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Efavirenz versus Nevirapine-based Initial Treatment of HIV Infection: Clinical and Virological Outcomes in Southern African Adults

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Abstract

Objective—To determine the effectiveness of efavirenz vs. nevirapine in initial antiretroviral therapy regimens for adults in sub-Saharan Africa

Design—Observational cohort study

Methods—Study subjects were 2,817 HIV-infected, HAART-naïve adults who began nevirapine- or efavirenz-based HAART between January 1998 and September 2004 via a private-sector HIV/AIDS program in nine countries of southern Africa. The primary outcome was time to virologic failure (two measurements of viral loads ≥ 400 copies/mL). Secondary outcomes included all-cause mortality, time to viral load < 400 copies/mL, pharmacy-claim adherence, and discontinuation of nevirapine or efavirenz without virologic failure.

Results—The median follow-up period was 2.0 years (interquartile range 1.2–2.6). Patients started on nevirapine were significantly less likely than those started on efavirenz to achieve high adherence,

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Conflict of interest

Consultant: R.E. Chaisson (Bristol-Myers Squibb). Consultant and/or honorarium: J.B. Nachega (GlaxoSmithKline, Merck-Sharp-Dohme) and G. Maartens (Merck-Sharp-Dohme). Grants received: G. Maartens (Merck-Sharp-Dohme). Other: J.B. Nachega (Aspen Pharmaceuticals); J.E. Gallant: Grants/Research Support (Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Roche, Tibotec), consultant and/or honorarium (Bristol Myers Squibb, Gilead Sciences, Roche, Abbott Laboratories, GlaxoSmithKline, Merck, Schering Plough, Pfizer, Tibotec).

whether defined as 100% (30.2% vs. 38.1%, $p < 0.002$) or $> 90\%$ (44.8% vs. 49.4%, $p < 0.02$) pharmacy-claim adherence. In a multivariate analysis, patients on nevirapine had greater risk of both virologic failure (HR 1.52; 95% CI 1.24–1.86), death (2.17; 1.31–3.60), and regimen discontinuation (1.67; 1.32–2.11). Switching from nevirapine to efavirenz had no significant virologic effect, whereas switching from efavirenz to nevirapine resulted in significantly slower time to suppression (HR 0.58, 95% CI 0.35–0.93) and faster time to failure (HR 3.92; 95% CI 1.61–9.55) than remaining on efavirenz.

Conclusions—In initial HAART regimens, efavirenz was associated with superior virologic and clinical outcomes than nevirapine, suggesting that efavirenz might be the preferred non-nucleoside reverse transcriptase inhibitor in resource-limited settings. However, its higher cost and potential teratogenicity are important barriers to implementation.

Keywords

Effectiveness; HAART; Efavirenz; Nevirapine; Southern Africa

INTRODUCTION

The World Health Organization (WHO) recommends that initial highly active antiretroviral therapy (HAART) regimens in resource-limited settings include a non-nucleoside reverse transcriptase inhibitor (NNRTI)—specifically efavirenz or nevirapine [1,2]. Despite the drugs' widespread use, direct comparisons of their effectiveness are limited and conflicting [3–6]. Currently, efavirenz is recommended over nevirapine for initial treatment by both the U.S. Department of Health and Human Services [7] and the International AIDS Society-USA guidelines [8] based on efavirenz' s more favorable toxicity profile and efficacy data [5,9–12]. However, a WHO survey found that most (67%) countries in sub-Saharan Africa recommended nevirapine-based regimens for first-line therapy because it costs less and is available in generic fixed-dose combination regimens [13,14]. Strong evidences that efavirenz produces more favorable virologic and clinical outcomes in a resource-limited population might influence recommendations as well as speed efforts to reduce the cost of efavirenz or to develop a generic efavirenz-containing fixed-dose combination regimen for use in such settings.

A preliminary analysis by our group suggested better virologic outcomes might exist for patients treated initially with efavirenz rather than with nevirapine [15]. However, that analysis was limited by a lack of clinical outcomes data, including mortality and change-in-therapy data. Also, in the earlier study we could only perform limited analyses of relative contributions of efavirenz and nevirapine on virologic outcomes, since the primary variable was adherence, not NNRTI choice.

We now report the results of a primary analysis of virologic and clinical outcomes by initial NNRTI in a large observational cohort study of adults in southern Africa.

METHODS

Study Population and Data Source

We evaluated records from HIV-1-infected adults enrolled in *Aid for AIDS*, a private-sector, employer-subsidized, disease-management program. While the majority of patients originate from South Africa, this program operates in nine countries of southern Africa, described in detail elsewhere [16]. This program does not manage clinics, but reviews HAART prescription requests from patients' private medical practitioners according to clinical guidelines [17], and

manages doctor's reimbursements. HAART and laboratory tests are fully covered by the patient's medical insurance fund (MIF).

In *Aid for AIDS*, patients become eligible for HAART with either a documented CD4 count <350 cells/ μ L on two occasions or a clinical confirmation of an AIDS-defining illness. The treating physician decides whether to prescribe efavirenz- or nevirapine-based HAART, but efavirenz is required for those patients on rifampicin for tuberculosis. Nevirapine is required for women of childbearing potential who do not commit to using two reliable methods of contraception (e.g., condoms and hormonal contraceptives) because of the risk of teratogenicity with efavirenz.[18–20] HAART is dispensed monthly via a pharmacy of the patient's choice. For reimbursement, patients submit a claim containing the date dispensed, the specific medication regimen, and the quantity supplied. Reimbursement requires no patient co-payment. In this population, short-course HAART is standard policy for prevention of mother-to-child transmission (pMTCT) of HIV; single-dose nevirapine was never used [17].

Aid for AIDS systematically collects demographic, laboratory, and clinical data at baseline and during enrollment and recommends semi-annual measurement of CD4 count and viral load, but physicians choose the timing and the laboratory in which these tests are performed. Physicians are asked to use the same laboratory for follow-up measurements, but the assays used are not recorded. During follow-up, deaths were identified by notification from the attending medical practitioner, the hospital case manager (for in-hospital deaths), the medical fund administrator, or a family member. Patients who left their MIF or whose MIF changed to a different disease-management program were censored as "lost to follow-up" at the date of departure.

For this study, we included all *Aid for AIDS* participants who met these criteria: (a) were qualified for and claimed at least one month of HAART between January 1998 and September 2004; (b) used an initial regimen containing either efavirenz or nevirapine plus two NRTIs; (c) were at least 18 years old at HAART initiation; (d) had no mention of prior HAART therapy in the medical record provided by the medical practitioner or attending physician; (e) had no viral load <400 copies/mL prior to HAART initiation; and (f) had at least one follow-up viral-load measurement 30 to 365 days after initiating HAART.

Analytic Variables and Definitions

The primary exposure variable for the current analysis was the initial NNRTI used. Patients were defined as being on efavirenz- or nevirapine-based HAART from the first pharmacy claim authorized until (a) authorization for that drug lapsed for 30 days, (b) another NNRTI or protease inhibitor was prescribed and authorized by *Aid for AIDS*, or (c) study end (September 1, 2004).

The primary outcome was time to virologic failure, defined as (a) two separate (consecutive or non-consecutive) measurements of viral load ≥ 400 copies/mL, each more than six months after HAART initiation, or (b) switch to another NNRTI or protease inhibitor after at least one such measurement. Patients who had a single viral load >400 copies/mL and who died or were subsequently lost to follow-up or censored were not eligible to be "virologic failures," except in the time-to-failure analyses for those patients who switched regimens. Secondary outcomes included time to all-cause mortality, time to viral-load suppression <400 copies/mL, and discontinuation of initial NNRTI without virologic failure. During the follow-up period, deaths were identified as noted above. Potential confounders evaluated are shown in Table 1.

Pharmacy-claim adherence was expressed as a percentage, calculated as the number of months with HAART claims submitted divided by the number of complete months from HAART commencement to (a) death, (b) withdrawal from *Aid for AIDS*, or (c) study end, with the result

multiplied by 100. Depending on the analysis, pharmacy-claim adherence was analyzed as a binary variable with a cut-off of 100%, 90%, or 80%; or in discrete pre-defined strata; or as a continuous variable for > 50% adherence. Of note, adherence based on pharmacy data has been validated with medication electronic monitor system (MEMS caps) adherence [21] and therapeutic drug levels [22,23], and it reliably predicts virologic success [5,17,24–26], drug resistance [27], and survival [16,28,29].

Statistical Analysis

Differences in baseline characteristics were assessed with two-sample Student's t tests (continuous variables with normal distributions on visual inspection), Wilcoxon rank-sum (other continuous variables), and χ^2 tests (categorical variables). Kaplan-Meier plots were used to estimate outcome probability according to initial NNRTI and adherence status (100% vs. <100%; >90% vs. <90%; >80% vs. <80%). Cox proportional hazards regression was used to model the individual and simultaneous effects of the initial NNRTI, baseline variables, and pharmacy-claim adherence on time to virologic failure, viral suppression, and regimen discontinuation. Plots of $-\log[-\log(\text{survival})]$ against $\log(\text{analysis time})$ and analyses of scaled Schoenfeld residuals were used to assess the proportionality assumption ($p = 0.67$ for efavirenz vs. nevirapine on time to virologic failure). All available variables were included a priori in multivariate models and were stratified into discrete categories: sex (male/female), race (black/other), CD4 count (≤ 50 , 51–200, or > 200 cells/ μL), viral load ($>$ or $< 5 \log_{10}$ copies/mL), prior history of antiretroviral therapy for pMTCT (yes/no), initial NRTI combination (zidovudine/lamivudine, stavudine/lamivudine, stavudine/didanosine, or zidovudine/didanosine), and date of HAART initiation (in four calendar-year strata). Interactions were tested by including multiplicative terms in regression models. All p-values reported are exact and 2-tailed, with a value of < 0.05 considered statistically significant. Statistical analyses were performed using STATA Release 8.0 (Stata Corporation, College Station, TX, USA).

Ethical Approvals

This study was approved by the University of Cape Town Research Ethics Committee and by the *Aid for AIDS* Executive Committee, Cape Town, South Africa.

RESULTS

Of 2817 patients meeting inclusion criteria, 1822 (64.7%) were started on efavirenz and 995 (35.5%) on nevirapine (Table 1). Compared to patients started on efavirenz, those on nevirapine were significantly younger, were more likely to be female, were less immunosuppressed (median CD4 counts: 171 cells/ μL , on nevirapine; 136 cells/ μL , on efavirenz), had lower viral loads at baseline (median 5.1 $\log_{10}$ copies/mL, on nevirapine, versus 5.2, on efavirenz), started treatment earlier in calendar time, and were more likely to receive zidovudine/lamivudine ($p < 0.01$ for all comparisons; Table 1).

The two groups did not differ in frequency of viral-load measurements (median 1.08 per year, IQR 0.59–1.60, for nevirapine; 1.10, 0.71–1.58, for efavirenz; $p = 0.15$) or time to first post-HAART viral-load measurement (median 122 days, IQR 92–209, for nevirapine; 114 days, 92–204, for EFV; $p = 0.19$). Women with baseline CD4 counts ≥ 250 cells/ μL were more likely to be started on nevirapine ($n = 157$, 23.4%) than efavirenz ($n = 203$, 18.5%). Exclusion of these patients did not materially change results.

Median (interquartile range [IQR]) length of follow-up was 1.9 (1.0–2.6) years for the nevirapine group and 2.0 (1.3–2.6) years for patients started on efavirenz ($p = 0.006$ for difference; Table 1). During this time, patients started on nevirapine were significantly less likely than those on efavirenz to achieve high adherence, whether defined as 100% (30.2% vs.

38.1%, $p < 0.002$) or $>90\%$ (44.8% vs. 49.4%, $p < 0.02$). Patients started on nevirapine were also more likely to experience virologic failure (20.4% vs. 13.8%) and NNRTI discontinuation without virologic failure (15.4% vs. 8.9%). Crude proportions of patients who died (2.3% for nevirapine vs. 1.8% for efavirenz) or were lost to follow-up (10.4% vs. 11.6%) were comparable (Figure 1), as was the median [IQR] gain in CD4 count among 510 patients who had a CD4 count measurement between 9 and 15 months post-HAART while still on their initial NNRTI regimen (gain of 173 cells/ μ L [94–283] on nevirapine vs. 168 [72–310] on efavirenz).

After adjusting for other variables, patients started on efavirenz had a significantly shorter time to virologic suppression (<400 copies/mL) than did those treated with nevirapine (median: 4.8 months versus 5.5 months, respectively; multivariate HR 1.27, 95% CI 1.15–1.40) (Table 2). Similarly, patients started on nevirapine were more likely to experience virologic failure than those on efavirenz (HR 1.52, 1.24–1.86, $p < 0.001$). Exclusion of patients with only one viral load measurement from analyses of virologic failure did not materially impact our findings (HR 1.65, 1.34–2.02). Other variables significantly associated with faster time to virologic failure in multivariate analysis included lower baseline CD4 counts (HR 1.52, 1.16–1.99, $p = 0.004$, for ≤ 50 vs. >200 cells/ μ L), initial use of stavudine/didanosine (HR 1.48, 1.15–1.91, $p = 0.001$, vs. zidovudine/lamivudine) or zidovudine/didanosine (HR 2.35, 1.07–5.18, $p = 0.03$), calendar year of HAART initiation (HR 1.57, 1.29–1.90, $p < 0.001$, per later year), and pharmacy-claim adherence (HR 11.74, 8.48–16.25, $p < 0.001$, for $<50\%$ vs. 100% adherence).

The increased risk of virologic failure associated with nevirapine was restricted to patients with $<90\%$ adherence in univariate analysis (Figure 2); however a test for interaction between NNRTI and adherence was not statistically significant ($p = 0.37$), and an increased risk of failure on nevirapine was observed in all patients after adjustment for potential confounders (multivariate HR = 1.46, 1.17–1.84, for $<90\%$ adherence; 1.63, 1.04–2.54, for $\geq 90\%$ adherence). Patients initially treated with nevirapine also had a significantly higher risk of both death (multivariate HR 2.17, 1.31–3.60, $p < 0.001$) and of NNRTI discontinuation in the absence of virologic failure (multivariate HR 1.67, 1.32–2.11, $p < 0.001$) than did patients initially treated with efavirenz. In an analysis that did not censor individuals at the date of stopping/switching NNRTI (i.e. using baseline regimen alone), the association between NNRTI regimen and risk of virologic failure was attenuated (multivariate HR 1.20, 0.97 – 1.48, $p = 0.10$).

In a secondary analysis, we compared outcomes in patients who switched from efavirenz to nevirapine or vice versa, excluding patients who had no viral-load measurement after switch or who switched NNRTI after achieving virologic suppression and subsequently experiencing virologic failure (viral load ≥ 400 copies/mL). Of 177 eligible patients, 54 (34.2%) switched while virologically suppressed (last known viral-load measurement <400 copies/mL). Of these 54, 4 of 18 (22.2%) who switched from nevirapine to efavirenz had a single viral-load measurement ≥ 400 copies/mL, and none experienced virologic failure, as defined here, over a median 0.81 (IQR 0.65–1.49) years of follow-up. By contrast, 9 of the 36 patients (25.0%) who switched from efavirenz to nevirapine had at least one viral-load measurement ≥ 400 copies/mL, and 5 (13.9%) experienced virologic failure over a median 0.93 (IQR 0.53–1.40) years of follow-up. In time-to-event analysis, the univariate hazard of virologic failure was 3.92 (95% CI 1.61–9.55) for patients who switched to nevirapine compared to those who remained on efavirenz.

The remaining 123 (65.8%) of 177 patients switched NNRTIs before achieving known virologic suppression (Figure 1); 78 (63.4%) of these had no viral-load measurement between HAART initiation and NNRTI switch. After adjusting for confounders, including time to next viral load measurement, those patients switching from nevirapine to efavirenz before virologic suppression had a chance of subsequent suppression comparable to those remaining on

nevirapine (HR 0.86, 95% CI 0.65–1.13). In contrast, those switching from efavirenz to nevirapine before virologic suppression achieved suppression significantly more slowly than those who remained on efavirenz (HR 0.58, 95% CI 0.35–0.93) (Figure 3).

DISCUSSION

This observational study from a private-sector HIV/AIDS disease-management program in southern Africa has shown that initial use of nevirapine was associated with a 52% greater risk of virologic failure and more than double risk of all-cause mortality compared to efavirenz, after adjusting for many potential confounders in a population for whom short-course HAART, not single-dose nevirapine, was the standard of care for pMTCT.

These data are consistent with comparable studies from the developed world. The Antiretroviral Therapy Cohort Collaboration (ART-CC), which combined data from 12 HIV/AIDS cohort studies, found that patients who started with nevirapine-based regimens were approximately twice as likely at six months to have a detectable viral load or to die than those started on efavirenz [4]. However, the ART-CC study could not control for adherence, perhaps the most important determinant of treatment outcome. A study of Veterans Affairs (VA) patients (97% male) in the United States did examine adherence and also reported worse virologic and immunologic outcomes with nevirapine than with efavirenz. [5] However, this VA study did not evaluate virologic failure after initial suppression and did not report clinical outcomes [5]. Only two clinical trials have directly compared efavirenz and nevirapine. A small trial in Spain ($n = 64$) showed no significant difference in the proportion of patients achieving virologic suppression at 48 weeks after starting either nevirapine (64%) or efavirenz (74%) ($p = 0.43$) [30]. In the larger 2NN trial [3], nevirapine was associated with more serious toxicities and did not satisfy protocol criteria for non-inferiority. In addition, among South African subjects in 2NN, rates of failure of nevirapine- (50.0%) and efavirenz-based regimens (38.3%) [3], defined as virologic failure or NNRTI switch, were comparable to the present study's rates of failure to complete follow-up on the initial NNRTI regimen (48.4% and 36.2%, respectively).

While informative, the results of our secondary analyses on the effects of switching from efavirenz to nevirapine or from nevirapine to efavirenz must be interpreted with caution, given the limited sample size, the low frequency of viral-load measurement, and the confounding potential of physician prescribing patterns (e.g., lead-in dose escalation of nevirapine when switching from efavirenz to nevirapine leading to sub-therapeutic nevirapine concentrations due to enzyme induction by residual efavirenz [31]). It would also be helpful to know the clinical indications used for switching regimens, but this information was not available in this database.

Efavirenz's observed advantages have important clinical and public health implications, particularly for resource-limited settings. However, other factors must be weighed, including nevirapine's lower cost, its different side-effect profile, its requirement for more careful clinical and laboratory monitoring [32–34], and its potential for complex drug interactions (e.g., with rifampicin) [35,36]. Furthermore, the currently unquantified teratogenicity of efavirenz [37] should be weighed against the increased risk of virologic failure on nevirapine. A formal cost-effectiveness comparison may be helpful.

The current study has some limitations. First, both unmeasured confounding and bias are risks with any observational study. Of particular concern is selection bias: patients more likely to adhere to HAART may be more likely to be prescribed efavirenz. Temporal bias may also be important, since physicians were more likely to prescribe nevirapine earlier in the study, and adherence counselling and monitoring may have improved over time. Our analysis, however,

showed that virologic outcomes did not improve. Additional limitations include small sample size for secondary analyses of clinical outcome and NNRTI switch; measurement of adherence using pharmacy claims alone; exclusion of patients with limited follow-up; a relatively short follow-up period, and the potentially limited generalizability from a private-sector program.

Given the rapid roll-out of antiretroviral programs worldwide and the frequent use of first-line nevirapine-based HAART in such programs, the assumption that efavirenz and nevirapine are equally effective needs to be reassessed. There is a critical need for a large, randomized, clinical trial to definitively compare the outcomes of efavirenz and nevirapine, and for acceleration of efforts to develop lower-cost formulations of efavirenz, including generic, fixed-dose combinations.

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Figure 1.
Characterization of Study Participants

NNRTI/Adherence		Number at Risk			
EFV/ $\geq 90\%$	900	534	186	21	
EFV/ $< 90\%$	922	475	158	14	
NVP/ $\geq 90\%$	446	240	102	27	
NVP/ $< 90\%$	549	266	94	14	
Total	2817	1515	540	76	

Figure 2.
Time to Virologic Failure, by initial NNRTI and adherence

<u>Regimen</u>	<u>Number at Risk</u>			
NVP (Initial)	381	142	76	43
EFV (After NVP)	41	24	17	9
EFV (Initial)	678	217	120	43
NVP (After EFV)	14	13	11	4
Total	1114	396	224	99

Figure 3.

Time to Virologic Suppression, by Initial and Second NNRTI Regimen for patients who switched NNRTI regimen due to virologic failure. The x-axis shows time from initiation of current (either initial or second) NNRTI regimen, among patients with HIV virus loads >400 copies/mL at initiation of current NNRTI regimen

Table 1
Characteristics of Study Population, by Initial NNRTI Regimen

Variable	Efavirenz QD (n=1822)	Nevirapine BD (n=995)	Total (N = 2817)	P value ^a
Age-yr: Mean (sd)	37.5 (7.6)	36.0 (8.0)	37.0 (7.8)	<0.001
Follow-up duration-yr: Median (IQR)	2.0 (1.3–2.6)	1.9 (1.0–2.6)	2.0 (1.2–2.6)	0.006
Sex– no. (%)				<0.001
Male	723 (39.7)	323 (32.5)	1046 (37.1)	
Female	1099 (60.3)	672 (67.5)	1771 (62.9)	
Race–no. (%)				0.46
Black	1769 (97.1)	961 (96.6)	2730 (96.9)	
Other	53 (2.9)	34 (3.4)	87 (3.1)	
Baseline CD4 count, cells/ μ L: Median (IQR)	136(58–216)	171(78–243)	147(64–228)	<0.001
Baseline virus load, log ₁₀ copies/mL: Median (IQR)	5.2 (4.7–5.7)	5.1 (4.6–5.6)	5.2 (4.7–5.6)	<0.001
pMTCT				<0.001
Yes	84 (4.6)	142 (14.3)	226 (8.0)	
No	1738 (95.4)	853 (85.7)	2591 (92.0)	
NRTI pair				<0.001
3TC + ZDV	1321 (72.5)	866 (87.0)	2187 (77.6)	
3TC + d4T	59 (3.2)	20 (2.0)	79 (2.8)	
d4T + ddI	432 (23.7)	91 (9.2)	523 (18.6)	
ddI + ZDV	10 (0.6)	18 (1.8)	28 (1.0)	
Date of HAART start				<0.001
1998–2000	10 (0.6)	46 (4.6)	56 (2.0)	
2001	620 (34.0)	462 (46.4)	1082 (38.5)	
2002	1072 (58.8)	441 (44.3)	1513 (53.6)	
2003	120 (6.6)	46 (4.6)	166 (5.9)	
Pharmacy-claim adherence				<0.001
<50%	206 (11.3)	119 (12.0)	325 (11.5)	
50–79%	410 (22.5)	248 (24.9)	658 (23.4)	
80–99%	511 (28.1)	327 (32.9)	838 (29.7)	
100%	695 (38.1)	301 (30.2)	997 (35.4)	

^aBased on the Student's t-test, Wilcoxon rank-sum test, or chi-square test (χ^2) with one degree of freedom, comparing patients initiated on efavirenz versus those initiated on nevirapine.

Table 2

Adjusted Associations between Patient Characteristics and Time to Initial Viral Suppression <400 copies/mL

Variable	Univariate HR (95% CI)	Multivariate HR (95% CI) ^a
NNRTI		
Efavirenz	1.21 (1.10–1.33)	1.27 (1.15–1.40)
Nevirapine	1	1
Age		
(per 10 years)	1.04 (0.99–1.10)	1.05 (0.99–1.11)
Sex		
Male	1	1
Female	1.20 (1.10–1.32)	1.11 (1.01–1.22)
Race		
Black	0.84 (0.66–1.07)	0.87 (0.68–1.11)
Other	1	1
Baseline CD4-cells/ μ L		
≤ 50	1	1
51–200	1.02 (0.91–1.15)	0.95 (0.84–1.06)
>200	1.14 (1.00–1.28)	1.12 (0.98–1.27)
Baseline VL-c/mL		
$\leq 10^5$	1.28 (1.17–1.40)	1.41 (1.29–1.55)
>10 ⁵	1	1
pMTCT		
Yes	1.10 (0.94–1.28)	1.27 (1.07–1.50)
No	1	1
NRTI pair		
3TC + ZDV	1	1
3TC + d4T	1.55 (1.22–1.97)	1.08 (0.84–1.37)
d4T + ddI	0.92 (0.82–1.03)	0.82 (0.73–0.92)
ddI + ZDV	0.44 (0.25–0.78)	0.43 (0.23–0.79)
Year of HAART start		
1998–2000	1.00 (0.72–1.39)	2.27 (1.58–3.27)
2001	1	1
2002	1.22 (1.11–1.33)	1.23 (1.12–1.36)
2003	1.13 (0.93–1.37)	1.08 (0.88–1.33)
Pharmacy-claim adherence		
50% vs. <50%	1.05 (0.77–1.42)	0.84 (0.61–1.14)
per 10% increase above 50%	1.14 (1.11–1.18)	1.15 (1.12–1.18)

^a Adjusted for all other variables in the table, plus frequency of viral load measurement and time to measurement of first viral load.