Adverse events associated with efavirenz in adults and children: a systematic review of randomized trials

1. Background

Efavirenz is associated with adverse drug reactions, in particular neuropsychiatric events, but the relative frequency and clinical importance of these events is unclear. This systematic review aims to assess the frequency and severity of adverse events associated with EFV in adults and children

2. METHODS

2.1. Search strategy

A compound search strategy will be used. The below table illustrates the search strategy for Pubmed.

1	adverse [tiab] OR side effect* [tiab] OR unintended [tiab] OR unintentional [tiab] OR unwanted [tiab] OR unexpected [tiab] OR undesirable [tiab] OR drug safety [tiab] OR drug surveillance [tiab] OR harm [tiab] OR harms [tiab] OR harmful [tiab] OR product surveillance [tiab] OR adverse drug reaction [tiab] OR complication* [tiab] OR safety [tiab] OR safe [tiab]
2	Efavirenz OR EFV OR Sustiva
3	meta-analy* [tiab] OR (meta[tiab] AND analysis[tiab]) OR (clinical[tiab] AND trial[tiab]) OR (single[tiab] AND blind[tiab] AND procedure[tiab]) OR (double[tiab] AND blind[tiab] AND procedure[tiab]) OR random*[tiab] OR randomization[tiab]
4	#1 AND #2 AND #3

2.2. Databases

- MEDLINE via PubMed
- EMBASE
- Cochrane database of systematic reviews

2.3 Restrictions

No search restriction will be applied

2.2. Inclusion criteria

Types of studies

- Randomized and quasi-randomized trials comparing EFV and non-EFV based regimens as part of an identical backbone regimen

Types of participants

Inclusions:

- Treatment naïve HIV-positive adults and children
- Treatment naïve HIV negative adults and children
    - Results of these two groups will be reported seperately

Types of interventions

- Efavirenz as part of triple-combination antiretroviral therapy

Types of comparitor

- Non-efavirenz-based triple-combination antiretroviral therapy

Types of outcomes

Primary

- Adverse events resulting in treatment interruption or termination

Secondary

- Frequency of adverse drug events, by event
    - Where multiple subcategories are reported for a particular category of adverse drug event (eg for sleep disturbances) the most frequent event was used to calculate the overall frequency of events for that category.
- Mortality due to adverse events
- Regimen substitution due to adverse events

Where results are stratified by time point, the earliest time point will be reported

2.3. Exclusion criteria

- Studies with non-identical background regimens
- Studies reporting outcomes for <28 days exposure
- Studies that excluded patients at risk of CNS events
- Switch studies

Heterogeneity

If appropriate and feasible, meta-regression and/or subgroup analyses will be undertaken to determine the potential influence of the following covariates on risk of adverse events:

- EFV dose
- Population characteristics
- Duration of exposure

ASSESSMENT OF METHODOLOGICAL QUALITY

Methodological quality will be assessed using Cochrane approach for randomized trials the GRADE framework.

DATA ANALYSIS

Prevalence estimates

Point estimates and 95% confidence intervals (95% CI) will be calculated for the frequency of occurrence of different types of adverse events. The variance of the raw proportions will be stabilised using a Freeman-Tukey type arcsine square-root transformation and estimates pooled using a DerSimonian-Laird random effects model. The odds of discontinuation will be compared between efavirenz and non-efavirenz regimens using odds ratio (ORs) and 95% CIs will be calculated and data pooled using the DerSimonian-Laird random effects method.

Statistical software

Analyses will be conducted using Stata (version 12, www.stata.com).

Table: characteristics of included studies

Study	Year	Setting	Duration of follow up	Comparator	Backbone regimen	Total number of patients included in analysis	
						Efavirenz	Comparitor
Nunez	2002	Spain	48 weeks	NVP	D4T+ddI	31	36
Fischl	2003	USA and Italy	48 weeks	NVP	D4T+ddI	173	176
Maggiolo	2003	Italy	52 weeks	NFV	AZT+3TC	29	18
Van Leth	2004	Multiple	48 weeks	NVP	D4T+3TC	381	586
Squires	2004	Multiple	48 weeks	ATV	AZT+3TC	401	404
Gaytan	2004	Mexico	48 weeks	NVP	AZT+3TC	30	28
Gallant	2005	USA	48 weeks	TDF	ABC+3TC	169	171
Clifford	2005	Multiple	24 weeks	ABC	AZT+3TC	200	103
Bartlett	2006	Multiple	96 weeks	APV/r or d4T	ABC+3TC	97	98
INITIO	2006	Multiple	144 weeks	NFV	DDI+d4T	297	311
Markowitz	2007	Multiple	48 weeks	RAL	TDF+3TC	38	160
Tashima	2008	USA + Europe	168 weeks	IND	AZT+3TC	422	415
Mallolas	2008	Spain	36 weeks	LPV/r	ABC+3TC +AZT	104	105
Van den Berg Wolf	2008	USA	65 months	NVP	NRTIs + PIs (various)	111	117
Riddler	2008	USA + South Africa	96 weeks	LPV/r	3TC+AZT or d4T or TDF	250	253
Manosuthi	2009	Thailand	48 weeks	NVP	D4t+3TC	71	71
Lennox	2009	Multiple	96 weeks	RAL	TDF+FTC	282	281
Echeverra	2009	Spain + Italy	48 weeks	LPV/r	ABC+3TC	63	63
Gutierrez-Valencia,	2009	Spain	24 weeks	EFV stepped dose	TDF+FTC (>65%)	50	58
Pozniak	2010	Multiple	48+96 weeks	RIL	AZT+3TC TDF+FTC	89	279
Cooper	2010	Multiple	48 weeks	MRV	AZT+3TC	361	360
Puls	2010	Multiple	48 weeks	LPV/r AZT+ABC (not included in analysis)	TDF+FTC	114	105
Phidisa II	2010	South Africa	96 weeks	LPV/r	D4T+3TC AZT+DDI	888	883
Wester	2010	Botswana	156 weeks	NVP	2 NRTI	325	325
Sierra-Madero	2010	Mexico	48 weeks	LPV/r	AZT+3TC	95	94
Swaminathan	2011	India	24 weeks	NVP	Ddi+3TC	59	57
Nelson	2011	Multiple	12 weeks	ETV	2 NRTIs	78	79
Daar	2011	Multiple	144 weeks	ATV	ABC+3TC TDF+FTC	461	462 464
Cohen	2011	Multiple	48 weeks	EVG/COBI	TDF+FTC	23	48
Honda	2011	Japan	96 weeks	ATV/r	ABC+3TC	36	35
Cohen	2011	Multiple	96 weeks	RIL	2 NRTIs	338	340
Molina	2011	Multiple	96 weeks	RIL	TDF+FTC	344	346
Van Lurzen	2012	Multiple	48 weeks	DTG	ABC+3TC TDF+FTC	50	155
Sax	2012	USA	48 weeks	EVG/COBI	TDF+FTC	352	348

Bonnet	2013	Mozambique	48 weeks	NVP	3TC+d4T	288	285
Kumar	2013	USA	96 weeks	FPV/r	ABC+3TC	50	51
Andersson	2013	Norway and Sweden	144 weeks	ATV/r LPV/r	2 NRTIs	77	81 81
Walmsley	2013	Multiple	48 weeks	DTG	ABC+3TC TDF+FTC	419	414
Sinha	2013	India	96 weeks	NVP	AZT+3TC	68	67
Cohen	2014	Multiple	48 weeks	RIL	TDF+FTC	392	394
ENCORE	2014	Multiple	48 weeks	EFV 400	TDF+FTC	309	321
Grinszstejn	2014	Brazil and France	48 weeks	Raltegravir	TDF+FTC	51	103