Lack of association between use of efavirenz and death from suicide: the D:A:D Study

Colette Smith, Lene Ryom, Antonella d'Arminio Monforte, Peter Reiss, Amanda Mocroft, Wafaa el Sadr, Rainer Weber, Mathew Law, Caroline Sabin, Jens Lundgren

On behalf of the D:A:D Study Group

D:A:D

Background

- A recent meta-analysis found a 2.28-fold increased rate of suicidality events among HIV-positive people receiving EFV compared to other, predominantly PI-based, regimens*

- There was an almost 3-fold higher rate of completed/ attempted suicides, but number of events was small (22 events)

- We investigated whether the association between use of EFV and death from suicide observed in the clinical trial setting was replicated in an large observational study

* Mollan et al. Ann Intern Med 2014. 161(1): 1-10

Methods 1

- 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 calculated using Poisson regression

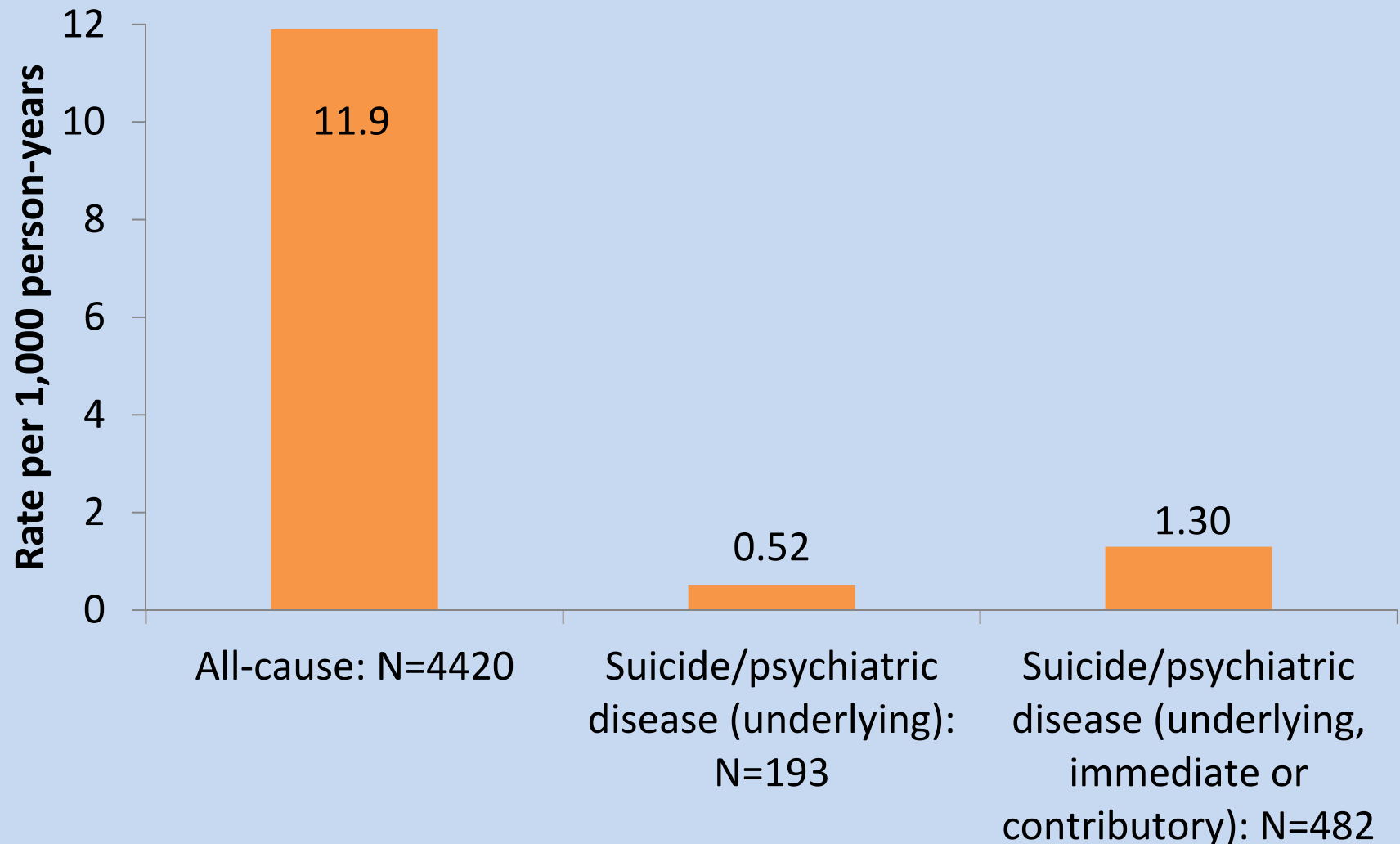* Kowalska et al. Epidemiology 2011. 22(4): 516-23

Methods 2

- CoDe methodology allows for multiple causes of death to be listed:
  - 1 underlying cause
  - 1 immediate cause
  - Up to 4 contributory causes

- 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
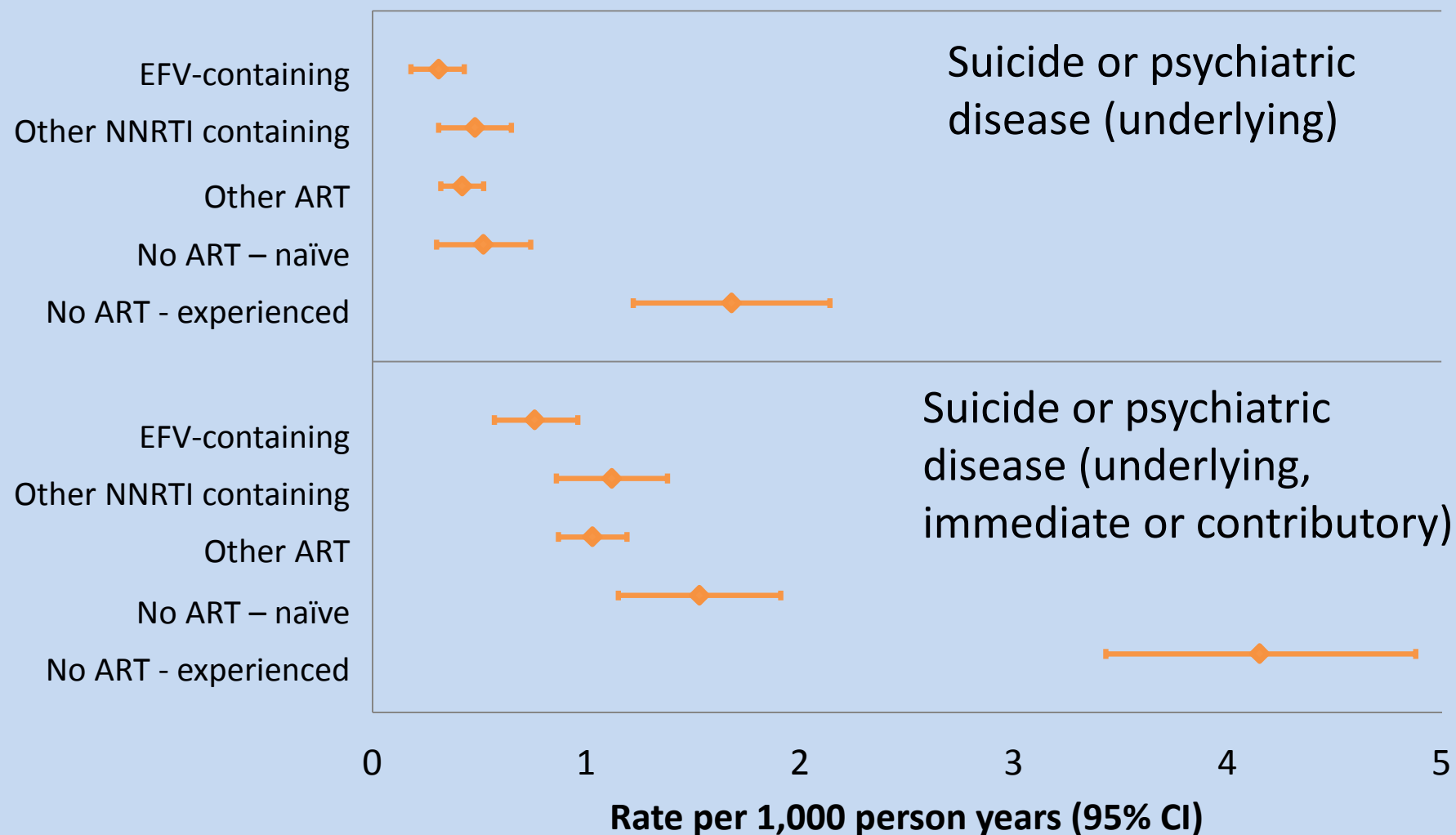
- Exposure: current ART use

Characteristics at study entry

		Number (n=49717)	%
Gender	Male	36664	74
Risk	MSM	21922	44
	IDU	7619	15
	Heterosexual	16202	33
	Other/Unknown	3974	8
Ethnicity	White	25171	51
	Black	4872	10
	Other/Unknown	19674	40
Previous AIDS	Yes	10491	21
Viral load<400 c/ml	Yes	20968/47423	44
CD4 (cells/μL)	Median (IQR)	400	243, 590
Age (years)	Median (IQR)	38	32, 45
Any ART	N	30383	61
Total years	Median (IQR)	2.9	1.2, 4.8

Death Rates (person-years=371,333)

Rate per 1,000 person-years

Value	Category
11.9	All-cause: N=4420
0.52	Suicide/psychiatric disease (underlying): N=193
1.30	Suicide/psychiatric disease (underlying, immediate or contributory): N=482

Death Rates according to ART regimen

Rate per 1,000 person years (95% CI)

Association between ART regimen and suicide/psychiatric disease

	Unadjusted	
	IRR	95% CI
Suicide or Psychiatric disease (underlying cause)		
EFV-containing	0.59	0.33, 1.06
Other NNRTI-containing	0.93	0.53, 1.62
Other ART	0.81	0.49, 1.32
No ART – naïve	1.00	-
No ART – experienced	3.24	1.95, 5.38

*Adjusted for nadir CD4 count, current CD4 count, age, gender, time since HIV diagnosis, cohort, previous clinical event and risk for HIV acquisition. All p<0.0001

Association between ART regimen and suicide/psychiatric disease

	Unadjusted		Adjusted	
	IRR	**95% CI**	**IRR**	**95% CI**
Suicide or Psychiatric disease (underlying cause)				
EFV-containing	0.59	0.33, 1.06	0.56	0.29, 1.07
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

*Adjusted for nadir CD4 count, current CD4 count, age, gender, time since HIV diagnosis, cohort, previous clinical event and risk for HIV acquisition. All p<0.0001

Association between ART regimen and suicide/psychiatric disease

	Unadjusted		Adjusted	
	IRR	**95% CI**	**IRR**	**95% CI**
Suicide or Psychiatric disease (underlying cause)				
EFV-containing	0.59	0.33, 1.06	0.56	0.29, 1.07
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	0.42	0.28, 0.63
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. All p<0.0001

Characteristics at time of suicide

		EFV-based ART	Other ART	No ART – naïve	No ART – experienced
N (%)		60	234	62	126
Gender	Male	49 (82)	201 (86)	48 (77)	104 (83)
Risk	IDU	31 (52)	74 (32)	32 (52)	51 (40)
Age (years)	Median [IQR]	44 [36-48]	44 [39-52]	37 [29-43]	44 [38-50]
VL<400 c/ml	Yes	32 (53)	140 (60)	1 (2)	44 (35)
CD4 (cells/μL)	Median [IQR]	350 [179-561]	407 [230-630]	501 [377-642]	338 [174-509]
Last ART regimen	EFV-based Other NNRTI Other	-	-	-	29 (23) 19 (15) 78 (62)
Time since last ART (years)	<0.5 0.5-1 1-2 2+	-	-	-	77 (61) 19 (15) 10 (8) 20 (16)

Other predictors

- Death from suicide/psychiatric disease was more common for:
  - Lower current CD4 count
  - Men
  - Older age
  - IDU risk for HIV transmission

Sensitivity analyses

- Re-defining outcome as:
  - Suicide (without psychiatric disease) listed as underlying cause of death
  - Any of: suicide; psychiatric disease; accident or other violent death; substance abuse; chronic alcohol abuse; chronic IVDU; CNS disease; acute intoxication as underlying, immediate or contributing cause

- Consider ART regimen received with 3- and 6-month time-lag

- Analyses stratified by mode of HIV acquisition

- Analyses restricted to those ART-naïve at baseline

Conclusions

- Amongst those in routine clinical care, observed rates of death from suicide/related causes for those receiving EFV-based ART similar to those for other regimens

- ART choices at clinician's and patient's discretion, and so likely that ART groups not comparable with respect to presence of underlying psychiatric and CNS-related disorders

- Findings do not rule out possibility EFV leads to increased risk of suicide, but do provide re-assurance that the way EFV is used is not leading to increased suicide rates for those on the drug

Acknowledgements