The Relationship Between Efavirenz as Initial Antiretroviral Therapy and Suicidal Thoughts Among HIV-Infected Adults in Routine Care

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Background: Evidence about the effect of initiating efavirenz-containing combination antiretroviral therapy (ART) as the first-line therapy on suicidal thoughts remains conflicting.

Methods: Using data from a cohort of HIV-infected adults enrolled in routine care across 5 sites in the United States, we included participants with a baseline patient-reported outcome measure and detectable viral load who initiated ART between 2011 and 2014. Participants were followed until the earliest of the following: first suicidal thoughts, discontinuation of initial ART regimen, death, loss to care (>12 months with no HIV appointments), or administrative censoring (2014–2015). Suicidal thoughts were measured using a Patient Health Questionnaire-9 item. We used weighted marginal structural Cox models to estimate the effect of initiating efavirenz-containing ART, versus efavirenz-free ART, on the hazard of active or passive suicidal thoughts after ART initiation, accounting for confounding by channeling bias.

Results: Overall, 597 participants were followed for a median of 19 months (13,132 total person-months); 147 (25%) initiated efavirenz-containing ART. At ART initiation, 38% of participants reported suicidal thoughts or depressive symptoms. Initiating efavirenz-based ART was associated with a hazard ratio (HR) for suicidal thoughts below the null in the crude analysis [HR, 0.88; 95% confidence interval (CI): 0.53 to 1.45] and above the null in the weighted analysis (HR, 1.21; 95% CI: 0.66 to 2.28). Among those with a prior mental health issue, the weighted HR was 1.76 (95% CI: 0.45 to 6.86).

Conclusions: After accounting for measured channeling bias, we observed no strong evidence that initiating efavirenz-containing ART increased the hazard of suicidal thoughts.

Key Words: HIV, efavirenz, suicidal thoughts, suicidal ideation, antiretroviral therapy

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INTRODUCTION

Efavirenz, a nonnucleoside reverse transcriptase inhibitor, has been a mainstay of antiretroviral therapy (ART) for more than 15 years. Use of efavirenz is declining in the United States because of the availability and tolerability of newer agents.[1] However, the World Health Organization continues to recommend efavirenz globally as first-line ART.[2,3] Efavirenz is attractive given its rapid and durable viral suppression, low cost, generic formulation, and availability in a fixed-dose combination pill.[4] However, serious psychiatric side effects, including suicidal thoughts, have been reported with efavirenz.[5] Given its widespread use, an accurate understanding of the relationship between efavirenz use and suicidal thoughts is critical.

Evidence about the effect of efavirenz on suicidal thoughts remains conflicting. Early clinical trials suggested

that efavirenz may increase the risk of depression and suicidal thoughts.[6] However, side effects were thought to be rare, transient, and, in most cases, not life threatening. More recently, efavirenz was associated with a 2-fold increase in the hazard of a combined outcome of suicidal thoughts, behaviors, or attempted or completed suicide in a pooled analysis of 4 randomized controlled trials from the AIDS Clinical Trials Group.[7] Efavirenz was also associated with suicidal behavior in a secondary analysis of the Strategic Timing of Antiretroviral Treatment (START) trial.[8] These results were not confirmed by data from the Food and Drug Administration Adverse Event Reporting System (FAERS)[9] or when the relationship between efavirenz and completed suicide was evaluated in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study.[10]

Two key considerations in studying the relationship between efavirenz and suicidal thoughts are accurate measurement of suicidal thoughts and the appropriate accounting for confounding by selective prescription or discontinuation of efavirenz. Previous analyses of efavirenz's effect on suicidal outcomes have relied on adverse event reporting[7–10] or insurance claims,[11] which may capture the most severe forms of suicidal thoughts. Additionally, the potential for clinicians to prescribe efavirenz-free regimens to persons with mental health issues (channeling-in bias) or to switch persons who develop mental health issues off efavirenz (channeling-out bias)[12] is an important consideration that has not been fully accounted for in previous observational analyses.[9,10]

To address these questions, we used data from a cohort of HIV-infected adults in routine care across the United States who complete routine systematic assessments of suicidal thoughts every 4–6 months. The goal of our analysis was to estimate the effect of initiating efavirenz-containing ART as first-line therapy on time to passive or active suicidal thoughts.

METHODS

Data for the present analysis come from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. The CNICS cohort includes more than 31,000 HIV-infected adults in routine care at 8 sites in the United States.[13] CNICS captures comprehensive clinical data that includes standardized diagnosis, medication, laboratory, and demographic information collected through electronic medical records and institutional data systems. Participants also complete self-administered questionnaires, or patient-reported outcomes (PROs), on touch-screen tablets as a part of routine care. PROs are completed approximately every 4–6 months, with variation based on clinical follow-up. Participants provide written informed consent to participate in CNICS. Ethical approval for the use of routinely collected clinical data was provided by the institutional review board at each CNICS site.

Study Population

Participants in CNICS were included if they initiated ART between 2011 and 2014 (time frame when PRO data were available and efavirenz was recommended as the first-line ART in the United States[4,14]; n = 2729), at a site collecting PRO information (n = 6 of 8 sites) and had a PRO measure within the 6 months prior or 1 week after initiating ART (n = 875). Participants who were already taking efavirenz when PRO collection began may have previously experienced psychiatric side effects from efavirenz that resolved and therefore were excluded. Information on previous ART use is not always available in CNICS. Therefore, participants with incomplete data on ART use (n = 40) or who had a suppressed viral load at ART initiation (indicating possible prior ART use; n = 223) were excluded. Participants from 1 site where no patients initiated efavirenz (n = 15 participants) were excluded because this site may differ from others where efavirenz was prescribed. Our interest was in understanding suicidal thoughts occurring as a result of initiating efavirenz. Furthermore, clinicians are unlikely to have access to information on a patient's suicidal thoughts when making decisions about initial ART regimen. For these reasons, patients with suicidal thoughts at ART initiation were not excluded. Participants were followed from ART initiation until the earliest of the following dates: a PRO measure indicating suicidal thoughts, discontinuation of ART (defined as switching to an efavirenz-containing or efavirenz-free regimen, depending on initial regimen, or ART discontinuation entirely), loss to HIV care (12 months with no attended HIV appointments), or administrative censoring (October 2014 to September 2015, depending on site).

Measures

The primary exposure was initial ART regimen, categorized as efavirenz containing or efavirenz free. An ART regimen was defined as being on ≥3 antiretroviral drugs, including at least 1 nonnucleoside reverse transcriptase inhibitor, protease inhibitor, or integrase inhibitor for ≥21 days.[1] The outcome of interest was passive or active suicidal thoughts (hereafter suicidal thoughts) following ART initiation. Suicidal thoughts are measured as part of the CNICS PROs using 1 item of the Patient Health Questionnaire-9 (PHQ-9),[15] which asks in a combined question whether participants had any thoughts of being better off dead (passive) or hurting themselves (active) in the previous 2 weeks. The PHQ-9 is a validated measure to identify suicidal thoughts, with a sensitivity of 65%–90% and specificity of 80% to >90%.[16,17] We did not evaluate attempted or completed suicide or ART discontinuation because of the psychiatric side effects. CNICS does not collect information on reasons for ART discontinuation or suicide attempts, and cause of death information is only available for a portion of the population. Of those with cause of death information, very few were reported as suicides.

CNICS PROs collect additional patient-reported data using validated measures, including ART adherence (AIDS Clinical Trials Unit-4 Visual Analog Scale, defined as no missed doses in the past week[18,19]), depressive symptom severity (defined as a binary measure with cutpoint PHQ-9 of ≥10 and a continuous score[15]), panic disorder (PHQ-5, defined as some panic disorder symptoms or panic disorder[20]), high-risk alcohol use [Alcohol Use Disorders

Identification Test (AUDIT), defined as AUDIT score ≥4 for males and ≥3 for females[21]], and current or past illicit drug use, excluding marijuana [Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[22,23]]. Baseline depressive symptoms and suicidal thoughts were combined into a 3-level variable: no depressive symptoms or suicidal thoughts, depressive symptoms without suicidal thoughts, or suicidal thoughts (with or without depressive symptoms), because of the collinearity issues in the weighted model between depressive symptoms and suicidal thoughts.

Self-reported race/ethnicity was categorized as white, black, Hispanic, or other and HIV acquisition risk group as men who had sex with men (MSM), heterosexuals, intravenous drug users, or other and collected at CNICS enrollment. CNICS captures prior clinician-documented mental health or medical diagnoses in the medical record. We defined a prior medical diagnosis as any previous medical diagnosis at the time of ART initiation. A prior mental health disorder was defined as any previous diagnosis of depression, bipolar disorder, posttraumatic stress disorder or psychosis, as these diagnoses are most likely to affect suicidal thoughts and influence efavirenz prescription.[24,25] Undetectable viral load was defined as <50 copies per milliliter.

Statistical Analysis

The goal of our analysis was to estimate the effect of initiating efavirenz-containing ART on time to suicidal thoughts. We used weighted Kaplan–Meier curves and marginal structural Cox models with inverse probability weights[26] to approximate a study in which individuals were randomized at baseline to initiate efavirenz-containing or efavirenz-free ART. We developed 3 sets of weights; inverse probability of treatment weights (IPTW) to account for potential channeling-in bias in receipt of efavirenz, inverse probability of censoring weights to account for bias because of loss to follow-up, and inverse probability of observation weights to account for the varying frequency of PRO measurements between participants. Additional details about the creation of the weighs are available in the Supplemental Digital Content, http://links.lww.com/QAI/B66. Directed acyclic graphs were used to identify covariates for inclusion in each set of weights.[27] For all weights, restricted cubic splines[28] were used for continuous variables whenever possible; any categorization was based on the functional form of the relationship between the covariate and outcome. Because of the limited sample size, for both race/ethnicity and HIV acquisition, participants reporting "other" were collapsed with the largest category (white and MSM) for statistical analyses.

We conducted 3 secondary analyses. First, we examined mental health status at baseline (defined as a prior mental health diagnosis, reported panic symptoms or disorder, depressive symptoms/suicidal thoughts, or an antidepressant prescription at ART initiation) as an effect measure modifier of the efavirenz–suicidal thoughts relationship. Second, we considered ART for ≥7 days as an ART regimen. Third, we examined an outcome of more frequent suicidal thoughts (defined as occurring half the days or more in the past 2 weeks). We compared crude and weighted estimates for both the primary and secondary analyses and assessed the proportional hazards assumption. All analyses were conducted in Stata version 13 (StataCorp, College Station, TX) or SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Overall, 597 CNICS participants met our inclusion criteria (Fig. 1). Characteristics between all those who initiated ART, those without a valid PRO, and the study population were similar (Table S2). At ART initiation, 147 (25%) initiated efavirenz-containing ART. Additional information on initial ART regimens in available in Table S3. Participants were followed for a median of 19 months and contributed 13,132 person-months of follow-up. Overall, participants were predominately male subjects (90%), white non-Hispanic/other (57%), and reported contracting HIV through being MSM/other (74%; Table 1). Mental health issues were common. At ART initiation, more than one-third (38%) reported depressive symptoms (20%) or suicidal thoughts and/or depressive symptoms (18%), 11% were prescribed antidepressants, and 31% had a prior depression, posttraumatic stress disorder, or bipolar or psychosis diagnosis. During the follow-up period, 89 participants (15%) reported suicidal thoughts after ART initiation, 4 (1%) died, 140 (23%) were lost to follow-up, 74 (12%) discontinued ART, and 290 (49%) were administratively censored.

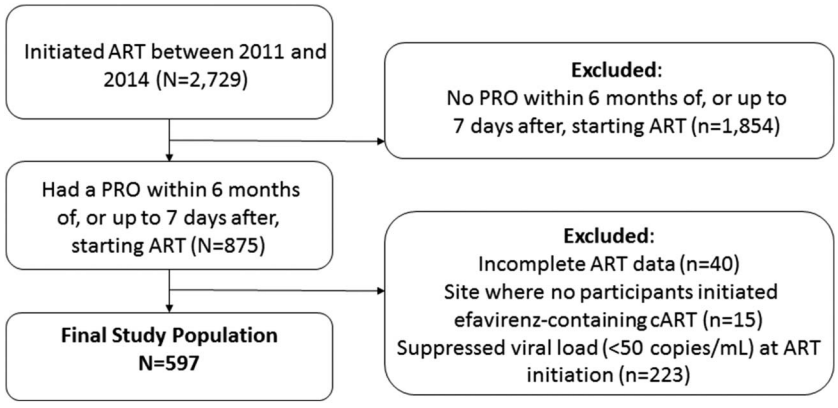


FIGURE 1. Inclusion criteria for 597 HIV-infected adults in CNICS who initiated ART between 2011 and 2014 and had a PRO within 6 months prior or up to 1 week after initiating ART and had a detectable viral load at ART initiation.

TABLE 1. Clinical and Demographic Characteristics at ART Initiation of 597 Participants in CNICS: 2011–2014

Baseline Characteristics	EFV-free ART; 450 (75.4) N (%) or Mean (SD)	EFV-containing ART; 147 (24.6) N (%) or Mean (SD)
Year initiated ART		
2011	79 (17.6)	76 (51.7)
2012	121 (26.9)	39 (26.5)
2013	138 (30.7)	25 (17.0)
2014	112 (24.9)	7 (4.8)
Age, yr	36 (28–44)	34 (29–47)
Gender		
Male	396 (88.0)	139 (94.6)
Female	54 (12.0)	8 (5.4)
Race/ethnicity		
White, non-Hispanic	219 (48.9)	75 (51.7)
Black, non-Hispanic	98 (21.9)	37 (25.5)
Hispanic	95 (21.2)	26 (17.9)
Other	36 (8.0)	7 (4.8)
HIV risk group		
MSM	304 (67.6)	114 (78.1)
IDU	56 (12.4)	13 (8.9)
Heterosexual	69 (15.3)	19 (13.0)
Other	21 (4.7)	0 (0.0)
Depression and suicidal ideation		
No depression or suicidal ideation	268 (59.6)	102 (69.4)
Depression	90 (20.0)	27 (18.4)
Suicidal ideation, with or without depression	92 (20.4)	18 (12.2)
Antidepressant use		
Not on an antidepressant	390 (87.4)	136 (93.8)
On an antidepressant	56 (12.6)	9 (6.2)
Panic disorder		
No symptoms	279 (62.3)	116 (80.6)
Some symptoms	93 (20.7)	16 (11.1)
Panic disorder	76 (17.0)	12 (8.3)
Drug use		
No use	166 (42.7)	72 (50.7)
Current use	113 (29.0)	29 (20.4)
Past use	110 (28.3)	41 (28.9)
Alcohol use		
Not at risk drinking	107 (24.3)	42 (29.2)
At risk drinking	333 (75.7)	102 (70.8)
Prior mental health diagnosis*		
No	305 (67.8)	107 (72.8)
Yes	145 (32.2)	40 (27.2)
Prior medical diagnosis*		
No	386 (85.8)	129 (87.8)
Yes	64 (14.2)	18 (12.2)
CD4 count, cells/mm^3	390 (241–545)	417 (276–530)

Missing data: race/ethnicity, n = 4; HIV risk group, n = 1; antidepressant use, n = 6; panic disorder, n = 5; drug use, n = 66; alcohol use, n = 13; CD4 count, n = 3.

*At the time of ART initiation.

IDU, intravenous drug use.

In the crude analysis, those starting efavirenz-containing ART reported a slightly lower hazard of suicidal thoughts than those starting efavirenz-free ART [hazard ratio (HR), 0.88; 95% confidence interval (CI): 0.53 to 1.45; Table 2]. At 36 months after ART initiation, the unadjusted risk of suicidal thoughts for persons initiating efavirenz-free ART was 21% and for persons initiating efavirenz-containing ART was 19% (risk difference, −0.02; 95% CI: −0.12 to 0.06; Table 3 and Fig. 2).

In the weighted analysis, those starting efavirenz-containing ART evidenced a slightly higher (but less precise) hazard of suicidal thoughts than those starting efavirenz-free ART (HR, 1.21; 95% CI: 0.65 to 2.28; Table 2). At 36 months after ART initiation, the weighted risk of suicidal thoughts for persons initiating efavirenz-free ART was 22% compared with 25% for persons initiating efavirenz-containing ART (risk difference, 0.03; 95% CI: −0.10 to 0.25; Table 3 and Fig. 2). Covariates included in the IPTW were no longer associated with efavirenz initiation in the weighted analysis (Table S1). The proportional hazards assumption was met in the crude analysis (exposure by log time interaction; *P* value of 0.33) but not in the weighted analysis (*P*-value 0.02); however, this is likely because of the relatively constant risk of suicidal thoughts for efavirenz users during year 2 (Fig. 2).

Weighted effect estimates were similar in a secondary analysis where the minimum time on an ART regimen was 7 days (HR, 1.28; 95% CI: 0.67 to 2.43). When baseline mental health status was considered as an effect measure modifier, effect estimates suggested that initiating efavirenz-containing ART may have a strong effect among those with mental health issues (HR, 1.76; 95% CI: 0.45 to 6.86; HR among those without mental health issues: 0.96; 95% CI: 0.23 to 4.01); however, confidence intervals were wide and overlapping. In a secondary analysis examining an outcome of more frequent suicidal thoughts, the HR was 0.61 (95% CI: 0.10 to 3.62), although there were a small number of events (n = 28).

DISCUSSION

In our cohort of HIV-infected adults initiating ART between 2011 and 2014, 25% of participants initiated ART-containing efavirenz and 15% of participants reported experiencing suicidal thoughts over a median of 19 months (76 weeks) of follow-up. The crude analysis indicated that those starting efavirenz-containing ART were slightly less likely to have suicidal thoughts. In contrast, in the weighted analysis, those starting efavirenz-containing ART were slightly more likely to have suicidal thoughts, after accounting for channeling bias, informative censoring, and missing data. In both cases, the effect estimates were modest and 95% confidence intervals included the null. When stratified by baseline mental health status, effect estimates suggested that efavirenz may have a stronger effect on suicidal thoughts among those with a prior mental health diagnosis. Our results were robust to changes in the specification of the minimum length of an ART regimen and when an outcome of more frequent suicidal thoughts was considered.

TABLE 2. HR for the Effect of Initiating Efavirenz-Containing ART on Time to Suicidal Thoughts Among 597 HIV-Infected Adults Initiating ART Between 2011 and 2014

Initial ART Regimen	No. Events	Person Months	Incidence Rate*	Unadjusted HR (95% CI)	Weighted HR (95% CI)[2]
Efavirenz-free ART	69	9690	7.12	1.00	1.00
Efavirenz-containing ART	20	3442	5.81	0.88 (0.53 to 1.45)	1.21 (0.65 to 2.28)

Weighted to account for potential channeling-in bias in efavirenz prescription, missing PRO assessments, and informative censoring because of loss to follow-up. Mean of combined weights is 0.99 (range, 0.15–7.67).

*Incidence rate per 1000 person-months.[2]

Our findings are consistent with the results of 2 observational analyses examining the relationship between efavirenz use and suicidal thoughts or behaviors.[9,11] An analysis of current efavirenz use and completed suicide, which did not account for channeling bias in efavirenz prescription, also showed no evidence of an association.[10] However, a pooled analysis of 4 clinical trials found that participants randomized to an initial ART regimen with efavirenz had twice the hazard of developing suicidal thoughts, attempting, or completing suicide (composite outcome) over a median of 96 weeks of follow-up, compared with those randomized to efavirenz-free ART.[7] A secondary analysis of the SMART trial, which randomized participants to immediate versus delayed ART initiation, also found an increased risk of suicidal behavior among participants who initiated efavirenz in the immediate arm, compared with those in the deferred arm before they initiated ART.[8]

Differences in the measurement of suicidal thoughts may lead to conflicting evidence about efavirenz's effect on suicidal behaviors. In our analysis, suicidal thoughts were measured systematically and at regular intervals using the PHQ-9, as part of the PROs.[15] In previous studies, including clinical trials, suicidal thoughts have been measured using adverse event–reporting systems.[7–10] Adverse event–reporting systems may be more likely to capture severe active suicidal thoughts rather than the broader pool of passive *or* active suicidal thoughts measured by the PHQ-9.[29] It is possible that efavirenz increases the more severe form of active suicidal thoughts, which may help to explain the effect of efavirenz on suicidal thoughts and behavior observed in clinical trials. However, this hypothesis has not been tested. Passive thoughts are much more common than active thoughts[29] and may help to explain the attenuated result in this study.

A strength of this study is the use if IPTWs to address channeling-in bias. Reports of psychiatric side effects from efavirenz have led many clinicians to avoid prescribing efavirenz for persons with a mental health diagnosis ("channeling-in") and to switch persons who develop mental health issues off efavirenz ("channeling-out").[12] Although CNICS does not collect information on provider reasons for prescription or discontinuation, our analysis, and others, addressed channeling-in bias by balancing measured covariates between those initiating efavirenz and those not through IPTWs.[11] In our weighted data, none of the variables included in the IPTW were associated with efavirenz use (Table S1), suggesting that the IPTW properly balanced the likelihood of receiving efavirenz conditional on included and measured covariates. However, residual confounding by unmeasured, and possibly difficult to measure, factors may remain. In our analysis, channeling-out bias was considered negligible because of the small number of persons who discontinued ART during the follow-up period.

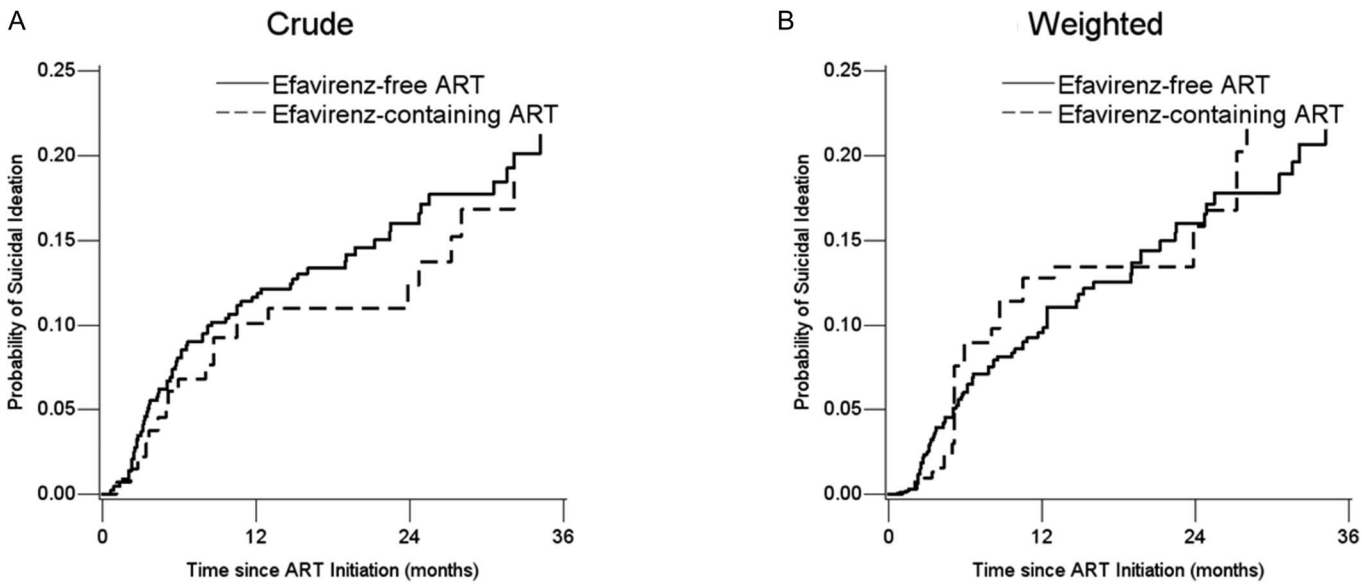
In our cohort, 89 persons experienced suicidal ideation during follow-up. This was higher than the number of events reported in the pooled analysis of 4 trials from the AIDS Clinical Trials Group (47 events in the efavirenz group and 15 events in the efavirenz-free group) that reported an HR of 2.28 for composite suicidal behaviors or suicide with efavirenz use.[7] Thus, the wide confidence intervals reported in our analysis are unlikely to be driven solely by a lack of statistical power. Of note, the confidence interval for our weighted estimate did overlap with the results reported in the pooled analysis. Although our sample size (N = 597) may be small relative to the larger CNICS cohort, a larger source of observational data with validated measures of suicidal thoughts is unlikely to be available in the future.

As with all observational data, the internal validity of our findings rests on several assumptions. Our analysis assumes no unmeasured confounding and correct model

TABLE 3. Risks and Risk Differences (RD) for Suicidal Thoughts 6, 12, and 36 Months After ART Initiation by Initial ART Regimen Among 597 HIV-Infected Adults Initiating ART Between 2011 and 2014

Months Since ART Initiation	Crude			Weighted		
	Efavirenz-Free ART	Efavirenz-Containing ART	RD (95% CI)*	Efavirenz-Free ART	Efavirenz-Containing ART	RD (95% CI)*
12 months	0.12	0.10	−0.02 (−0.07 to 0.04)	0.10	0.13	0.03 (−0.02 to 0.10)
36 months	0.21	0.19	−0.02 (−0.12 to 0.06)	0.22	0.25	0.03 (−0.10 to 0.25)

*95% CI are derived from bootstraps (n = 1000 for crude risk differences and n = 100 for weighted risk differences, due the large size of the data set).



Months	0	6	12	18	24	36
Initiated EFV-free ART						
Cumulative Events	0	34	50	56	62	69
Events	0	34	16	6	6	7
Number at Risk	450	400	362	272	169	76
Initiated EFV-containing ART						
Cumulative Events	0	9	13	14	15	19
Events	0	9	4	1	1	4
Number at Risk	147	123	108	96	65	45

FIGURE 2. Unadjusted (A) and weighted (B) Kaplan–Meier curves showing the cumulative probability of suicidal ideation for individuals who initiated efavirenz-containing ART and those who initiated efavirenz-free ART in CNICS between 2011 and 2014 through 36 months (1 event occurred after 36 months). Weighted estimates are weighted by the product of IPTW to account for challenging-in bias, inverse probability of censoring weights to account for potentially informative loss to follow-up, and inverse probability of observation weights to account for not having an observed PRO assessment at least once within a 6-month period.

specification.[30] We note the possibility of residual or unmeasured confounding and a violation of the proportional hazards assumption in the weighted analysis as limitations. Second, we assume consistency, or the idea that initiating efavirenz represents a well-defined treatment,[31] a reasonable assumption given standardized current ART treatment guidelines. Finally, our analysis assumes that there is a nonzero probability for all participants of being in either exposure category (efavirenz containing or efavirenz free) within all strata of measured covariates in the data, also a plausible assumption.[30] Finally, we note that our analysis focuses on an outcome of suicidal ideation; evidence about efavirenz's relationship with major depression and other neuropsychiatric side effects, which may be independent of suicidal ideation,[32,33] have been reported elsewhere.[12]

Clinicians face difficult choices about whether to prescribe efavirenz, given its possible neuropsychiatric side effects. Our results from the largest cohort of HIV-infected adults in care in the United States suggest that initiating an efavirenz-containing regimen does not meaningfully increase the risk of suicidal thoughts. For participants with a history of mental health issues, efavirenz may have a stronger effect on suicidal thoughts. Differences in our results from those seen in randomized controlled trials may stem from important differences in study populations, or more likely, from the fact that adverse event–reporting systems in clinical trials are more likely to capture more sever forms of suicidal thoughts. Notably, similar proportions of participants with prior mental health diagnoses were included in our study and clinical trials,[7] suggesting that differences in study populations are unlikely to fully explain disparate results.

In our analysis of HIV-infected adults in routine care, initiating efavirenz-containing ART did not result in an increased hazard of suicidal thoughts. Our results come from one of the largest sources of data on efavirenz use among HIV-infected adults in the United States; however, they may be less generalizable to resource-limited settings where fewer drug choices could lead to less channeling of efavirenz, and mental health issues may be less likely to be recognized or treated.[34,35] Given the widespread and continuing use of efavirenz globally, screening for and monitoring suicidal thoughts among efavirenz users is recommended. Further research is needed, particularly in global settings, to clarify the relationship between efavirenz and suicidal thoughts.

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