gazzard BG, on behalf of the BTGWG. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med*. 2008;9(8):563-608.
13. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials*. 2002;3(3):186-194.
14. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004; 363(9417):1253-1263.
15. Mbuagbaw LC, Irlam JH, Spaulding A, Rutherford GW, Siegfried N. Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naive individuals. *Cochrane Database Syst Rev*. 2010;(12):CD004246.

16. The effect of efavirenz versus nevirapine-containing regimens on immunologic, virologic and clinical outcomes in a prospective observational study. *AIDS*. 2012;26(13):1691-1705.
17. Braithwaite RS, Kozal MJ, Chang CC, et al. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. *AIDS*. 2007;21(12): 1579-1589.
18. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study. J Infect Dis. 2002;185(8):1062-1069.
19. Bannister WP, Ruiz L, Cozzi-Lepri A, et al. Comparison of genotypic resistance profiles and virological response between patients starting nevirapine and efavirenz in EuroSIDA. *AIDS*. 2008;22(3):367-376.
20. Pillay P, Ford N, Shubber Z, Ferrand RA. Outcomes for efavirenz versus nevirapine-containing regimens for treatment of HIV-1 infection: a systematic review and meta-analysis. *PLoS ONE*. 2013;8(7):e68995.
21. Nachega JB, Hislop M, Dowdy DW, et al. Efavirenz versus nevirapine-based initial treatment of HIV infection: clinical and virological outcomes in Southern African adults. *AIDS*. 2008; 22(16):2117-2125.
22. Keiser P, Nassar N, White C, Koen G, Moreno S. Comparison of nevirapine- and efavirenz-containing antiretroviral regimens in antiretroviral-naive patients: a cohort study. *HIV Clin Trials*. 2002;3(4):296-303.
23. de Beaudrap P, Etard JF, Gueye FN, et al. Long-term efficacy and tolerance of efavirenz- and nevirapine-containing regimens in adult HIV type 1 Senegalese patients. *AIDS Res Hum Retroviruses*. 2008;24(6):753-760.
24. Wester CW, Thomas AM, Bussmann H, et al. Non-nucleoside reverse transcriptase inhibitor outcomes among combination antiretroviral therapy-treated adults in Botswana. *AIDS*. 2010; 24(suppl 1): S27-S36.