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Factors Associated with Remaining on Initial Randomized Efavirenz-containing Regimens in the AIDS Clinical Trials Group

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Abstract

Objective—Efavirenz (EFV) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) is a recommended initial antiretroviral (ARV) regimen. Understanding characteristics related to EFV success is clinically useful.

Design—Data from 2,220 ARV-naïve participants randomized to EFV + 2/3 NRTIs in 4 ACTG trials plus a long-term cohort, were analyzed.

Methods—Logistic regression, using inverse probability of censoring weighting to address selective-followup bias, was used to identify factors associated with EFV success (no treatment interruptions of >30 days, HIV RNA<200 copies/mL) 1 year (yr) post initiation and at yrs 2-5 if successful at yr 1.

Results—Pre-treatment characteristics were: median age 38 yrs, 82% male, 40% white, 10% history of injection drug use (HxIDU), median CD4+ T-lymphocyte 227 cells/uL and 33% HIV RNA>100,000 copies/mL. In a multivariable model, factors associated with yr 1 EFV success were: race (white OR: 1.5; p<0.001; Hispanic OR: 1.5; p=0.003 vs. black), no pre-treatment sign/symptom grade 3 (OR: 1.7; p=0.008) and no HxIDU (OR: 1.7; p=0.001). Predictors of EFV success at yrs 2-5 were: no HxIDU (yrs 2-5; ORs 1.9-2.2); self-reported complete (4-days prior to study visit) adherence during yr 1 (yrs 2-4; ORs 1.6-1.9); fewer missed visits during yr 1 (yrs 2,4,5; ORs 0.92-0.98/1% increase); HIV RNA <50 copies/mL at yr 1 (yrs 2,3; ORs 1.9-2.2); and older age (>50 v. ≤30 yrs) (yrs 2,3,4; ORs 2.3-3.7).

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Findings from this analysis have not been previously published, but were presented at the 49th Annual Meeting of the Infectious Diseases Society of America (IDSA), October 20 -23, 2011, in Boston, MA [Abstract 32306].

Conclusions—Characteristics predictive of EFV success in the short-and longer-term differed except for HxIDU. Behaviors occurring during yr 1 were associated with EFV success over 5 years.

Keywords

Efavirenz; human immunodeficiency virus; highly active antiretroviral therapy; cohort study; clinical trials

Introduction

A combination antiretroviral (ARV) regimen consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) can provide durable viral suppression and immunologic enhancement for human immunodeficiency (HIV) positive individuals. Efavirenz (EFV) is the preferred initial NNRTI in the United States [1, 2]. Individuals taking EFV-containing regimens can have a more favorable virologic response than those taking protease inhibitor (PI)-based or triple-NRTI regimens [3-6]. EFV-containing regimens are associated with lower mortality and incidence of AIDS-defining events (ADEs), and better immunologic and virologic outcomes than those containing nevirapine [7]. Central nervous system side effects are common with EFV-containing regimens but are usually mild, resolve within several weeks, and are rarely treatment-limiting [8,9].

With tolerable, effective initial regimens, persons can achieve long-term HIV viral suppression; however, durability is affected by a variety of factors. Chances of success are greatest with initial as opposed to subsequent regimens [10]. With newer agents, less frequent dosing, and simplified combination drugs, duration of use of initial ARV regimens has increased [11,12]. Shorter initial ARV regimen durations have been associated with higher baseline HIV RNA level, injection drug use (IDU), prior ADEs, calendar year of ARV initiation, regimen type and non-Hispanic black race/ethnicity [10-13]. Blacks were more likely than other races to have virologic failure and regimen discontinuation when randomized to an initial EFV-containing regimen [14,15]; pharmacogenomic differences in drug-metabolizing enzymes might partially explain these differences [16].

To evaluate whether EFV-based regimens are optimal initial regimens [17] it is useful to understand factors related to longer-term success. Randomized ACTG studies of initial highly active antiretroviral therapy (HAART) along with a long-term observational study (ACTG Longitudinal Linked Randomized Trials (ALLRT)) provide an opportunity to identify characteristics related to successfully remaining on initial EFV-containing regimens a year after initiating ARVs, and in addition, for those still on an EFV-containing regimen at year one, it is possible to examine whether baseline or factors collected during the first year on EFV are related to remaining on an EFV-containing regimen while virally suppressed two to five years after randomization.

Methods

ART-naïve patients with confirmed HIV infection in four randomized ACTG clinical trials (ACTG 384 [18], A5095 [19], A5142 [20] and A5202 [21]) were included in this analysis (N=2220). Subjects were randomized to EFV-containing treatment arms with at least 2 NRTIs (excluding arms with didanosine(ddI)/stavudine(d4T) because of the increased toxicity of this combination and subjects from non-United States based sites who weren't eligible to enroll in ALLRT). ACTG 384 was a blinded study while A5142 and A5202 were open-label studies; A5095 was initially blinded but became open-label in February 2003, following a data safety monitoring board (DSMB) review. Clinical trial participants were eligible to enroll into the ACTG long-term observational ALLRT study [22]; 67% of these 2,220 clinical trial participants opted to co-enroll in ALLRT. Data from the clinical trials and ALLRT were used for these analyses.

Frequency of visits and date of clinical trial final visit were determined by the clinical trial protocols; for subjects who co-enrolled in ALLRT, study visits were every 16 weeks after the clinical trial ended. Data were analyzed beginning at clinical trial entry (October 1998-December 2007) with follow-up continuing through the first of: June 2010 (data sets frozen), last known study visit, or death. Institutional Review Boards at participating sites approved the protocols; subjects provided written informed consent.

Data were collected from participants at the ACTG sites and reported on standardized case report forms; lab work was processed as outlined in standardized operating ACTG laboratory procedure manuals. Information on ARV use was reviewed and updated at each study visit and assessed through year 10. Baseline demographics collected from the participants included: age, sex, self-reported race/ethnicity and HxIDU. CD4+ T-lymphocyte count (CD4), HIV RNA copies/mL (HIV RNA), signs/symptoms (peripheral neuropathy grade 2, others grade 3) [23, 24] and ADEs [25] were assessed at baseline and during the first year, while factors assessed only during the first year included evidence of a short treatment interruption (<30 days off EFV), laboratory toxicities (grade 3), self-reported adherence to medications (number of missed doses in the past 4 days) [26] and percentage of missed clinic visits.

The main outcome of interest was 'EFV success' defined as remaining on an EFV-containing regimen regardless of a switch in background NRTIs or treatment interruptions of <30 days and the most recent HIV RNA viral load (VL) <200 copies/ml on/before the evaluable year.

A subset of subjects had information available on the CYP2B6 metabolizer genotype, a composite of 516G→T and 983T→C genotypes. Subjects were either intensive metabolizers (0 polymorphisms in the composite genotype), intermediate (1 polymorphism) or slow (2 polymorphisms) metabolizers; slow and intermediate metabolizers generally have higher plasma concentrations of EFV compared to intensive metabolizers [7,27].

Statistical Analysis

The primary objective of this analysis was to identify factors associated with EFV success. There were two foci of the primary objective. A first aim was to examine baseline and pre-treatment factors related to 'EFV success' at year one. As a second aim, subjects who had initial EFV success at year one were analyzed to examine baseline and year one characteristics related to 'EFV success' at years 2-5.

Participants who went off EFV for >30 days regardless of HIV RNA level, or who died, were considered off EFV on the last reported date of EFV use. If a subject was reportedly taking EFV when s/he went off study or as of June, 2010, the censor date was off-study date or June, 2010, respectively.

Inverse probability of censoring weighting (IPCW) techniques, redistributing weights of subjects without a known outcome to subjects with an observed outcome and with similar characteristics and history, were used to reduce informative censoring bias due to selective follow-up. IPCW attempts to estimate the probability of EFV success in the whole cohort, not just in those who were not censored before the time point of interest. When a patient on EFV is lost to follow-up, his or her weight gets transferred to "similar" patients still in follow-up. If there are factors associated both with being lost to follow-up and EFV success then simply excluding subjects due to an unknown outcome will lead to biased results; IPCW techniques can help reduce this drop-out bias [28, 29, 30]. Pooled logistic regression was used to estimate the IPCW.

Different approaches were used to estimate probabilities in the year one model and models for years 2-5. In year one only 2% of subjects had an unknown outcome; factors related to censoring due to drop-out included IDU and HIV RNA level; inverse probability (IP) weights for year one were constructed using the proportion of observed subjects in these groups, estimating the probability of remaining in followup among each group.

For years 2-5, unstabilized IP weights were calculated from pooled logistic regression models using predicted probabilities of not remaining in follow-up given past observed patient characteristics. Pre-determined baseline covariates included: age, sex, race, HxIDU, site location; time-varying covariates included: 16-week CD4 and HIV RNA level [31]. Separate models were built for individuals while on parent study and during ALLRT only. Similar pooled logistic regression models were fit for administrative censoring (i.e., subjects on study, receiving EFV as of June 2010 but without an outcome for a certain year).

Probability of successfully remaining on EFV at years 1-10 was estimated using IPCW weights. Kaplan-Meier estimates, which provide a non-parametric estimate in the absence of informative censoring, were calculated for comparison.

An IPCW multivariable logistic regression model was fit to examine predictors of 'EFV success' at year one. Pre-determined baseline covariates included: sex, race/ethnicity, age, HxIDU, CD4, HIV RNA, signs/symptoms and ADEs. Among participants who had 'EFV success' at year one, an IPCW multivariable logistic regression was fit to predict 'EFV success' at years 2-5. Models included baseline characteristics from the year one model, as

well as additional pre-determined variables collected at year one (CD4, HIV RNA) and events occurring during the first year on study (signs/symptoms, toxicities, ADEs, adherence, missed clinic visits).

Due to variation in estimated IPCW weights not accounted for in logistic regression models, standard errors and confidence intervals derived directly from the model are biased; therefore 95% confidence intervals and p-values were calculated using a bootstrap method (5,000 replicates).

A sensitivity analysis was performed to examine the role of the CYP2B6 metabolizer genotype in remaining on an EFV-based regimen among 70% of subjects with genotype information (N=1,553). In yearly models, using the same variables noted above, CYP2B6 metabolizer genotype (slow and intermediate metabolizers compared to intensive metabolizers) was added; this analysis was done separately by race/ethnicity.

Results

Of the 2,220 subjects in the analysis, 727 subjects enrolled only in a clinical trial and 1,493 subjects were also followed in ALLRT. Subjects were predominantly male (Table 1); 40% were white with median age 38 years. Twenty percent had CD4 count ≤ 50 cells/ μ L (median 227 cells/ μ L) and 33% had HIV RNA $>100,000$ copies/mL at baseline (Table 1). There was no evidence that subjects who enrolled in ALLRT differed from those who did not by baseline factors or demographic status ($p>0.05$) with the exception of race (whites more likely to enroll than blacks; $p<0.001$).

Between baseline and year one, 526 of the 2,220 persons in the analysis were observed to have discontinued efavirenz. An additional 48 subjects went off study while still on EFV (52% not able to get to clinic, 15% withdrew consent, 10% not willing to adhere, 10% lost to follow-up, 8% severely debilitated, 4% at sites that closed), leaving a total of 1,646 subjects eligible for further analysis. Of these 1,646 participants, 46 had an HIV RNA VL >200 copies/mL, and subsequently were not considered successful under the definition of EFV success. Thus, 1600 subjects were included in further analyses of subjects who had initial EFV success at year one.

Among 1600 subjects successfully remaining on EFV at year one (Table 1), median CD4 was 405 cells/ μ L with a median increase of 180 cells/ μ L from baseline. Almost all (94%) subjects had HIV RNA VL <50 copies/mL. Fifteen percent of subjects had a grade 3/4 sign/symptom (excluding CNS) and 17% had an ADE prior to the end of year one. The majority of subjects never missed a clinic visit.

Initial regimens

EFV-containing regimens included at least two NRTIs; NRTIs varied by parent study [17,18,19,20]. The estimated percentage of subjects successfully remaining on a randomized EFV-based regimen at year one was 74%; given a participant had EFV success at year one, the percentages of subsequent EFV success were, year 2: 88%, year 3: 78%, year 4: 61%, year 5: 50% (Table 2). The probability of remaining on an EFV-containing regimen 10 years

after initiation was 21%, although only a small number of subjects reached this milestone (Table 2).

In the first year, 526 participants reported EFV discontinuation for at least 30 days (Figure 1). Most participants switched to another ARV regimen (n=335; 64%). Among this group, the majority (n=284) switched within 60 days of discontinuing EFV. A smaller number returned to an EFV-containing regimen with at least 2 NRTIs before the end of year one (n=66); 25 of these participants had HIV RNA <200 copies/mL at year one. Among the remaining 191 subjects who did not switch ARV regimens, 71 went off study, 9 died and 111 subjects remained in follow-up (Figure 1). A total of 345 subjects had short-term treatment interruptions of ≥ 30 days; reasons for interruptions included drug hypersensitivity, rash, subject requested ARV break, incarceration and nausea.

Among this group of 526 participants who went off treatment, the most common reasons recorded were clinician/study participant/guardian decision (17%) and non-compliant with study visits medication (16%). Virologic failure was reported as the reason for treatment discontinuation in 13% of cases. Clinical symptoms and signs were reported as an off-treatment reason and were primarily comprised of rash/allergic reaction (11%), CNS related symptoms (10%) and neuropsychiatric/mood alteration (6%). One percent of participants discontinued treatment because they became pregnant. Between year one and year two the most prevalent reason for discontinuing medication remained clinician/study participant/guardian decision (21%), with virologic failure (16%) and non-compliance (15%) having similar reported rates. Neuropsychiatric/mood alteration (7%) remained a leading reason for discontinuation, whereas there were no reports of rash/allergic reaction and only 3% reported CNS symptoms as a reason to discontinue. Three percent of subjects reported pregnancy as the reason for discontinuation. Reason for study medication discontinuation was only available during the time participants were on parent clinical trials, thus, this information could not be incorporated into the latter years of the analysis.

Factors associated with EFV success at year one

Being older, white or Hispanic/other (versus black), having no IDU history, and having no signs/symptom of grade 3/4 prior to beginning ARVs were associated with EFV success at year one (Table 3). Sex, baseline CD4, baseline HIV RNA, and having an ADE prior to beginning ARVs were not significantly associated with success.

Sex, race, age and IDU were then included in models as covariates to examine the predictive role of baseline signs/symptoms (Table 3; Sensitivity Model: A), ADEs (Sensitivity Model: B) and baseline HIV RNA and CD4 levels (Sensitivity Model: C). In these models the absence of signs/symptoms ($p=0.005$) was associated with EFV success and history of an ADE prior to baseline ($p=0.13$) was not associated with EFV success. Baseline HIV RNA ($p=0.72$) was not predictive and low CD4 was just on the edge of statistical significance (Table 3).

Factors associated with EFV success at years 2-5

Among people with EFV success at year one (n=1,600) self-reported high adherence to ARVs during the first year and older age were predictive of continued EFV success at years

2-4 ($p<0.05$) (Table 4). Persons with year one HIV RNA <50 (v. 50-199) copies/mL had greater odds of EFV success at years 2-3 ($p<0.05$) but this was not evident at years 4-5. As percentage of year one missed visits increased, probability of remaining on suppressive EFV decreased; this relationship was significant at years 2, 4 and 5 ($p<0.05$). People with no history of IDU were approximately two times more likely to have EFV success at years 2-5. For years 2-5, sex, race, baseline CD4 and HIV RNA and year one CD4 did not predict EFV success; neither did diagnosis with an ADE, nor signs/symptoms (including CNS signs/symptoms) at baseline nor reported toxicities during year one.

Of note, 75% of participants who discontinued EFV between year one and year two had HIV RNA <50 copies/mL and 42% had CD4 ≥ 500 cells/uL at the point closest to when they stopped EFV; this trend continued with the percentages rising in years 4-5 (Year 4/Year 5: 87%/78% VL <50 copies/mL; 64%/62% CD4 ≥ 500 cells/uL).

CYP2B6 metabolizer genotype/subgroups

In the subgroup analysis of CYP2B6 metabolizer genotype polymorphisms there was no association ($p>0.05$) seen between metabolizer polymorphisms and EFV success, separately by race. At year one, when adding this variable to the final multivariable model, no significant relationship was seen between intermediate versus intensive metabolizers and EFV success (black: OR 1.1, $p=0.63$; white: OR 0.8, $p=0.24$; Hispanic: OR 0.9, $p=0.70$) and slow versus intensive metabolizers and EFV success (black: OR 1.1, $p=0.86$; white: OR 0.6, $p=0.23$; Hispanic: OR 1.0, $p>0.9$). Similar findings were identified in years 2-4 although a statistically significant association was seen among blacks at year 5 (intermediate versus intensive metabolizer: OR 2.1, $p=0.008$; slow versus intensive metabolizer: OR 1.1, $p=0.8$).

Discussion

A majority (74%) of 2,220 ACTG study participants randomized to initiate HAART containing EFV with concurrent NRTIs, remained on an EFV-containing regimen with virologic suppression after one year, based on methods that address informative loss-to-follow-up; 88% and 50% of these participants continued to have EFV success after 2 and 5 years. Factors associated with year one EFV success included being older, white or Hispanic, having no or minimal clinical signs/symptoms prior to ARV initiation and no HxIDU. Factors that were not significant included: sex, pre-treatment CD4 and HIV RNA, and pre-ARV ADEs.

Older participants were more likely to remain on EFV than younger participants; this association remained after adjusting for adherence and missed visits. As expected, higher adherence [32] and a lower number of missed visits [33] during year one were predictive of long-term EFV success. In persons with HIV, pain and mood disorders (such as depression) have been associated with missed clinic visits [34]; unmeasured behavioral factors related to pain, mood disorders, or other behavioral issues might affect medication and visit adherence and thus impact subsequent EFV success. Factors potentially amenable to interventions, such as attention to pain issues, treatment of mood disorders and support to facilitate clinic attendance and guidance on how to enhance linkage to and retention in HIV clinic care could potentially increase EFV success [35].

Self-reported race/ethnicity was related to successfully remaining on EFV in the first year, but not related to long-term continued EFV success. At year one, whites and Hispanics were more likely to remain on EFV as compared to people who self-identified as black race. While we anticipated that CYP2B6 polymorphisms that impact EFV metabolism might explain these findings [16, 27], the results did not support this hypothesis. . Other potential explanations include that these polymorphisms do not significantly affect EFV effectiveness, or that unmeasured confounders obscured the relationship between CYP2B6 polymorphisms and EFV success. Additional data on social characteristics that impact antiretroviral adherence may have helped to address these issues, however, these analyses could not be explored given limited data on social characteristics.

Signs/symptoms of grades 3/4 prior to ART initiation were associated with discontinuation of EFV during year one, but as might be expected, having a grade 3/4 sign/symptom during year one was not related to success in later years. Participants experiencing complications pre-treatment or with active symptoms at ARV initiation may have had a lower tolerance for drug-associated side-effects or side effects in addition to pre-existing signs/symptoms may make it more difficult to continue an ARV regimen. Another possibility is that subjects reporting signs/symptoms of grade 3/4 may have Immune Reconstitution Inflammatory Syndrome (IRIS); IRIS could dissipate and will not be relevant to success in later years, if someone remains on EFV through the end of year one.

A history of IDU was negatively associated with EFV success; participants who reported being current (<1%) or prior (10%) IDU were more likely to discontinue EFV during year one, and if still on an EFV-containing regimen at year one, in subsequent years. Others have reported that persons with a history of IDU, taking EFV-based regimens, were less likely to achieve viral suppression than persons taking atazanavir/ritonavir based regimens [36]; thus, EFV may not be the ideal third drug for some persons with IDU history. One potential explanation could be differences in pharmacokinetics among substance versus non-substance users [37], although most participants did not report current use. Other possible explanations for failure to remain on EFV with history of IDU include higher rates of concomitant hepatitis C viral (HCV) infection which is associated with higher rates of hepatotoxicity [38], the need for, but potential unavailability of, increases doses of methadone in drug substitution programs, to achieve similar effects among former IDUs receiving EFV [39]; higher rates of depression, poorer social support and/or lower tolerance for side-effects. HCV serologic results and diagnoses were not available at baseline for all subjects and thus were not included as a potential predictor of EFV success. However, among the subset with HCV data available (n=1,972), a larger percentage of participants with HxIDU had detectable HCV antibody (40%) compared to participants without HxIDU (<4%). It seems likely that HCV co-infection and accompanying complications [37] may have contributed to lower EFV success rates.

CD4 counts were not predictive of EFV success. A large proportion of people who discontinued EFV in years 2-5 had CD4 >500 cells/uL (40%-62%) and the majority (75%-87%) had HIV RNA <50 copies/mL suggesting factors other than virologic and immunologic failure are related to EFV discontinuation. Portions of follow-up among these participants occurred when CD4-guided and structured treatment interruptions were popular

treatment strategies, prior to the Strategies for Management of Antiretroviral Therapy (SMART) Study findings [40]; thus, discontinuation may be construed as a treatment success rather than failure.

IPCW methods were used to account for possible informative dropout; this method can be compared to the redistribute-to-the-right algorithm that leads to the Kaplan Meier estimator [41]. In this analysis, weights never became extreme (range in year 1: 1.011-1.079; years 2-5: 1.047-3.395). Using the IPCW method, the percentage of subjects successfully remaining on EFV at year seven is estimated to be 45. By contrast, the Kaplan Meier method (52% EFV success rate at year seven) likely provides an overestimate of success since it is based on the assumption that censoring is non-informative.

Even with appropriate statistical methods, a limitation of our study is that outcomes were not available for all study enrollees. There may be variables related to remaining on EFV that were not measured in ALLRT or the clinical trials; HIV-1 drug resistance (EFV-resistant minority HIV variants), host inflammatory markers or additional genetic traits could potentially, significantly affect EFV success. In addition, generalizability is a potential concern when reporting clinical trial results; however, when specifically comparing virologic failure outcomes from two of these clinical trials to the Antiretroviral Therapy Cohort Collaboration, results were similar, demonstrating that findings from these trials may be generalizable to a wider group of HIV patients [42].

Conclusion

In conclusion, these analyses focused on baseline and characteristics during year one of EFV-containing ART that predicted longer-term successful EFV use. Whereas selected baseline factors were associated with first year success, other than HxIDU, baseline factors were not predictive of longer-term success on EFV over 5 years. In contrast, behavioral characteristics during the initial year of treatment were associated with long-term EFV success. These results suggest that assessment of behavior after initiating ART and interventions designed to improve clinic attendance, increase medication adherence and better linkage to and retention in HIV care, might result in longer-term success on first-line EFV-containing regimens.

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Figure 1.

Disposition at the end of year one for subjects who discontinued at efavirenz-containing regimen for at least 30 days during year one (N=526). ARVs=antiretrovirals; NNRTI=Non-nucleoside reverse transcriptase inhibitor; NRTI=Nucleoside reverse transcriptase inhibitor; PI=Protease inhibitor.

Table 1

Demographic, baseline and year one variables for all subjects, and subjects remaining on initial efavirenz regimen and HIV RNA < 200 copies/ml at year one.

Characteristic		All subjects (N=2220)	Subjects remaining on initial efavirenz regimen and HIV RNA<200 copies/ml at year one (N=1600)
Baseline Variables			
Sex	Male	1,814 (82%)	1,312 (82%)
Race/Ethnicity	White	899 (40%)	680 (43%)
	Black	786 (35%)	526 (33%)
	Hispanic	474 (21%)	349 (22%)
	Other	61 (3%)	45 (3%)
Age at BL (years)	Median (Q1, Q3)	38 (31, 44)	38 (31, 45)
	30	526 (24%)	362 (23%)
	31-40	851 (38%)	601 (38%)
	41-50	623 (28%)	471 (29%)
	>50	220 (10%)	166 (10%)
Injection drug reported use at BL	Currently/Previously use	220 (10%)	139 (9%)
	Never used	2,000 (90%)	1,461 (91%)
CD4 at BL(cells/μl)	Median (Q1, Q3)	227 (84, 341)	228 (90, 342)
	50	441 (20%)	302 (19%)
	51-200	545 (25%)	401 (25%)
	>200	1,233 (56%)	896 (56%)
HIV RNA at BL(copies/ml)	100,000	1,490 (67%)	1,078 (67%)
	>100,000	730 (33%)	522 (33%)
ADE history on/before BL		368 (17%)	255 (16%)
Grade 3 signs and symptoms on/before BL		131 (6%)	80 (5%)
CYP2B6 metabolizer genotype	Intensive metabolizer	744 (34%)	578 (36%)
	Intermediate metabolizer	637 (29%)	482 (30%)
	Slow metabolizer	172 (8%)	124 (8%)
	Unavailable	667 (30%)	416 (26%)
Year One Variables			
CD4 at year 1 (cells/μl) *	Median (Q1, Q3)	383 (252, 546)	405 (274, 574)
	350	978 (44%)	642 (40%)
	>350	1,242 (56%)	958 (60%)
HIV RNA at year 1 (copies/ml) *	<50	1,758 (79%)	1,507 (94%)
	50-199	163 (7%)	93 (6%)
	200	299 (13%)	0 (0%)
Lowest adherence in first year	100%	1,306 (59%)	1,092 (68%)
	<100%	675 (30%)	466 (29%)
	Not on ARVs	205 (9%)	42 (3%)
	Missing	34 (2%)	0 (0%)

Characteristic		All subjects (N=2220)	Subjects remaining on initial efavirenz regimen and HIV RNA<200 copies/ml at year one (N=1600)
Percent of missed clinic visits in first year	Median(Q1, Q3)	0 (0, 14)	0 (0, 10)
ADEs at BL and in first year		398 (18%)	271 (17%)
Grade 3 toxicity in first year		251 (11%)	151 (9%)
Grade 3 signs and symptoms at BL and in first year (excluding CNS in first year)		419 (19%)	238 (15%)
CNS-related signs and symptoms, and diagnoses in first year		606 (27%)	351 (22%)

BL=baseline.

Median (Q1, Q3): median (first quartile, third quartile).

ADE=AIDS defining event.

Adherence: reported any missed dosage of ARV medication in the past 4 days; =100%, if subject reported zero missed doses;

100%, if subject reported missed doses.

CNS= central nervous system.

* If off study before the end of year 1, CD4 or HIV RNA available is last known/available; otherwise, CD4 or HIV RNA is from the end of year 1.

Table 2

Rate of “EFV success” (remaining on an EFV containing regimen and HIV RNA < 200 copies/ml) by year; time starts when subjects initiated antiretrovirals.

Year	Number of subjects successfully remaining on an EFV regimen	Number of subjects in follow-up*	KM: initial EFV success rate (%)**	IP weighted: initial EFV success rate (%)***
1	1600	2060	76%	74%
2	1344	1522	89%	88%
3	927	1152	79%	78%
4	508	750	67%	61%
5	317	517	60%	50%
6	270	459	56%	50%
7	192	356	52%	45%
8	129	270	48%	38%
9	53	113	46%	24%
10	36	78	45%	21%

EFV= efavirenz.

* Subjects who were still in follow up by the end of year *i*.

** KM (Kaplan-Meier) estimator: non-parametrically estimates the probability of successfully remaining on an EFV-containing regimen by year *i* by assuming that censoring is independent of survival times.

IP=Inverse probability.

*** Sum of IP weights for those successfully remaining on EFV-containing regimens divided by sum of IP weights for all subjects with known status on initial EFV-containing regimens.

Note: Rates at years 2 through 10 based on subjects who successfully remained on an EFV regimen at year one.

Table 3

Sensitivity models							
Variables	Final Model		A		B		C
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)
Sex (vs Female)							
Race/Ethnicity (vs Black)							
Age at BL (vs 30)							
Injection drug use at BL (vs reported current/prior use)							
CD4 at BL (vs 50)							
HIV RNA at BL (vs >100,000)							
No ADE history on/before BL (vs Yes)							
No grade 3 signs and symptoms on/before BL (vs Yes)							

95% CI= (2.5th percentile, 97.5th percentile) from 5,000 bootstrap samples.

p-value is calculated based on z-score=estimated parameter value/standard deviation for 5,000 bootstrap samples.

BL=baseline.

ADE=AIDS defining event.

Median of area under the curve (AUC) from 5,000 bootstrapping samples for final model, and Models A-C are 0.6, 0.59, 0.59, and 0.6 respectively.

Table 4

Models for remaining on an initial EFV regimen and HIV RNA < 200 copies/ml at years two through five; N=1,600 remained on an EFV-containing regimen and HIV RNA < 200 copies/ml at the end of year one.

Final models								
Variables	Year 2		Year 3		Year 4		Year 5	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Sex (vs Female)								
Male	0.97 (0.62,1.46)	0.89	0.94 (0.62,1.34)	0.73	1.06 (0.73,1.52)	0.77	0.95 (0.63,1.44)	0.82
Race/Ethnicity (vs Black)								
White	1.16 (0.79,1.69)	0.45	1.24 (0.9,1.73)	0.19	1.16 (0.84,1.65)	0.39	1.19 (0.81,1.73)	0.38
Hispanic/Other	1.16 (0.77,1.82)	0.5	1.29 (0.9,1.88)	0.18	1.32 (0.91,1.94)	0.15	1.21 (0.78,1.89)	0.39
Age at BL (vs 30)								
31-40	1.59 (1.12,2.32)	0.01	1.18 (0.85,1.67)	0.32	1.45 (1.02,2.08)	0.04	1.56 (0.92,2.08)	0.15
41-50	2.16 (1.46,3.38)	<0.001	1.61 (1.12,2.36)	0.01	1.88 (1.28,2.81)	0.002	1.58 (1.01,2.46)	0.05
>50	3.68 (1.99,9.29)	<0.001	2.52 (1.49,4.84)	0.002	2.27 (1.33,4.1)	0.005	1.65 (0.9,3.18)	0.12
Injection drug use at BL (vs reported current/prior use)								
Use never reported	2.06 (1.24,3.34)	0.005	2.24 (1.43,3.58)	<0.001	1.89 (1.16,3.26)	0.01	1.87 (1.06,3.73)	0.05
CD4 at BL (vs 50)								
51-200	0.96 (0.56,1.62)	0.89	1.15 (0.73,1.81)	0.54	1.07 (0.69,1.66)	0.76	0.84 (0.51,1.41)	0.51
200+	0.91 (0.47,1.66)	0.77	1.29 (0.77,2.19)	0.34	1.03 (0.63,1.73)	>0.90	1.13 (0.62,2.07)	0.7
HIV RNA at BL (vs >100,000)								
100,000	0.98 (0.68,1.42)	>0.90	0.91 (0.66,1.24)	0.56	0.95 (0.69,1.31)	0.77	0.74 (0.5,1.08)	0.12
CD4 at year 1 (vs 350)								
>350	1.18 (0.76,1.86)	0.47	1.05 (0.73,1.53)	0.8	0.97 (0.67,1.41)	0.87	0.72 (0.46,1.08)	0.13
HIV RNA at year 1 (vs 50-199)								
<50	2.16 (1.2,3.63)	0.007	1.86 (1.09,3.13)	0.02	1.66 (0.92,3.16)	0.11	1.89 (0.95,4.66)	0.12
Adherence in first year (vs incomplete)								
Complete adherence	1.94 (1.43,2.66)	<0.001	1.7 (1.3,2.26)	<0.001	1.58 (1.19,2.13)	0.002	1.36 (0.99,1.91)	0.06
Percent of missed clinic visits in first year								
every 1 percent higher	0.98 (0.97,1)	0.05	0.99 (0.97,1)	0.13	0.96 (0.94,0.98)	0.001	0.92 (0.88,0.95)	<0.001
No ADEs at BL and in first year (vs Yes)								
No ADEs at BL and in first year (vs Yes)	0.91 (0.54,1.45)	0.71	0.74 (0.47,1.1)	0.15	1.12 (0.73,1.66)	0.6	1.13 (0.72,1.78)	0.61
No grade 3 toxicity in first year (vs Yes)								
3 toxicity in first year (vs Yes)	1.1 (0.6,1.78)	0.74	1.4 (0.88,2.16)	0.15	1.24 (0.79,1.96)	0.35	1.22 (0.75,2.18)	0.46
No grade 3 signs and symptoms at BL and in first year (excluding CNS in first year) (vs Yes)								
3 signs and symptoms at BL and in first year (excluding CNS in first year) (vs Yes)	1.33 (0.87,1.99)	0.18	1.06 (0.7,1.56)	0.76	0.84 (0.56,1.26)	0.41	1.12 (0.7,1.89)	0.64
No CNS related signs and symptoms, and diagnoses in first year (vs Yes)								
No CNS related signs and symptoms, and diagnoses in first year (vs Yes)	1.29 (0.89,1.85)	0.17	1.15 (0.83,1.58)	0.4	1.27 (0.92,1.77)	0.15	1.28 (0.89,1.91)	0.2

95% CI=median (2.5th percentile, 97.5th percentile) from 5,000 bootstrap samples.

p-value is calculated based on z-score=estimated parameter value/standard deviation for 5,000 bootstrap samples.

BL=baseline.

ADE= AIDS defining event.

CNS= central nervous system.

Median of area under the curve (AUC) from 5,000 bootstrapping samples for models year 2 - year 5 are 0.69, 0.66, 0.65, 0.69 respectively.