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Association between Efavirenz as Initial Therapy for HIV-1 Infection and Increased Risk of Suicidal Ideation, Attempted, or Completed Suicide

Katie R. Mollan, M.S.[1,2], **Marlene Smurzynski, Ph.D.**[1,3], **Joseph J. Eron, M.D.**[2], **Eric S. Daar, M.D.**[4], **Thomas B. Campbell, M.D.**[5], **Paul E. Sax, M.D.**[6], **Roy M. Gulick, M.D.**[7], **Lumine Na, M.S.**[1], **Lauren O'Keefe, B.S.**[1], **Kevin R. Robertson, Ph.D.**[2], and **Camlin Tierney, Ph.D.**[1]

[1] Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA

[2] Center for AIDS Research, University of North Carolina at Chapel Hill, NC

[3] George Washington University School of Public Health and Health Services, Washington, DC

[4] Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA

[5] University of Colorado Denver, Aurora, CO

Corresponding Authors: Katie R. Mollan, M.S., University of North Carolina at Chapel Hill, 3126 McGavran-Greenberg Hall, CB #7420, Chapel Hill, NC, 27599 Camlin Tierney, Ph.D., Harvard School of Public Health, Boston, MA 651 Huntington Avenue, Boston, MA 02115.

Contributors

KRM, MS, JJE, ESD, TBC, PES, RMG, KRR, and CT planned the analyses. KRM, MS, TBS, PES, and CT reviewed death data for classification. KRM, LN, and KRR reviewed psychiatric events. LO collated the database, with oversight from KRM and CT. KRM and LN analyzed the data, which were reviewed and interpreted by KRM, MS, JJE, ESD, TBC, PES, RMG, KRR, and CT. The initial draft of this report was written by KRM, and edited by MS, JJE, ESD, TBC, PES, RMG, LN, LO, KRR, and CT. KRM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

KRM has received research support to University of North Carolina at Chapel Hill from Gilead.
MS has no conflicts of interest to report.
JJE has received research support to University of North Carolina at Chapel Hill from Bristol Myers Squibb, GlaxoSmithKline/ViiV, and Merck and consulting fees from Bristol Myers Squibb, Gilead, GlaxoSmithKline/ViiV, Janssen, and Merck.
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TBC has been a consultant for Gilead.
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RMG served as an ad-hoc consultant to Bristol-Myers, Gilead, GlaxoSmithKline, Janssen, Koronis, and ViiV and serves as an investigator on studies sponsored by GlaxoSmithKline, Janssen, Pfizer, and ViiV (grants to Weill Cornell Medical College).
LN has no conflicts of interest to report.
LO has no conflicts of interest to report.
KRR has been a consultant for ViiV and Abbott.
CT is a paid member of a data monitoring committee for a Tibotec hepatitis drug.

Trial Registration: A5095 (NCT00013520), A5142 (NCT00050895), A5175 (NCT00084136), and A5202 (NCT00118898).

Previous Presentation

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[6] Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[7] Weill Cornell Medical College, New York, NY

Abstract

Background—The relationship between efavirenz use and suicidality is not well defined.

Objective—Compare time to suicidality with efavirenz-containing versus efavirenz-free antiretroviral regimens for initial treatment of HIV.

Design—Participant-level data were analyzed from four AIDS Clinical Trials Group (ACTG) antiretroviral-naïve studies conducted from 2001 to 2010. Within each study, participants were randomly assigned to an efavirenz-containing (n=3241) or efavirenz-free regimen (n=2091).

Setting—ACTG sites; 74% enrolled in the United States.

Patients—Antiretroviral-naïve participants.

Intervention—Efavirenz versus efavirenz-free regimens.

Measurements—Suicidality was defined as suicidal ideation, attempted or completed suicide. Groups were compared with a hazard ratio (HR) and 95% confidence interval (CI) estimated from a Cox model stratified by study.

Results—73% were men, median age was 37 years; 32% had documented psychiatric history or received psychoactive medication within 30 days prior to study entry. Median follow-up was 96 weeks. Suicidality incidence per 1000 person-years was 8.08 (47 events) in the efavirenz group and 3.66 (15 events) in the efavirenz-free group, HR: 2.28 (95% CI: 1.27 to 4.10, p=0.006). Incidence of attempted or completed suicide was 2.90 (17 events) and 1.22 (5 events) in the efavirenz and efavirenz-free groups, respectively, HR: 2.58 (95% CI: 0.94 to 7.06, p=0.065). Eight suicide deaths in the efavirenz group and one in the efavirenz-free group were reported.

Limitations—There was not a standardized questionnaire regarding suicidal ideation or attempt. Efavirenz was open-label in three of four studies.

Conclusions—Initial treatment with an efavirenz-containing antiretroviral regimen was associated with a two-fold increased hazard of suicidality compared to a regimen without efavirenz.

Keywords

efavirenz; suicide; suicidal ideation; suicidal behavior; HIV; adverse event; psychiatry

Introduction

Efavirenz is a preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment of HIV (1-4). Although generally safe and effective, efavirenz is associated with central nervous system side effects (5-8), and prescribing information contains warnings of rare but serious psychiatric experiences, including suicide, but also notes that a causal relationship cannot be determined from post-marketing reports (5). Likewise, published cases and case series report suicidal thoughts or behavior with efavirenz (9-17). A recent

literature review stated that clear evidence of association between efavirenz and suicide was not available, and thus psychiatric history should not exclude patients from efavirenz treatment (18).

Given the widespread use of efavirenz and uncertainty regarding its relationship to suicide, suicide attempt or suicidal ideation, we report here an AIDS Clinical Trials Group (ACTG) cross-protocol analysis of four studies in which participants were randomly assigned to an initial efavirenz-containing or efavirenz-free antiretroviral regimen. Our primary goal was to compare the hazard of suicidality between participants assigned to an efavirenz-containing versus efavirenz-free antiretroviral regimen for initial treatment of HIV-1, a potential safety issue not reported in the original studies.

Methods

Study design and participants

Individual-level data from HIV-1-infected antiretroviral-naïve participants in ACTG studies conducted from 2001 to 2010 with random assignment to an efavirenz-containing or efavirenz-free regimen were included in this pre-specified retrospective cross-study analysis. Four studies met these criteria: A5095 (ClinicalTrials.gov registration number: NCT00013520) (19, 20), A5142 (NCT00050895) (21), A5175 (NCT00084136) (22), and A5202 (NCT00118898) (23). Except for nucleoside analogue choice in A5142, components of the antiretroviral regimen were randomly assigned.

The studies varied by antiretroviral regimen and slightly by duration and eligibility criteria (Table 1), though each study excluded participants with substantially abnormal baseline laboratory values. Histories of suicidal ideation or attempt were not exclusion criteria. Studies A5095 and A5202 enrolled in the United States and Puerto Rico; A5142 enrolled in the United States and South Africa. Study A5175 enrolled participants from nine countries in North and South America, the Caribbean, Africa, and Asia.

Study protocols required report of signs, symptoms, or diagnoses at each visit, recorded with both open-text and data-entry codes. In A5175, diagnosis reporting instructions included specific codes for suicidality; the other studies used general psychiatric event codes (e.g. “psychiatric disorder, specify”) plus open-text description. Each study required reporting of severe and life-threatening graded signs or symptoms per the Division of AIDS grading table (24), as well as any sign or symptom, regardless of grade, that led to change in study treatment; diagnoses were not graded. Furthermore, study A5142 required report of all moderate signs or symptoms, A5095 and A5202 required all moderate central nervous system symptoms. Site institutional review boards approved each study; participants provided written informed consent.

Randomization

Each study used permuted-block randomization; stratification factors and treatment arms are listed in Table 1. Efavirenz was formulated as one 600-mg pill given once daily, with three 200-mg pills given initially in A5095. Efavirenz assignment was open-label in A5142, A5175 and A5202, and was blinded and placebo-controlled in A5095 prior to a data safety

and monitoring board (DSMB) recommendation to unblind efavirenz. The DSMB released recommendations mid-study regarding inferior efficacy in the efavirenz-free arm of A5095 (February 20, 2003) and A5175 (May 23, 2008), after which participants in the efavirenz-free arms were given the option to switch treatment (19, 22).

Outcomes

The primary outcome of this cross-study analysis was suicidality, defined as suicidal ideation, attempted, or completed suicide, and identified from signs, symptoms, diagnoses, adverse events, and death data via Medical Dictionary for Regulatory Activities (MedDRA) coding version 15.0. Pre-specified MedDRA preferred terms were: “Completed suicide”, “Suicide attempt”, “Intentional overdose”, “Multiple drug overdose intentional”, “Poisoning deliberate”, “Suicidal ideation”, “Suicidal behaviour”, and “Depression suicidal”. Attempted or completed suicide was a secondary outcome. Clinical investigators, blinded to treatment and prior adverse events, independently reviewed death data categorized as suicide, substance abuse, homicide, accident, unknown cause, or other cause (e.g. infection, cancer, organ failure); a secondary outcome included suicidality or fatal injury attributed to potentially-related causes (substance abuse, homicide or accident).

Covariates

Each study protocol required report of prescription medication ongoing within 30 days prior to entry (denoted “recent pre-study”); pre-study psychoactive and antidepressant medications were identified from a medication list on the National Institute of Mental Health website (25). Psychiatric history was defined as any event in the MedDRA system organ class “Psychiatric disorders”, and depression-related events were classified according to review of psychiatric events data by a psychologist. Pre-study psychiatric measures included psychiatric event history, recent psychoactive medication, depression-related event history, and recent antidepressant medication; presence of event history or pre-study medication was combined into one covariate. Additional *a priori* baseline covariates included: geographic region, sex, race or ethnic group, age, pre-treatment CD4 count, history of AIDS-defining event, and history of injection drug use (IDU); pre-treatment HIV-1 RNA, body weight, and body mass index (BMI) at study entry were evaluated *post hoc* (Appendix Table 1). Analysis of race or ethnic group was limited to white, black, and Hispanic from the United States due to potential social-ethnic differences between countries and low frequencies in other groups, and was self-reported and classified according to NIH categories. Covariate misclassification was possible; for example history of psychiatric events or IDU could have been undisclosed or under-reported.

Statistical analysis

The primary analysis approach was intent-to-treat (ITT). Participant-level data were analyzed according to randomized treatment allocation, with follow-up from randomization to last on-study contact or death; all follow-up in A5095 and A5175 was censored after a DSMB recommendation related to the efavirenz comparison (denoted “ITT DSMB”). In sensitivity analysis, follow-up included time from randomization to last on-study contact or death, regardless of DSMB recommendations (denoted “ITT”); deaths are summarized using the ITT approach. As-treated analyses excluded participants who never started treatment and

included follow-up from treatment-initiation through the earliest of: discontinuation of the assigned efavirenz-containing or efavirenz-free strategy +28 days for washout, discontinuation of all antiretroviral therapy +28 days, or last on-study contact (denoted "as-treated"). A sensitivity approach further censored as-treated follow-up at the time of DSMB recommendations (denoted "as-treated DSMB"). Antiretroviral modifications were allowed for reasons such as toxicity, virologic failure, or DSMB recommendations. Missing baseline data were rare (<1%), thus covariate-adjusted analyses used a complete-case approach.

Crude incidence rate was calculated as the number of cases per total person-years (PY) at-risk, presented as events per 1,000 PY. Incidence rate difference (IRΔ) between treatment groups was quantified by a Mantel-Haenszel estimate stratified by study; with a 95% confidence interval computed using a rare-events variance estimator (26). The primary endpoint, time to suicidality, is presented with cumulative incidence curves, and compared between groups with Gray's test (27), stratified by study, with non-suicide death considered a competing risk. Estimated efavirenz and baseline covariate associations were quantified by a hazard ratio (HR) from a Cox proportional hazards model stratified by study. Modification of efavirenz association by covariates was evaluated with interaction terms. The Cox model proportional hazards assumption was evaluated with a piece-wise constant hazard with time (at ≤24 weeks; >24 weeks), and with a log-transformed time variable; the proportional hazards assumption was not violated. An incidence rate ratio for the efavirenz association was estimated from an exact Poisson model stratified by study, to evaluate sensitivity of the Cox model to low event frequencies. Analyses were conducted two-sided with a significance level of 0.05, without adjustment for multiplicity, in SAS version 9.2 and 9.3 (phreg, genmod, SAS Institute, Cary, NC) and in R version 2.15.1 competing risks package (cmprsk, http://www.r-project.org/).

Role of the funding source

The National Institute of Allergy and Infectious Diseases funded all four studies and this combined data analysis. Industry sponsors provided most antiretroviral medications, including efavirenz, and served as members of individual study teams, but were not involved with this analysis.

Results

Participant characteristics and study follow-up

In total, 5332 antiretroviral-naïve participants were randomly assigned to an initial efavirenz-containing regimen (n=3241) or efavirenz-free regimen (n=2091). At entry, median age was 37 years, 73% were men, 8% reported history of IDU, 13% had received recent pre-study psychoactive medication, 10% had received antidepressant medication, and 32% had documented psychiatric history or recent pre-study psychoactive medication use. Through randomization, baseline characteristics were balanced between groups (Appendix Table 1). Median (Q1-Q3) follow-up was 96 (62-132) weeks for the primary analysis; the efavirenz and efavirenz-free groups had a similar length of follow-up within each study (Table 1).

Suicidality: suicidal ideation, attempted or completed suicide

In the primary analysis, suicidality was reported for 62 participants; attempted or completed suicide accounted for 36% (17/47) of cases in the efavirenz group, and 33% (5/15) in the efavirenz-free group. During ITT follow-up, suicidality was reported for 83 participants, 43% (27/63) of cases in the efavirenz group and 35% (7/20) in the efavirenz-free group involved attempted or completed suicide.

Incidence of first suicidality event was 8.08 per 1000 PY (47 events) in the efavirenz group and 3.66 (15 events) in the efavirenz-free group (stratified IRΔ 4.62 per 1000 PY, 95% CI: 1.62 to 7.62). Time to suicidality was shorter in the efavirenz group; while time to non-suicide death did not differ significantly between groups (Figure 1). The efavirenz association with time to suicidality did not differ significantly by study (Figure 2).

Participants in the efavirenz group had greater hazard of suicidality compared to the efavirenz-free group, (HR 2.28, 95% CI: 1.27 to 4.10, p=0.006). The estimated efavirenz association appeared larger in the first 24 weeks, with HR (95% CI) of 3.69 (1.41, 9.63) versus 1.54 (0.71, 3.34) beyond 24 weeks; this difference was not statistically significant and did not violate the proportional hazards assumption (p=0.165, continuous log-transformed time p=0.24). Increased hazard of suicidality with efavirenz was observed across multiple sensitivity analyses (Table 2). In a secondary analysis of time to suicidal ideation, attempted or completed suicide, or death attributed to substance abuse, homicide, or accident, incidence was 9.28 (54 events) and 4.64 per 1000 PY (19 events) in the efavirenz and efavirenz-free groups, respectively (stratified IRΔ 4.84 per 1000 PY, 95% CI: 1.59 to 8.10), with an estimated two-fold higher hazard in the efavirenz group (HR 2.06, 95% CI: 1.21 to 3.50, p=0.007).

Attempted or completed suicide

In a secondary ITT DSMB analysis, the outcome was restricted to attempted or completed suicide (Appendix Figure 1); incidence was 2.90 per 1000 PY (17 events) in the efavirenz group and 1.22 (5 events) in the efavirenz-free group, (stratified IRΔ 1.86 per 1000 PY, 95% CI: 0.03 to 3.69). The ITT DSMB analysis of association between efavirenz and time to attempted or completed suicide resulted in an estimated HR of 2.58 (95% CI: 0.94 to 7.06, p=0.065). Results from the ITT sensitivity analysis reached statistical significance (HR 2.56, 95% CI: 1.10 to 5.92) while the as-treated result was not significant (HR 2.24, 95% CI: 0.88 to 5.69) (Table 2).

Participant characteristics and hazard of suicidality

In a multivariable analysis, the following covariates were significantly associated with an increased hazard of suicidality, HR (95% CI): efavirenz compared to efavirenz-free assignment, 2.08 (1.16, 3.75), p=0.014, history of IDU, 2.26 (1.15, 4.46), p=0.019, documented psychiatric history or recent pre-study psychoactive medication, 4.07, (2.32, 7.13), p<0.001, and lower baseline weight, 2.69 (1.25, 5.79) for <60 kg, 1.21 (0.64, 2.29) for 60-<80 kg, reference group ≥80 kg, p=0.022 (Appendix Table 2). In a sensitivity analysis including all study follow-up (ITT), efavirenz assignment, history of IDU, and documented psychiatric history were again associated with an increased hazard of suicidality;

furthermore, younger age, but not body weight, was associated with an increased hazard of suicidality. Associations with suicidality limited to United States participants were similar (Supplement). Documented psychiatric history included suicidality, which was infrequent, with 16 pre-study suicidality cases (0.5%) in the efavirenz group and 9 (0.4%) in efavirenz-free group; 5/16 and 1/9 of these participants experienced suicidality during ITT follow-up, respectively.

Causes of death

Incidence of suicide was 0.90 per 1000 PY (8 deaths) in the efavirenz group and 0.18 (1 death) in the efavirenz-free group. The nine reported suicides were among men; seven were white non-Hispanic from the United States and two were Asian from India. Incidence of death from suicide, injury or unknown cause in the efavirenz and efavirenz-free groups, respectively, was 2.93 and 1.73 per 1000 PY (17 and 7 deaths) among United States participants, and 3.58 and 0 per 1000 PY (11 and 0 deaths) among multinational participants. Other causes of death (e.g. infection, cancer, or organ failure) occurred with similar incidence in the efavirenz and efavirenz-free groups among United States participants (5.17 and 5.18 per 1000 PY, respectively); among multinational participants incidence of other causes of death was 8.46 and 9.66 per 1000 PY in the efavirenz and efavirenz-free groups (Supplement).

Discussion

Among HIV-1-infected treatment-naïve patients from four ACTG studies, the hazard of suicidality (suicidal ideation, attempted or completed suicide) was significantly higher with a randomly assigned efavirenz-containing regimen, about twice that observed with an efavirenz-free regimen. This increased hazard was seen across studies and sensitivity analyses. Moreover, eight of nine completed suicides were in the efavirenz group.

In multivariable analyses, factors associated with increased hazard of suicidality were random assignment to efavirenz, self-reported history of IDU, and documented psychiatric history or recent pre-study psychoactive medication. In some analyses, younger age and lower body weight were also associated with increased hazard of suicidality. The efavirenz association did not appear to differ substantially by any particular baseline characteristic (Supplement), yet the subgroup analyses are limited by small event numbers within groups, and have potential for confounding by concurrent cultural and patient characteristics (28).

To our knowledge, this is the first reported analysis to demonstrate a statistically significant association between randomly-assigned efavirenz for initial treatment of HIV and suicidal thoughts or behavior. A French patient-recall questionnaire showed that 9% of patients receiving efavirenz reported emergent suicidal ideation >1 month after treatment initiation (29). In contrast, a study of treatment-experienced patients (ALIZE-ANRS 099) did not detect an association between randomly assigned efavirenz and depressive disorder (HR, 1.32; p=0.47), 4 suicide attempts were reported—1/178 in the efavirenz group and 3/177 in the protease inhibitor group (30). Extended 4-year follow-up restricted to the ALIZE-ANRS 099 efavirenz group reported attempted suicide in 3 participants, including 1 suicide death after 3 years on-study (31). In HPTN 052, a randomized study of early versus delayed

initiation of antiretroviral-therapy for HIV-1-infection, 81% used an initial efavirenz-containing regimen; as of February 2011 there were 10 deaths in the early group, including 3 suicides and 3 unknown cause deaths (all 10 were prescribed efavirenz); in the delayed group, there were 13 deaths—including 6 unknown cause deaths and 0 suicides (32).

The efavirenz prescribing information describes psychiatric events from two early randomized studies (5, 6, 33), with open-label indinavir and double-blinded nelfinavir-containing comparator regimens, respectively; the frequency of suicidal ideation was 0.7% of 1008 patients in the efavirenz group and 0.3% of 635 patients in the efavirenz-free group, with nonfatal suicide attempts among 0.5% and 0%, respectively (5). Publicly-available medical and statistical review documentation for traditional FDA approval of efavirenz states that efavirenz-containing treatment (relative risk=2.1, confidence interval not reported) and history of psychiatric disorder (relative risk=4.2) were associated with serious nervous system or psychiatric experiences; events included aggravated or severe depression, hallucination, suicidal ideation or attempt, seizure, aggressive reaction, paranoid reaction, and manic reaction (34); the prescribing information contains comparable qualitative statements (5). Similar estimates were identified in the current analysis with respect to relative hazard of suicidality. The data presented in the current analysis contribute important information on suicidality; with a total of 83 patients with reported suicidality (34 attempted or completed suicide).

The overall incidence of suicidality observed here was similar to the 5.4 per 1000 PY incidence of depression, attempted or completed suicide reported in an HIV-infected French cohort (35). Nonetheless, it remains possible that suicidal ideation was underreported here. Secondary analysis of suicidality or fatal injury (substance abuse, homicide, or accident) was conducted to help capture deaths possibly related to suicidal behavior; this analysis also demonstrated a two-fold increased hazard with efavirenz; consistent with the primary result. Death attributed to suicide, injury or unknown cause was reported for 28 participants in the efavirenz group and 7 in the efavirenz-free group. Suicide is sometimes misclassified as accidental death or unknown cause, and could have been underreported (36, 37).

Combined with a stratified analysis, the four randomized studies presented here provide a large and diverse patient population that enhances the strength of our findings. Each study had a concurrent efavirenz-free comparison group and patient characteristics were balanced through randomization. Patients were followed closely every 2-3 months for a median of nearly 3 years, regardless of treatment modification or adverse events. Our primary analyses were ITT, an approach supported by the better reporting of harms CONSORT extension (38), and results from as-treated and multivariable analyses supported the primary results. While several published case reports describe suicidality onset within a month following efavirenz initiation (9-13, 15); late onset suicidality has also been documented (14, 34). In our analysis, suicidality occurred throughout follow-up, both early and late (Figure 1), emphasizing the importance of long-term assessment.

This study has limitations. Three of four trials were open-label, thus suicidality, particularly suicidal ideation, may have been susceptible to reporting bias; suicide was listed under post-marketing experiences in the efavirenz prescribing information prior to the timeframe of

these studies (5). There was no standardized questionnaire regarding suicidality or depression, such as the Hamilton scale (39), and psychiatric or suicidal history may have been under-reported or undisclosed to care providers. Furthermore, patients with psychiatric history could have been selectively not referred or recruited to these clinical trials due to concerns for potential adverse events. The efavirenz-free comparison arms here included two or three nucleosides with or without a protease inhibitor, respectively; efavirenz was not compared to another NNRTI or integrase inhibitor in these studies. Occurrence, disclosure and method of suicidality may vary by sex, race, and across regions of the world due to social, cultural, and economic differences (40-44). This large study included 5332 patients enrolled from nine countries; yet small suicidality event numbers limited our ability to assess potential differences between countries (Supplement).

Efavirenz is associated with central nervous system side effects and reports of suicidality (5, 9-17), and there is limited mechanistic evidence linking efavirenz to neurotoxicity (45-48). In our analysis, suicidal ideation, suicide attempt, suicide death, and unknown death each followed a pattern of greater frequency with efavirenz. The random assignment to efavirenz or non-efavirenz therapy increases the likelihood that these results represent a causal relationship between efavirenz and suicidality. Given the widespread use of efavirenz and severity of this adverse event, the observed increased risk is clinically relevant. Suicidality occurred uncommonly, but with increased frequency in patients treated with efavirenz or those with a history of psychiatric comorbidities or injection drug use. In general, suicide risk factors include, but are not limited to, previous suicide attempt, substance or alcohol abuse, fixed hopelessness, agitation, severe depression, anxiety or panic, impulsiveness, complete loss of pleasure, uncontrolled pain, and poor social support (40, 49, 50). Care should be taken to avoid stigmatization of persons living with HIV and psychiatric comorbidities (51-53). When efavirenz is used as a component of antiretroviral therapy there should be careful monitoring for exacerbation of depression or evidence of suicidal thoughts or behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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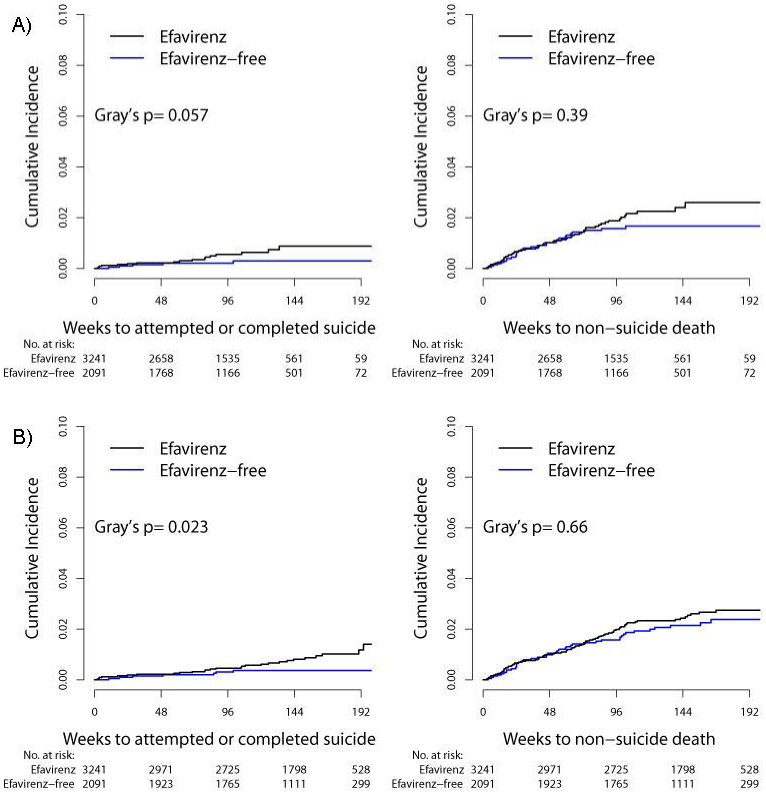
Appendix



Appendix Figure 1. Cumulative incidence of attempted or completed suicide and non-suicide death

Appendix Figure 1A (Attempted or completed suicide ITT DSMB)

Appendix Figure 1B (Attempted or completed suicide ITT)

Cumulative incidence of attempted or completed suicide is presented on the left, and cumulative incidence of death attributed to causes other than reported suicide (competing risk) is presented on the right. Range of y-axis is limited to 0 through 0.10. Gray's test was stratified by study. Panel A: follow-up was censored after data safety monitoring board recommendations pertaining to the efavirenz comparisons, Panel B: intention-to-treat approach, including follow-up from randomization to last on-study contact.

Appendix

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Appendix Table 1

Baseline characteristics

Characteristic		Efavirenz (n=3241)	Efavirenz-free (n=2091)
Region	United States	2,324 (72%)	1,627 (78%)
	Multinational *	917 (28%)	464 (22%)
Sex	Male	2,352 (73%)	1,549 (74%)
	Female	889 (27%)	542 (26%)
Race or ethnic group, United States †	n	2,324	1,627
	White Non-Hispanic	910 (39%)	635 (39%)
	Black Non-Hispanic	831 (36%)	577 (35%)
	Hispanic	516 (22%)	365 (22%)
	Asian	35 (2%)	28 (2%)
	American Indian/Alaska Native	14 (1%)	10 (1%)
	Other	18 (1%)	12 (1%)
Race or ethnic group, Multinational (non-US)	n	917	464
	White Non-Hispanic	55 (6%)	22 (5%)
	Black Non-Hispanic	454 (50%)	227 (49%)
	Hispanic	170 (19%)	96 (21%)
	Asian	238 (26%)	119 (26%)
Age (years)	Median (Q1, Q3)	36 (30, 43)	37 (30, 43)
Age categories	<30 years	737 (23%)	452 (22%)
	30-44 years	1,832 (57%)	1,183 (57%)
	≥45 years	672 (21%)	456 (22%)
CD4 count, $\times 10^9$ cells/L	Median (Q1, Q3)	0.195 (0.082, 0.285)	0.200 (0.082, 0.295)
CD4 count categories	0-0.049 $\times 10^9$ cells/L	589 (18%)	353 (17%)
	0.050-0.199 $\times 10^9$ cells/L	1,078 (33%)	686 (33%)
	0.200-0.349 $\times 10^9$ cells/L	1,097 (34%)	724 (35%)
	>0.349 $\times 10^9$ cells/L	474 (15%)	327 (16%)
	Missing	3	1
HIV-1 RNA level ($\log_{10}$ copies/mL)	Median (Q1, Q3)	4.81 (4.42, 5.32)	4.76 (4.41, 5.29)
HIV-1 RNA categories	<100,000 copies/mL	2,001 (62%)	1,306 (63%)

Characteristic		Efavirenz (n=3241)	Efavirenz-free (n=2091)
	≥100,000 copies/mL	1,240 (38%)	783 (37%)
	Missing	0	2
History of AIDS	Yes	494 (15%)	329 (16%)
Injection drug use history	Current or Previously (Yes)	250 (8%)	150 (7%)
Psychiatric history or psychoactive medication[‡]	Yes	1,009 (31%)	699 (33%)
Psychoactive medication[‡]	Yes	422 (13%)	285 (14%)
Depression-related history or antidepressant medication[‡§]	Yes	622 (19%)	455 (22%)
Antidepressant medication[‡]	Yes	325 (10%)	218 (10%)
Body mass index (kg/m^2)	Median (Q1, Q3)	23.9 (21.3, 27.1)	24.1 (21.4, 27.2)
BMI categories	Underweight (< 18.5)	178 (6%)	119 (6%)
	Normal (18.5 to <25)	1,736 (54%)	1,099 (53%)
	Overweight (25 to <30)	894 (28%)	591 (28%)
	Obese (30+)	392 (12%)	271 (13%)
	Missing	41	11
Body weight (kg)	Median (Q1, Q3)	70 (60, 82)	71 (62, 83)
Body weight categories	<60 kg	810 (25%)	457 (22%)
	60-<80 kg	1,543 (48%)	1,017 (49%)
	≥80 kg	881 (27%)	613 (29%)
	Missing	7	4

[*] Multinational (n): Brazil (231), Haiti (100), India (255), Malawi (221), Peru (134), South Africa (230), Thailand (100), Zimbabwe (110).

[†] Other: More than one race (22), Unknown or missing (8).

[‡] Prescription psychoactive (or antidepressant) medication ongoing within 30 days prior to study entry.

[§] Depression-related history included documented previous diagnosis, signs or symptoms of depression, depressed mood, bipolar disorder, suicidal ideation, suicide attempt, intentional self-injury, mood swings, adjustment disorder, affect lability, affective disorder, dysthymic disorder, or seasonal affective disorder.

Appendix Table 2

Association between baseline characteristics and hazard of suicidality (ITT DSMB)*

				Univariate Models		Multivariable model† (n=5318, 62 events)	
	Characteristic	**DF**	**n**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Randomly assigned treatment group	Efavirenz-containing vs. Efavirenz-free	1	5332	2.28 (1.27, 4.10)	0.006	2.08 (1.16, 3.75)	0.014
Sex	Female vs. Male	1	5332	0.70 (0.36, 1.34)	0.28	0.58 (0.29, 1.15)	0.117
Race or ethnic group, United States only	White vs. Black	2	3834	1.67 (0.89, 3.12)	0.107		
	Hispanic vs. Black			0.81 (0.34, 1.92)			
Age categories	<30 vs. ≥45 years	2	5332	2.21 (1.00, 4.91)	0.139	2.58 (1.14, 5.83)	0.071
	30-44 vs. ≥45 years			1.56 (0.74, 3.26)		1.71 (0.81, 3.60)	
CD4 count categories	0-0.049 vs. >0.349 $\times 10^9$ cells/L	3	5328	0.31 (0.11, 0.87)	0.111	0.22 (0.07, 0.69)	0.058
	0.050-0.199 vs. >0.349 $\times 10^9$ cells/L			0.60 (0.28, 1.27)		0.57 (0.26, 1.26)	
	0.200-0.349 vs. >0.349 $\times 10^9$ cells/L			0.84 (0.43, 1.65)		0.82 (0.42, 1.63)	
HIV-1 RNA categories	≥100,000 vs. <100,000 copies/mL	1	5330	1.01 (0.59, 1.73)	0.96	1.15 (0.65, 2.06)	0.63
History of AIDS	Yes vs. No	1	5332	1.15 (0.60, 2.21)	0.68	1.66 (0.80, 3.41)	0.172
Injection drug history	Yes vs. No	1	5332	2.85 (1.47, 5.52)	0.002	2.26 (1.15, 4.46)	0.019
Psychiatric history or psychoactive medication	Yes vs. No	1	5332	4.08 (2.37, 7.04)	<0.001	4.07 (2.32, 7.13)	<0.001
BMI categories	Underweight (< 18.5) vs. Normal (<25)	3	5280	1.39 (0.54, 3.54)	0.22		
	Overweight (<30) vs. Normal (<25)			0.59 (0.31, 1.12)			
	Obese (30+) vs. Normal (<25)			0.60 (0.25, 1.43)			
Weight categories	<60 vs. ≥80 kg	2	5321	2.02 (0.98, 4.15)	0.128	2.69 (1.25, 5.79)	0.022
	60-<80 vs. ≥80 kg			1.20 (0.64, 2.26)		1.21 (0.64, 2.29)	

ITT=intent-to-treat. DSMB=data safety monitoring board. DF=degrees of freedom. HR=hazard ratio. CI=confidence interval.

*Cox model Wald CI and p-values are presented, each model was stratified by study. Follow-up was censored using the primary ITT DSMB analysis approach.

†In multivariable analysis, race or ethnic group was omitted because analysis of this covariate was restricted to the United States, and BMI category was omitted due to collinearity with body weight and missing height observations; otherwise covariates were included in this multivariable model.

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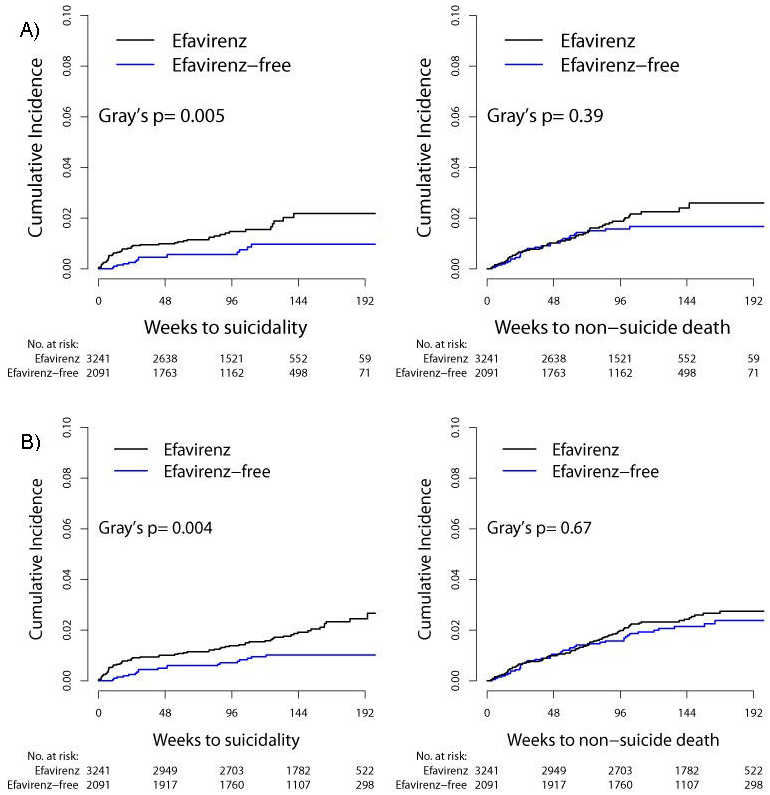

Figure 1. Cumulative incidence of suicidality and non-suicide death

Figure 1A (Suicidality ITT DSMB)

Figure 1B (Suicidality ITT)

Cumulative incidence of suicidal ideation, attempted, or completed suicide (suicidality) is presented on the left, and cumulative incidence of death attributed to causes other than reported suicide (competing risk) is presented on the right. Range of y-axis is limited to 0 through 0.10. Gray's test was stratified by study. Panel A: follow-up was censored after data safety monitoring board recommendations pertaining to the efavirenz comparisons, Panel B: intention-to-treat approach, including follow-up from randomization to last on-study contact.

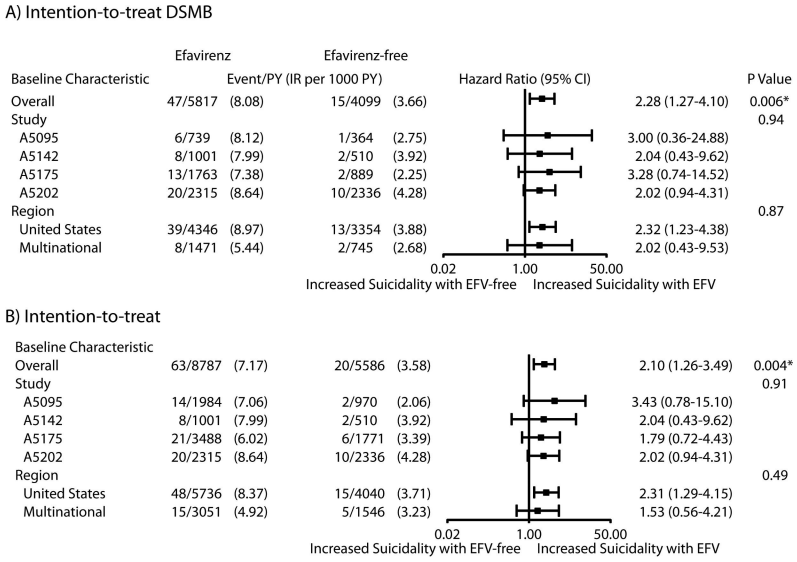

Figure 2. Association between efavirenz and the hazard of suicidality

DSMB= data safety monitoring board, IR=crude incidence rate, PY=person-years, CI=confidence interval. Univariate estimated hazard ratios were quantified from a Cox model with a Wald CI and p-value, stratified by study, and are plotted on a logarithm scale. Panel A: follow-up was censored after data safety monitoring board recommendations pertaining to the efavirenz comparisons, Panel B: intention-to-treat approach, including follow-up from randomization to last on-study contact.

*p-value for efavirenz association, p-values for interaction with efavirenz are presented for study and region

Table 1

Summary of included studies

Study	Efavirenz-containing regimen	n	Efavirenz-free regimen	n	Enrollment Period	Median Age [Min-Max], years	Randomization stratification factors	Planned follow-up period	Median weeks of follow-up [25th -75th percentile]		Clinical Assessment Schedule Weeks
									Efavirenz-containing	Efavirenz-free	
A5095		**765**		**382**			HIV-1 RNA < vs. ≥100k	96 weeks after completion of accrual	48 [29-72] *	48 [28-72] *	0, 2, 4, 8, 12, 16, 20, 24, Q8 onward
	EFV+ ZDV/3TC/ABC	383	ZDV/3TC/ABC		2001-2002	37 [18-77]			145 [122-172]	144 [120-170]	
	EFV+ZDV/3TC	382									
A5142		**502**		**255**			HIV-1 RNA < vs. ≥100k; Chronic hepatitis NRTI choice †	96 weeks beyond March 2004			0, 1, 4, 8, 12, 16, 20, 24, Q8 onward
	EFV + 3TC + NRTI †	250	LPV/r + 3TC + NRTI †		2003-2004	38 [17-73]			112 [96-129]	112 [96-129]	
	EFV + LPV/r	252									
A5175		**1045**		**526**			HIV-1 RNA < vs. ≥100k; Country of enrollment	The longer of 2.5 years after start of accrual or when 30% reach primary endpoint ‡	87 [67-107] *	87 [69-105] *	0, 2, 4, 8, 12, 16, 20, 24, Q8 onward
	EFV + 3TC/ZDV	519	ATV + ddI-EC +FTC		2005-2007	34 [18-73]			184 [161-205]	184 [164-204]	
	EFV + FTC/TDF	526									
A5202		**929**		**928**			HIV-1 RNA < vs. ≥100k; Intent to enroll to A5224s substudy	96 weeks after completion of accrual			0, 4, 8, 16, 24, Q12 onward
	EFV + FTC/TDF	464	ATV/r + FTC/TDF	465	2005-2007	38 [18-71]			137 [107-168]	138 [106-169]	
	EFV + 3TC/ABC	465	ATV/r + 3TC/ABC	463							
Total		**3241**		**2091**					96 [62-132] * 150 [112-181]		

EFV=efavirenz, ZDV=zidovudine, 3TC=lamivudine, ABC=abacavir, 100k=100,000 copies/mL, Q8=every 8 weeks, NRTI=nucleoside reverse transcriptase inhibitor, LPV=lopinavir, /r=boosting ritonavir, ATV= atazanavir, ddI EC= didanosine enteric-coated, FTC=emtricitabine, TDF=tenofovir disoproxil fumerate, Q12=every 12 weeks. All four studies required that participants be antiretroviral-naive, have documentation of HIV-1 infection, and have absence of active drug or alcohol use or dependence (or current substance abuse) that would interfere with adherence to the study. Each study allowed for exclusion based upon any condition that, in the opinion of the site investigator, would compromise the candidate's ability to participate in the study. Histories of suicidal ideation or attempt were not exclusion criteria, but participants with psychiatric history may have been selectively not referred or recruited.

* Prior to data safety monitoring board (DSMB) recommendation pertaining to inferior efficacy of efavirenz-free regimen.

† NRTI was not randomized in A5142, 3TC was given with choice of TDF, ZDV, or stavudine extended release (d4T XR).

‡ Per recommendation of the DSMB, A5175 was closed in May 2010.

Table 2

Suicidal ideation, attempted or completed suicide with efavirenz versus efavirenz-free regimens

	Primary Analysis Approach		Sensitivity Analyses					
	Intention-to-treat DSMB*		Intention-to-treat regardless of DSMB		As-treated DSMB*†		As-treated regardless of DSMB†	
	Efavirenz (n=3241)	Efavirenz-free (n=2091)	Efavirenz (n=3241)	Efavirenz-free (n=2091)	Efavirenz (n=3220)	Efavirenz-free (n=2075)	Efavirenz (n=3220)	Efavirenz-free (n=2075)
Median (Q1-Q3) follow-up, weeks	94 (59-128)	100 (66-142)	151 (113-182)	146 (109-180)	82 (41-119)	96 (53-134)	134 (72-176)	111 (74-149)
Suicidal ideation, attempted or completed suicide								
Events / PY	47 / 5817	15 / 4099	63 / 8787	20 / 5586	40 / 5070	14 / 3770	52 / 7527	16 / 4311
Crude IR	8.08	3.66	7.17	3.58	7.89	3.71	6.91	3.71
IRΔ per 1000 PY (95% CI)	4.62 (1.62, 7.62)		3.84 (1.43, 6.26)		4.32 (1.14, 7.50)		3.65 (0.89, 6.42)	
HR (95% CI)	2.28 (1.27,4.10), p=0.006		2.10 (1.26,3.49), p=0.004		2.16 (1.16, 4.00), p=0.015		2.05 (1.15,3.64), p=0.015	
IRR (exact 95% CI)	2.28 (1.24, 4.42), p=0.006		2.10 (1.24, 3.68), p=0.004		2.17 (1.15, 4.37), p=0.016		2.01 (1.11, 3.84), p=0.019	
Attempted or completed suicide								
Events / PY	17 / 5858	5 / 4111	27 / 8855	7 / 5602	14 / 5077	5 / 3780	22 / 7538	6 / 4323
Crude IR	2.90	1.22	3.05	1.25	2.76	1.32	2.92	1.39
Suicide death [N]	[5]	[1]	[8]	[1]	[3]	[1]	[5]	[1]
IRΔ per 1000 PY (95% CI)	1.86 (0.03, 3.69)		1.90 (0.37, 3.43)		1.68 (−0.30, 3.66)		1.72 (−0.08, 3.52)	
HR (95% CI)	2.58 (0.94,7.06), p=0.065		2.56 (1.10, 5.92), p=0.028		2.31 (0.82, 6.52), p=0.112		2.24 (0.88, 5.69), p=0.091	
IRR (exact 95% CI)	2.58 (0.90, 9.03), p=0.078		2.55 (1.07, 7.00), p=0.031		2.33 (0.78, 8.40), p=0.107		2.29 (0.87, 7.07), p=0.102	

DSMB=data safety and monitoring board. PY=person-years. IR=incidence rate, number of participants with an event per 1000 PY at risk. IRΔ=incidence rate difference per 1000 PY, quantified with a Mantel-Haenszel estimate and rare-events variance estimator, stratified by study. CI=confidence interval. HR=hazard ratio, quantified from a Cox model with a Wald CI and p-value, stratified by study. IRR=incidence rate ratio, quantified from an exact Poisson model with an exact CI and Score p-value, stratified by study. Efavirenz-free is the reference group in all comparisons. Univariate analyses are presented; statistical inference was stratified by study.

*Follow-up in A5095 and A5175 was censored following release of DSMB recommendations pertaining to the efavirenz comparisons.

†Thirty-seven participants who never started treatment with the assigned efavirenz strategy were excluded from the as-treated analysis (21 efavirenz, 16 efavirenz-free).