Poster No. O315

HIV Glasgow Drug Therapy 2014

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D:A:D

Lack of Association Between Use of Efavirenz and Death from Suicide: D:A:D Study

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on behalf of the D:A:D Study Group

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BACKGROUND

- A recent meta-analysis performed by the ACTG of 4 RCTs in previously ART-naïve individuals showed a 2.28-fold increased rate of suicidality events among HIV-positive people receiving EFV compared to other, predominantly PI-based, regimens*
- There was also a trend towards an almost 3-fold higher rate of completed/attempted suicides, but the number of events was small (17 and 5 events)
- We investigated whether the association between use of EFV and death from suicide observed in the clinical trial setting was replicated in an observational setting

METHODS

- Participants were from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) Study, a collaboration of 11 cohort studies in Europe, USA, and Australia
- Consistent classification categories for causes of death was used across the study period following Coding of Causes of Death (CoDe) methodology
- Individuals were followed from D:A:D entry to the first of death, 6 months after last clinic visit or 1st February 2013. Incidence rate ratios were calculated using Poisson regression
- The primary outcome was defined in two ways as:
  - Suicide or psychiatric disease listed as underlying cause of death
  - Suicide or psychiatric disease listed as any of the underlying, immediate or contributing causes of death
- We hypothesized that any psychiatric-related effects of EFV would appear upon initiation and remain whilst the drug is taken, so our models focus on current ART use
- A number of sensitivity analyses were performed, including:
  - Considering an outcome of suicide (without psychiatric disease) listed as the underlying cause of death
  - Considering an outcome of suicide, psychiatric disease, accident or other violent death, substance abuse, chronic alcohol abuse, chronic IVDU, CNS disease or acute intoxication listed as underlying, immediate or contributing death cause
  - Considering the ART regimen received with a 3- and 6-month time-lag
  - All analyses were re-performed stratified by mode of HIV acquisition
  - All analyses were re-performed restricted to those ART-naïve at baseline

RESULTS

- There were 49,717 individuals participating in the D:A:D study (**Table 1**)
- In 371,333 person-years of follow-up there were:
  - 4,420 total deaths; rate=11.9 /1000 person-years; (95% CI 11.6, 12.3)
  - 193 deaths with underlying cause of suicide or psychiatric disease rate=0.52 (95% CI 0.45, 0.59)
  - 482 deaths with suicide or psychiatric disease was mentioned anywhere on the death report; rate=1.30 (95% CI 1.18, 1.41)
- There was a strong association between current CD4 and suicide-related deaths (**Figure 1**)
- The highest rates of suicide deaths were seen amongst ART-experienced people currently off ART and ART-naïve individuals. For those on ART, similar suicide death rates were seen regardless of type of ART regimen (**Figure 2**)
- After adjusting for potential confounders, similar associations remained (**Table 3**)
- All sensitivity analyses provided consistent results

CONCLUSIONS

- This study provides evidence that, amongst individuals in routine clinical care, rates of death from suicide and related causes for those receiving EFV-based ART are similar to those seen in individuals receiving other ART regimens
- Treatment choices are at the clinician's and patient's discretion, and so it is possible and likely that the ART treatment groups are not comparable with respect to presence of underlying psychiatric and CNS-related disorders due to channelling bias. Unfortunately, information on history of psychiatric disease is not available
- Thus these findings do not rule out the possibility that EFV leads to increased risk of suicide but they do provide re-assurance that the way in which the drug is used is not leading to increased suicide rates in those on the drug

Table 1

Characteristics of D:A:D participants at Study Entry

		Study population	Suicide or psychiatric disease as underlying cause of death
Total		49717 (100.0)	193 (100.0)
Gender	Male	36664 (73.8)	171 (88.6)
Risk	Injecting drug use	7619 (15.3)	48 (24.9)
	Heterosexual sex	16202 (32.6)	33 (17.1)
	Other/Unknown	3974 (8.0)	6 (3.1)
	Sex between men	21922 (44.1)	106 (54.9)
Ethnic	Black	4872 (9.8)	8 (4.2)
	Other	1416 (2.9)	1 (0.5)
	Unknown	18258 (36.7)	92 (47.7)
	White	25171 (50.6)	92 (47.7)
Previous AIDS	Yes	10491 (21.1)	55 (28.5)
Viral load<400 c/ml	Yes	20968/47423 (44.2)	83/188 (44.2)
CD4 (cells/µL)	Median (IQR)	400 (243, 590)	397 (209, 610)
CD4 nadir (cells/µL)	Median (IQR)	260 (120, 425)	240 (98, 401)
Age (years)	Median (IQR)	38 (32, 45)	38 (35, 46)
Total ART (years)	N (%); median (IQR)	N=30383 (61.1%) 2.9 (1.2, 4.8)	131 (67.9%) 3.3 (2.2, 4.7)

Figure 1

Rates of death from suicide per 1,000 person years, according to current CD4 count

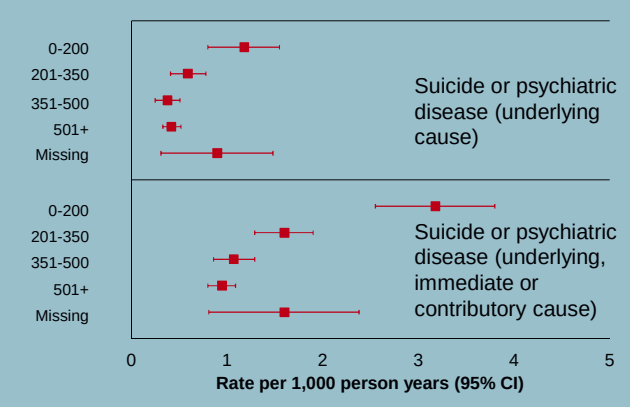

Figure 2

Rates of death from suicide per 1,000 person years, according to current ART regimen

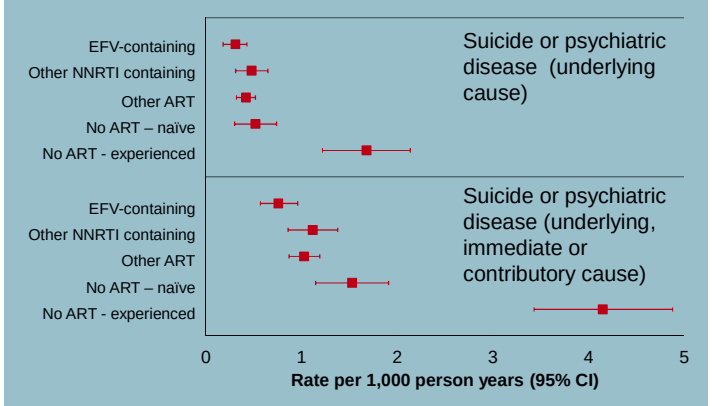

Table 2

Incidence Rate Ratios (IRRs) for death from suicide, according to current ART regimen

	Unadjusted			Adjusted		
	IRR	95% CI	p-value	IRR	95% CI	p-value
Suicide or Psychiatric disease (underlying cause)						
EFV-containing	0.59	0.33, 1.06	<0.0001	0.56	0.29, 1.07	<0.0001
Other NNRTI-containing	0.93	0.53, 1.62		0.94	0.50, 1.77	
Other ART	0.81	0.49, 1.32		0.76	0.43, 1.36	
No ART – naïve	1.00	-		1.00		
No ART – experienced	3.24	1.95, 5.38		3.38	1.91, 5.97	
Suicide or Psychiatric disease (underlying, immediate or contributory cause)						
EFV-containing	0.50	0.35, 0.71	<0.0001	0.42	0.28, 0.63	<0.0001
Other NNRTI-containing	0.73	0.52, 1.03		0.68	0.46, 1.00	
Other ART	0.67	0.50, 0.90		0.52	0.37, 0.73	
No ART – naïve	1.00			1.00		
No ART – experienced	2.71	2.00, 3.67		2.29	1.63, 3.21	

*Adjusted for nadir CD4 count, current CD4 count, age, gender, time since HIV diagnosis, cohort, previous clinical event and risk for HIV acquisition.

*KR Mollan et al. Association Between Efavirenz as Initial Therapy for HIV-1 Infection and Increased Risk for Suicidal Ideation or Attempted or Completed Suicide: An Analysis of Trial Data. Ann Intern Med. 2014;161:1-10

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External endpoint reviewer: A Sjøl (CVD), P Meidahl (oncology), JS Iversen (nephrology). **Funding**: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMA and a consortium of AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck, Pfizer, F. Hoffmann-La Roche and Janssen Pharmaceuticals

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