# The Nucleoside Backbone Affects Durability of Efavirenz- or Nevirapine-Based Highly Active Antiretroviral Therapy in Antiretroviral-Naive Individuals

*Naa Torshie Annan, MB, BS, MRCP,* Mark Nelson, MD, FRCP,* Sundhiya Mandalia, MSc,† Mark Bower, MA, FRCP, FRCPath, PhD,† Brian G. Gazzard, MD, FRCP,* and Justin Stebbing, MA, MRCP, FRCPath, PhD†*

**Objectives:** We wished to determine the efficacy of nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens in antiretroviral-naive patients commencing highly active antiretroviral therapy (HAART) and to evaluate the effect of calendar year, nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone, sex, and ethnicity on treatment outcome.

**Methods:** Antiretroviral-naive individuals commencing efavirenz or nevirapine with dual-nucleoside analogue backbones were identified from a prospective database. Virological success was defined as HIV viral load <500 copies per milliliter. Treatment failure was defined as a switch or discontinuation of NNRTI or documented virological failure (2 measurements with viral load >500 copies/mL).

**Results:** From a cohort of 994 individuals, 73% commenced efavirenz- and 27% nevirapine-containing regimens. We found no differences between the 2 treatment groups for the time to virological success (proportion with virological success: efavirenz 71%, nevirapine 72%, $P = 0.77$) or treatment failure (proportion failing treatment: efavirenz 23%, nevirapine 26%, $P = 0.58$). There was a significant difference in the calendar year for commencing HAART for the time to virological success and treatment failure ($P < 0.001$). In the multivariable model, the likelihood of virological success for stavudine/lamivudine was 52% [relative hazard (RH) 1.52, 95% confidence interval (CI) 1.17 to 1.97, $P = 0.002$]. The nonthymidine analogue backbones as a group seemed to be least likely associated with virological success (RH 0.62, 95% CI 0.48 to 0.80, $P < 0.001$). This was however largely driven by tenofovir/didanosine being significantly associated with treatment failure (RH 6.48, 95% CI 3.81 to 11.0, $P < 0.001$). Sex and ethnicity were not associated with treatment outcome.

**Conclusions:** We found no significant differences between nevirapine and efavirenz for the time to virological success or treatment failure. Calendar year of commencing HAART and NRTI backbones were significant predictors of virological success and treatment failure, explaining differences in data to the 2NN study. The weaker the NNRTI (or the weaker the protease inhibitor) the more important the NRTI backbone becomes.

**Key Words:** calendar year, NNRTI, NRTI, sex, treatment failure, virological success

(*J Acquir Immune Defic Syndr* 2009;51:140–146)

## INTRODUCTION

It is well known that highly active antiretroviral therapy (HAART) has had considerable beneficial effects in reducing mortality and morbidity in HIV-infected patients. First-line HAART must be effective and durable and must have minimal side effects to have the greatest chance of achieving viral suppression.[1] Nonnucleoside reverse transcriptase inhibitors (NNRTIs) have become increasingly popular as first-line HAART regimens partly because of convenient dosing, low pill burdens, and lack of food restrictions.[2–6] The demonstrated efficacy of NNRTIs has also played a role in this choice.[4,7–15] Riddler et al presented the results of a controlled study (the AIDS Clinical Trials Group 5142 trial) in which 89% of patients commencing efavirenz and 77% lopinavir/ritonavir achieved viral suppression (<50 copies/mL) at 96 weeks ($P = 0.003$). The time to virological failure was shorter in the lopinavir arm ($P = 0.006$), but there was no significant difference in treatment limiting toxicity.[12]

To date, there has only been one large, randomized, controlled trial, the 2NN study, comparing efavirenz with nevirapine in antiretroviral-naive HIV-infected patients, and this failed to demonstrate noninferiority of nevirapine over efavirenz.[2–3] Several cohort studies have suggested that efavirenz is more effective than nevirapine.[4,7–9] Important confounding factors are calendar year of treatment and nucleoside analogue reverse transcriptase inhibitors (NRTIs) that may explain the differences between cohort studies and the 2NN trial. We have evaluated this in a large prospective cohort of patients.

## METHODS

Antiretroviral-naive patients were identified, and information was collected from a large prospective database at the Chelsea and Westminster Hospital, London, United Kingdom.

Received for publication June 13, 2008; accepted February 17, 2009.
From the *Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; and †Imperial College School of Medicine, London, United Kingdom.
Funding source: none.
Conflicts of interest: none declared.
All authors contributed to the design and analysis of data.
S.M. specialized in the statistics; N.T.A., J.S., and M.N. wrote the final article; and all authors approved the final version submitted.
Correspondence to: Dr. Justin Stebbing, MA, MRCP, FRCPath, PhD, Imperial College Healthcare NHS Trust, Fulham Palace Road, London, W6 8RF (e-mail: j.stebbing@imperial.ac.uk).

This database contains patient information including demographic details, antiretroviral history [including dates of starting, switching, or stopping antiretroviral therapy (ART)], and clinical events. HIV viral load (VL) and CD4 cell counts recorded at regular intervals corresponding to routine clinical visits are also contained in the database. For the purposes of this study, HIV-1 VL <500 copies per milliliter (Chiron assay) was the lower limit of detection.

All antiretroviral-naive patients commencing efavirenz or nevirapine with 2 NRTIs who had documented a pretreatment VL >500 copies per milliliter within 6 months of commencing therapy were included. Individuals commencing efavirenz or nevirapine simultaneously, efavirenz or nevirapine, and a protease inhibitor (PI) or those with a pretreatment VL <500 copies per milliliter were excluded. All baseline characteristics were compared between the 2 groups (efavirenz- and nevirapine-containing HAART), and any differences were tested using the $\chi^2$ test.

The baseline CD4 count and VL parameters were categorized into quartiles. The nonthymidine analogue reverse transcriptase inhibitors [lamivudine (3TC)/abacavir, lamivudine/didanosine (3TC/DDI), tenofovir (TFV)/DDI), TFV/3TC, and TFV/emtricitabine] have been grouped together due to small numbers.

Data were analyzed using 2 defined events. For virological success, the defined event was achieving HIV-1 VL <500 copies per milliliter within 6 months of commencing first-line HAART. For those not achieving VL <500 copies per milliliter, data were censored at discontinuation of therapy or at most recent visit before the end of the study period. A comparison between the 2 treatment groups and the effect of calendar year of commencing HAART, dual-NRTI backbones, sex, and ethnicity were assessed.

Treatment failure was defined as toxicity failure (NNRTI only) or virological failure after 12 weeks of commencing HAART. Virological failure was defined as 2 successive VLs >500 copies per milliliter performed at least 4 weeks apart. Switching from one NRTI backbone to another due to intolerance was not considered treatment failure. Data were censored at stopping first-line HAART for any reason including non–failing regimens or loss to follow-up. For patients who did not fail treatment, the data were censored at the end of the study period.

Kaplan–Meier survival plots were produced for the "time-to-event" analysis. Univariate and multivariate Cox proportional hazards regression analyses were used to identify factors associated with the likelihood of virological success or treatment failure. For both events, variables found to be significant ($P < 0.15$ including baseline VL, NRTI backbone, and year) in the univariate model were used to build the multivariable model. Due to the interaction between the changing patterns of prescribing, the multivariable model was stratified by year, NNRTI and adjusted for the residual or confounding effects of other variables in the model. Only the significant variables have been presented in the multivariable models.

## RESULTS

A total of 994 antiretroviral-naive patients were included in the analysis of whom 723 (72.7%) commenced a HAART regimen containing efavirenz and 271 (27.3%) nevirapine.

Table 1 summarizes the baseline characteristics of all the patients. There were no significant differences in the 2 treatment groups with respect to the age at starting first-line HAART or ethnicity. The median baseline CD4 count measured 173 $\times$ $10^6$ per liter (interquartile ratio 89–260 $\times$ $10^6$/L), and the median baseline VL was 4.9 $\log_{10}$ copies per milliliter (interquartile ratio 4.4–5.4 $\log_{10}$). A significantly greater number of females were prescribed nevirapine compared with efavirenz. Patients in the nevirapine treatment group had a significantly lower baseline VL and a higher baseline CD4 count.

**TABLE 1.** Baseline Characteristics of All Patients Commencing First-Line HAART

| | Total No. Patients Who Started First-Line NNRTI-Containing HAART (N = 994) | | | |
|---|---|---|---|---|
| | | Efavirenz | Nevirapine | |
| Variable | Total | n = 723 (%) | n = 271 (%) | *P* |
| Sex | | | | <0.001 |
| Female | 141 | 86 (12) | 55 (20) | |
| Male | 853 | 637 (88) | 216 (80) | |
| Mean age (yrs) | 38 | 38 | 37 | 0.210 |
| Ethnicity | | | | 0.084 |
| White | 687 | 509 (70) | 178 (66) | |
| Black African | 149 | 97 (13) | 52 (19) | |
| Other | 99 | 70 (10) | 29 (11) | |
| Unknown | 59 | 47 (7) | 12 (4) | |
| Baseline VL ($\log_{10}$), copies/mL | | | | <0.001 |
| >5.4 | 248 | 205 (28) | 43 (16) | |
| 5.1–5.4 | 249 | 182 (25) | 67 (25) | |
| 4.4–5.0 | 248 | 169 (24) | 79 (29) | |
| ≤4.4 | 249 | 167 (23) | 82 (30) | |
| Baseline CD4 (cells/$mm^3$) | | | | 0.054 |
| Missing | 9 | 9 (1) | 0 (0) | |
| >260 | 246 | 171 (24) | 75 (28) | |
| 173–260 | 244 | 182 (25) | 62 (23) | |
| 90–172 | 247 | 170 (24) | 77 (28) | |
| ≤89 | 248 | 191 (26) | 57 (21) | |
| Year of start of therapy | | | | <0.001 |
| 1998 | 70 | 21 (3) | 49 (18) | |
| 1999 | 194 | 116 (16) | 78 (29) | |
| 2000 | 143 | 79 (11) | 64 (24) | |
| 2001 | 156 | 105 (15) | 51 (19) | |
| 2002 | 139 | 124 (17) | 15 (5) | |
| 2003 | 189 | 181 (25) | 8 (3) | |
| 2004 | 103 | 97 (13) | 6 (2) | |
| NRTI backbone | | | | <0.001 |
| Other NRTIs | 24 | 18 (3) | 6 (2.5) | |
| 3TC + ABC | 34 | 30 (4) | 4 (1.5) | |
| 3TC + D4T | 122 | 75 (10) | 47 (17) | |
| 3TC + DDI | 47 | 44 (6) | 3 (1) | |
| D4T + DDI | 130 | 52 (7) | 78 (29) | |
| 3TC + TFV | 93 | 89 (12) | 4 (1.5) | |
| DDI + TFV | 42 | 42 (6) | 0 (0.0) | |
| TFV + FTC | 22 | 21 (3) | 1 (0.5) | |
| 3TC + AZT | 480 | 352 (49) | 128 (47) | |

ABC, abacavir; FTC, emtricitabine.

There was a marked change in the prescription trend of NNRTIs over time, with nevirapine being prescribed less frequently in more recent years. There were also differences in the nucleoside backbone prescribed with nevirapine versus efavirenz (Table 1).

## Virological Success

The Kaplan–Meier survival plot (Fig. 1) illustrates the time to virological success and demonstrates no significant difference between the 2 treatment groups within 6 months of commencing HAART ($P = 0.77$). The percentage of patients who achieved virological suppression by our definition (VL < 500 copies/mL) was 71% (514 of 994) for efavirenz- and 72% (195 of 271) for nevirapine-containing HAART.

In the univariable analysis (Table 2), baseline VL, NRTI backbone, and calendar year of commencing therapy were the only significant independent predictors of virological success. There was a strong difference in calendar year of commencing HAART with improvements in virological success in more recent years.

The multivariable model was adjusted for sex, age, and baseline CD4 count and stratified by year, NNRTI, and baseline VL. We found that the patients who received stavudine (D4T)/3TC had a 52% greater likelihood of virological success [relative hazard (RH) 1.52, 95% confidence interval (CI) 1.17 to 1.97, $P = 0.002$]. Results for the nonthymidine analogue backbones, which were predominantly driven by the effect of TFV and DDI, were less likely to achieve virological success (RH 0.62, 95% CI 0.48 to 0.80, $P < 0.001$).

## Treatment Failure

A total of 237 of 994 patients (24%) experienced treatment failure. This equated to 166 of 723 in the efavirenz group (23%) and 71 of 271 in the nevirapine group (26%). For the time to treatment failure (unadjusted), we found no difference between patients who commenced either regimen (Fig. 2).

Calendar year of starting HAART and NRTI backbone were significant predictors of treatment failure in the univariable model (Table 3). Data for patients who commenced therapy in the year 2004 are censored at the end of the study period (July 2004), and therefore, no observations can be made for these individuals.

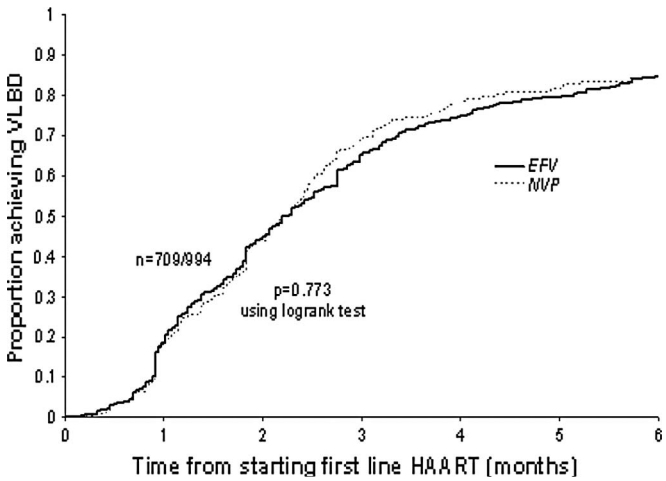


**FIGURE 1.** Kaplan–Meier plot showing time to virological success. EFV, efavirenz; NVP, nevirapine.

Patients commencing nonthymidine analogues seemed to be more likely to experience treatment failure (RH 2.16, 95% CI 1.58 to 2.96, $P < 0.001$) in the unadjusted analysis. This was however driven by the effect of TFV/DDI, which were significantly associated with treatment failure (RH 6.48, 95% CI 3.81 to 11.0, $P < 0.001$). In the multivariable model, none of the significant factors in the univariable model were associated with treatment failure (data not presented).

## Effect of Sex and Ethnicity

In the unadjusted analysis, females who commenced nevirapine were more likely to achieve virological success (RH 1.46, 95% CI 1.03 to 2.08, $P = 0.040$). In the multivariable model, however, this association was not replicated (RH 1.39, 95% CI 0.97 to 1.98, $P = 0.70$). Neither white ethnicity nor black African ethnicity was associated with virological success in the efavirenz ($P = 0.279$) or nevirapine ($P = 0.100$) treatment groups (unadjusted analysis).

Similarly, neither sex (efavirenz, $P = 0.06$; nevirapine, $P = 0.38$) nor ethnicity (efavirenz, $P = 0.550$; nevirapine, $P = 0.250$) was associated with treatment failure (unadjusted analysis).

# DISCUSSION

These data demonstrate that efavirenz- and nevirapine-containing HAART regimens are equivalent in terms of virological success and that the backbone remains a critical determinant. The weaker the NNRTI (or the weaker the PI) the more important the NRTI backbone becomes.

Cohort studies provide the opportunity to study multiple outcomes related to a specific exposure and are also advantageous as they minimize recall bias. They are however potentially subject to the effect of factors (confounding) that may affect the outcome. Second, exposure patterns may change over time, including the pattern of use of different NRTI backbones prescribed as part of first-line HAART. Maintaining high rates of follow-up within cohort studies can be difficult and is unsuitable for studying outcomes where the time between exposure and disease manifestation is long.

In this antiretroviral-experienced cohort, we have shown equivalence between efavirenz- and nevirapine-containing HAART regimens for both the time to virological success and treatment failure. These results are in contrast to other cohort studies, which have suggested that efavirenz is more effective than nevirapine.[4,7–9] Although variation in the NRTI backbone decreases power, as does the complexity of comparing antiretrovirals and the conflicting results between registration trials, prospective comparative trials, and cohorts, these data we present suggest that backbone remains a critical determinant.

Data from Matthews et al[8] of antiretroviral-naive patients commencing HAART before December 1999 at Chelsea and Westminster Hospital, London, United Kingdom, demonstrated improved virological responses within 6 months favoring efavirenz over nevirapine and PI (nelfinavir or

**TABLE 2.** Univariable and Multivariable Cox Proportional Hazards Regression Model Showing Likelihood of Virological Success

| Variable | No. Patients Achieving VL Success 709/994 (71.3%) | Relative Hazard (Unadjusted) | 95% CI | *P* |
|---|---|---|---|---|
| Sex | | | | 0.294 |
| Female | 101/141 (72) | 1.12 | 0.91–1.38 | |
| Male | 608/853 (71) | 1 | — | |
| Age (yrs) | 38 | 1.00 | 0.99–1.01 | 0.927 |
| Baseline VL ($log_{10}$), copies/mL | | | | 0.037 |
| >5.4 | 172/248 (69) | 0.94 | 0.76–1.16 | |
| 5.1–5.4 | 182/249 (73) | 1.09 | 0.88–1.34 | |
| m4.4–5.0 | 184/248 (74) | 1.26 | 1.02–1.55 | |
| <4.4 | 171/249 (69) | 1 | — | |
| Baseline CD4 (cells/$mm^3$) | | | | 0.210 |
| Missing | 8/9 (89) | 1.05 | 0.52–2.14 | |
| >260 | 178/246 (72) | 0.86 | 0.69–1.06 | |
| 173–260 | 161/244 (66) | 0.81 | 0.65–1.01 | |
| 90–172 | 190/247 (77) | 0.99 | 0.81–1.22 | |
| ≤89 | 172/248 (69) | 1 | — | |
| NNRTI | | | | 0.777 |
| Efavirenz | 514/723 (71) | 0.98 | 0.83–1.15 | |
| Nevirapine | 195/271 (72) | 1 | — | |
| NRTI backbone | | | | <0.001 |
| Other NRTIs | 14/24 (58) | 0.62 | 0.36–1.06 | |
| D4T/3TC | 97/122 (80) | 1.24 | 0.99–1.55 | |
| D4T/DDI | 96/130 (74) | 0.97 | 0.77–1.21 | |
| Nonthymidine analogues | 120/238 (50) | 0.57 | 0.46–0.70 | |
| AZT/3TC | 382/480 (80) | 1 | — | |
| Year | | | | <0.001 |
| 1998 | 46/70 (66) | 0.86 | 0.61–1.20 | |
| 1999 | 155/194 (80) | 1.12 | 0.89–1.41 | |
| 2000 | 123/143 (86) | 1.55 | 1.23–1.99 | |
| 2001 | 124/156 (80) | 1.40 | 1.10–1.79 | |
| 2002 | 108/139 (78) | 0.95 | 0.74–1.22 | |
| 2003 | 136/189 (72) | 1 | — | |

| Variable | | Relative Hazard (Adjusted) | 95% CI | *P* |
|---|---|---|---|---|
| NRTI backbone* | | | | |
| Other NRTIs | — | 0.73 | 0.40–1.31 | 0.284 |
| D4T/3TC | — | 1.52 | 1.17–1.97 | 0.002 |
| D4T/DDI | — | 1.24 | 0.93–1.65 | 0.140 |
| Nonthymidine analogues | — | 0.62 | 0.48–0.80 | <0.001 |
| AZT/3TC | — | 1 | — | — |

*Adjusted for sex, age, baseline CD4 count and stratified by year, NNRTI, and baseline VL.

indinavir). It is interesting to note that over time, the results from this cohort are different and may be explained by the effect of calendar year, the choice of backbones prescribed over time, or changes in practice with respect to managing toxicities.

The use of NRTI backbones has evolved over time, and recently, nonthymidine analogues have been the recommended backbone[16,17] as a result of the toxicities associated with thymidine analogues.[18–22] The majority of patients (74%) in this cohort were prescribed thymidine analogues [azidothymidine (AZT)/3TC, D4T/3TC, and D4T/DDI], which reflects clinical practice in late 1990s and early 2000s. Although we have shown differences between the nonthymidine analogues as a group, this result must be interpreted with caution due to the small numbers and the effect of TFV/DDI on treatment failure.

The 2NN study failed to show noninferiority between efavirenz versus nevirapine in combination with D4T/3TC. Even though this complements our results, we are cautious about making comparisons given the inherent biases of cohort studies. Second, 2NN patients were prescribed 1 backbone (D4T/3TC), and hence, a comparison between NRTI backbones and their impact on treatment outcome was not evaluated. The only other randomized controlled trial of

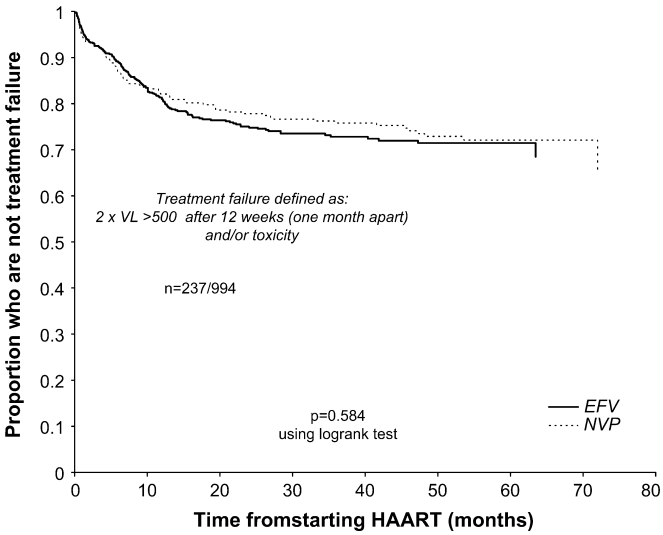


**FIGURE 2.** Kaplan–Meier plot showing time to treatment failure. EFV, efavirenz; NVP, nevirapine.

efavirenz and nevirapine with D4T/DDI as the NRTI backbone reported achieving virological success of 74% with efavirenz compared with 64% with nevirapine.[23] These studies were both in ART-naive individuals, and without making direct comparisons, the different outcomes raised the question whether NRTI backbone is a significant contributory factor.

Murphy et al[24] evaluated the effect of different backbones in patients who received D4T/3TC or D4T/DDI or AZT/3TC with indinavir and showed no significant difference for virological and immunologic responses in treatment-naive patients. More recently, the GILEAD 934 study[25] has demonstrated statistically significant results for achieving and main taining viral suppression with tenofovir/emtricitabine compared with AZT/3TC. The 903 study has also demonstrated favorable results with TDF/3TC and efavirenz compared with D4T/3TC.[26] Fewer studies have been conducted with nevirapine and different backbones. A recent cohort study from Benzie et al[27] of patients commencing twice-daily nevirapine with different NRTI backbones reported that 85% of subjects had a VL <50 copies per milliliter at week 48, with no statistically significant association with NRTI backbone. Other

**TABLE 3.** Univariable and Cox Proportional Hazards Regression Model Showing Likelihood of Treatment Failure

| Variable | Treatment Failures 237/994 (23.8%) | Relative Hazard (Unadjusted) | 95% CI | *P* |
|---|---|---|---|---|
| Sex | | | | 0.337 |
| Female | 39/141 (28) | 1.18 | 0.89–1.67 | |
| Male | 198/853 (23) | 1 | — | |
| Age (yrs) | 36.6 (7.2) | 0.98 | 0.97–1.00 | 0.034 |
| Baseline VL ($log_{10}$), copies/mL | | | | 0.154 |
| >5.4 | 49/248 (20) | 0.67 | 0.46–0.96 | |
| 5.1–5.4 | 56/249 (23) | 0.76 | 0.54–1.08 | |
| 4.4–5.0 | 61/248 (25) | 0.85 | 0.60–1.19 | |
| ≤4.4 | 71/249 (29) | 1 | — | |
| Baseline CD4 (cells/$mm^3$) | | | | 0.692 |
| Missing | 3/9 (33) | 1.30 | 0.41–4.16 | |
| >260 | 66/246 (27) | 1.09 | 0.77–1.55 | |
| 173–260 | 57/244 (23) | 1.08 | 0.75–1.55 | |
| 90–172 | 51/247 (21) | 0.86 | 0.59–1.24 | |
| ≤89 | 60/248 (24) | 1 | — | |
| NNRTI | | | | 0.583 |
| Nevirapine | 71/271 (26) | 0.93 | 0.70–1.22 | |
| Efavirenz | 166/723 (23) | 1 | — | |
| NRTI backbone | | | | <0.001 |
| Other NRTIs | 4/24 (17) | 0.77 | 0.28–2.08 | |
| D4T/3TC | 20/122 (17) | 0.68 | 0.42–1.08 | |
| D4T/DDI | 40/130 (31) | 1.19 | 0.83–1.72 | |
| Nonthymidine analogues | 66/238 (28) | 2.16 | 1.58–2.96 | |
| AZT/3TC | 107/480 (22) | 1 | — | |
| Year | | | | <0.001 |
| 1998 | 25/70 (36) | 0.67 | 0.41–1.11 | |
| 1999 | 53/194 (27) | 0.52 | 0.35–0.77 | |
| 2000 | 28/143 (20) | 0.37 | 0.23–0.59 | |
| 2001 | 30/156 (19) | 0.41 | 0.26–0.64 | |
| 2002 | 29/139 (21) | 0.48 | 0.31–0.76 | |
| 2003 | 55/189 (29) | 1 | — | |

studies have been prematurely halted due to high virological failure with nevirapine and TDF/3TC.[28,29]

We found no difference in the time to treatment failure between the 2 regimens ($P = 0.584$). Keiser et al[7] reported a shorter time to treatment failure and a smaller decrease in plasma HIV-I RNA for patients on nevirapine. Results from the Eurosida[4] cohort favored efavirenz over nevirapine for virological failure in both the unadjusted and adjusted analyses (RH 0.57, 95% CI 0.47 to 0.69, $P < 0.0001$). The Eurosida cohort however differs from our cohort, in that the majority of patients were treatment experienced having had prior exposure to PIs and NRTIs. As a group, the thymidine and non-thymidine nucleoside analogues were not associated with treatment failure in the multivariable model; however, when we looked at the effect of the dual NRTIs in this study, only TFV/DDI was significantly associated with treatment failure. Several studies have reported this link between treatment failure and TFV/DDI.[30–32]

In the univariable models for both virological success and treatment failure, calendar year of treatment was a significant independent predictor of outcome. Individuals commencing treatment in recent years were more likely to achieve viral suppression by our definition. Conversely, treatment failure was more likely to occur in recent years, and this finding may represent a better approach to managing toxicity and switching therapy early in patients who experienced HAART-related toxicity. Neither sex nor ethnicity was associated with virological success or treatment failure in this cohort. This finding is supported by data from other published trials.[33–35]

In summary, this cohort study of antiretroviral-naive patients commencing first-line HAART showed no significant difference between efavirenz and nevirapine. Our cohort suggests that any difference between the 2 drugs may be explained by the use of different NRTI backbones and the year of commencing therapy. Unlike other cohort studies, this study included only ART-naive patients and eliminates the confounding effects of previous ART. Cohort studies are however difficult to analyze due to inherent biases, and physicians should individualize their choice of drugs for patients, using controlled clinical data.

## REFERENCES


1. Fischl MA. Antiretroviral therapy in 1999 for antiretroviral-naïve individuals with HIV infection. *AIDS*. 1999;13:S49–S59.
2. 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;363:1253–1264.
3. van-Leth F, Andrews S, Grinsztejn B, et al. The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. *AIDS*. 2005;19:463–471.
4. Phillips AN, Pradier C, Lazzarin A, et al. Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens for 2203 mainly antiretroviral-experienced patients. *AIDS*. 2001;15:2385–2395.
5. Mannheimer S, Friedland G, Matts J, et al. The consistency of adherence to antiretroviral therapy predicts biological outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis*. 2002;34:1115–1121.
6. Garcia de Olalla P, Knobel H, Cgroupona A, et al. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2002;30:105–110.
7. Keiser P, Nassar N, White C, et al. Comparison of nevirapine and efavirenz-containing antiretroviral regimens in antiretroviral-naïve patients: a cohort study. *HIV Clin Trials*. 2002;3:296–303.
8. Matthews GV, Sabin CA, Mandalia S, et al. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naïve patients: a cohort study. *AIDS*. 2002;16:53–61.
9. 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 naïve antiretroviral (I.Co.N.A.) study. *J Infect Dis*. 2002;185:1062–1068.
10. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med*. 1999;341:1865–1873.
11. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naïve patients (the Combine Study). *Antivir Ther*. 2002; 7:81–90.
12. Riddler SA, Haubrich R, DiRienzo G, et al. A prospective, randomized, phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection: ACTG 5142. Presented at: XVI International AIDS Conference; August 2006; Toronto, Canada. Abstract THLB0204.
13. Montaner JS, Sang MS, Barylski C, et al. FOCUS Study: saquinavir qd regimen versus efavirenz qd regimen 48 week analysis in HIV infected patients. Presented at: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 2002; San Diego, CA. Abstract H-167.
14. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349:2304–2315.
15. Bartlett JA, Johnson J, Herrera G, et al. Long term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir or stavudine. *J Acquir Immune Defic Syndr*. 2006;43:284–292.
16. Gazzard B on behalf of the BHIVA Writing Committee. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). *HIV Med*. 2006;7:487–503.
17. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection. 2006 recommendations of the International AIDS Society—USA Panel. *JAMA*. 2006;296:827–843.
18. Dubé M, Komarow L, Mulligan K, et al; the AIDS Clinical Trials Group A5005s and 384 Study Teams. DEXA outcomes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz or both plus dual nucleosides: long-term results from A5005s, a substudy of ACTG 384. Presented at: XVI International AIDS Conference; August 2006; Toronto, Canada. Abstract WEPE0167.
19. Podzamcer D, Ferrer E, Sanchez P, et al. A randomised comparison of abacavir and stavudine, combined with lamivudine/efavirenz in antiretroviral-naive patients. Final 96-week results (ABCDE Study). Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 2005; Boston, MA. Abstract 587.
20. Gallant JE, Staszewski S, Pozniak A, et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naive patients. A 3-year randomised trial. *JAMA*. 2004;292:191–201.
21. Waters LJ, Nelson MR. Are all non-thymidine analogue backbones appropriate for treating antiretroviral-naive patients? *Int J Clin Pract*. 2005;59:1452–1458.
22. Martin A, Smith DE, Carr A, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from thymidine analogue to abacavir: the MITOX Extension Study. *AIDS*. 2004;18:1029–1036.
23. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz versus nevirapine comparison) trial: a randomized, open-label study in HIV-infected naïve individuals. *HIV Clin Trials*. 2002;3:186–194.
24. Murphy R, Santana J, Squires K, et al. START observational study: longitudinal follow-up of virologic and immunologic responses in START I and START II patients. Presented at: 8th Conference on Retroviruses and Opportunistic Infections; February 2001; Chicago, IL. Abstract 314.
25. Arribas J, Pozniak A, Gallant J, et al. Three-year safety and efficacy of emtricitabine/tenofovir and efavirenz compared to fixed dose zidovudine/lamivudine and efavirenz in antiretroviral treatment naïve patients. Presented at: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 2007; Sydney, Australia. Abstract WEPEB029.
26. Havlir DM, Koelsch KK, Strain MC, et al. Predictors of residual viraemia in HIV-infected patients successfully treated with efavirenz and

lamivudine plus either tenofovir or stavudine. *J Infect Dis*. 2005;191: 1164–1168.
27. Benzie A, Marett B, Portsmouth S, et al. High success rates when switching to once daily nevirapine. Presented at: 11th European AIDS Conference; October 2007; Madrid, Spain. Abstract P7.9/02.
28. Rey D, Schmitt MP, Hoizey G, et al. Early virologic non-response to once daily combination of lamivudine, tenofovir and nevirapine in antiretroviral naïve HIV-infected patients; preliminary results of the DAUFIN study. Presented at: 14th Conference of Retroviruses and Opportunistic Infection; March 2007; Los Angeles, CA. Abstract 503.
29. Towner W, Kerrigan H, LaRiviere M, et al. Efficacy of once daily regimen of nevirapine, lamivudine, and tenofovir in treatment-naïve HIV-infected patients; a pilot study. Presented at: 7th International Congress on Drug Therapy in HIV infection; November 2004; Glasgow, Scotland. Abstract P49.
30. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS*. 2005; 19:1183–1188.
31. Negredo E, Molto J, Burger D, et al. Unexpected $CD_4$ cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load. *AIDS*. 2004;18:459–463.
32. Clotet B, Negredo E, Bonjoch A, et al. Concurrent administration of tenofovir (TDF) and didanosine (ddI) compromises immunologic recovery in treatment-experienced patients. Results from the TORO studies. Presented at: Seventh International Congress on Drug Therapy in HIV Infection; November 2004; Glasgow, Scotland. Poster 3.
33. Kumar PN, Rodrigues-French A, Thompson MA, et al. A prospective, 96-week study of the impact of trizivir, combivir/nelfinavir and combivir/stavudine/nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naive patients: effect of sex and ethnicity. *HIV Med*. 2006;7: 85–98.
34. Silverberg M, Wegner SA, Milazzo MJ, et al. Effectiveness of highly active antiretroviral therapy by race/ethnicity. *AIDS*. 2006;20:1531–1538.
35. Jensen-Fangel S, Pedersen L, Pedersen C, et al. The effect of race/ethnicity on the outcome of highly active antiretroviral therapy for human immunodeficiency virus type 1-infected patients. *Clin Infect Dis*. 2002;35:1541–1548.

 