Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis

Zara Shubber,[1] Alexandra Calmy,[2,3] Isabelle Andrieux-Meyer,[3] Marco Vitoria,[4] Francoise Renaud-Thery,[4] Sally Hargreaves,[5] Edward J Mills,[6] Nathan Ford.[3]

1. Department of Epidemiology and Biostatics, Faculty of Medicine, Imperial College, London, UK.
2. HIV/AIDS Unit, Infectious Disease Service, Geneva University Hospital, Geneva. Switzerland.
3. Médecins Sans Frontières, 78 rue de Lausanne, 1211 Geneva, Switzerland
4. Department of HIV/AIDS, World Health Organization, Geneva, Switzerland
5. The International Health Unit, Department of Infectious Diseases and Immunity, Hammersmith Hospital, Imperial College London, London, United Kingdom
6. Faculty of Health Sciences, University of Ottawa, Ottawa, Canada

Correspondence: Dr Nathan Ford, Médecins Sans Frontières 78 rue de Lausanne, 1211 Geneva, Switzerland. Email: nathan.ford@msf.org

GRADE TABLES

GRADE table - Adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nevirapine	Efavirenz	Relative (95% CI)	Absolute		
Treatment discontinuation												
18	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[3]	no serious indirectness	no serious imprecision	None	613/11221	315/6291	OR 2.18 (1.86 to 2.56)	53 more per 1000 (from 39 more to 69 more)	⊕⊕⊕O MODERATE	CRITICAL
Hepatotoxicity - overall (assessed with: symptom and laboratory monitoring)												
23	randomised trials and cohort studies	no serious risk of bias[1,2]	very serious[4]	no serious indirectness	no serious imprecision	none	535/11481	256/4706	OR 2.51 (2.04 to 3.1)	72 more per 1000 (from 51 more to 97 more)	⊕⊕OO LOW	IMPORTANT
Hepatotoxicity - severe (assessed with: symptom and laboratory monitoring)												
16	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[5]	no serious indirectness	no serious imprecision	none	249/9202	97/9221	OR 3.25 (2.54 to 4.17)	23 more per 1000 (from 16 more to 32 more)	⊕⊕⊕O MODERATE	CRITICAL
Skin - any (assessed with: symptom and laboratory monitoring)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nevirapine	Efavirenz	Relative (95% CI)	Absolute		
19	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[6]	no serious indirectness	no serious imprecision	none	707/10386	177/3886	OR 1.80 (1.51 to 2.17)	32 more per 1000 (from 19 more to 46 more)	⊕⊕⊕O MODERATE	IMPORTANT
Skin - severe (assessed with: symptom and laboratory monitoring)												
15	randomised trials and cohort studies	no serious risk of bias[1,2]	very serious[7]	no serious indirectness	no serious imprecision	none	217/10574	38/2714	OR 3.68 (2.50 to 5.39)	30 more per 1000 (from 16 more to 47 more)	⊕⊕OO LOW	CRITICAL
Severe hypersensitivity reaction (assessed with: symptom and laboratory monitoring)												
9	randomised trials and cohort studies	no serious risk of bias[1,2]	no serious inconsistency[8]	no serious indirectness	no serious imprecision	none	272/8340	72/2220	OR 2.18 (1.63 to 2.90)	36 more per 1000 (from 19 more to 56 more)	⊕⊕⊕O MODERATE	CRITICAL
CNS - overall (assessed with: symptom monitoring)												
13	randomised trials and cohort studies	no serious risk of bias[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	285/6177	404/2269	OR 0.31 (0.26 to 0.38)	115 fewer per 1000 (from 102 fewer to 125 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
CNS - severe (assessed with: symptom monitoring)												
11	randomised trials and cohort studies	no serious risk of bias[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/5853	62/1619	OR 0.29 (0.18 to 0.46)	27 fewer per 1000 (from 20 fewer to 31 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Neurology (assessed with: symptom monitoring)												
10	randomised trials and cohort studies	no serious risk of bias[1,2]	serious	no serious indirectness	serious[9]	none	196/5663	84/1592	OR 0.88 (0.66 to 1.17)	6 fewer per 1000 (from 17 fewer to 8 more)	⊕⊕OO LOW	IMPORTANT
Lipid changes (assessed with: symptom and laboratory monitoring)												
7	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[10]	serious[11]	serious[12]	none	105/5715	48/1693	OR 0.85 (0.59 to 1.23)	4 fewer per 1000 (from 11 fewer to 6 more)	⊕OOO VERY LOW	IMPORTANT

[1] Only 1 RCT reported allocation concealment
[2] Baseline prognostic factors balanced; non-differential loss to follow up.
[3] 4 studies reported odds ratios in the opposite direction to the pooled estimate, but only 1 of these was statistically significant. However, a further 5 studies reported odds ratios with confidence intervals consistent with either an increase or a decrease in the risk of adverse events, and several studies had non-overlapping confidence intervals.
[4] 7 of 23 studies reported odds ratios in the opposite direction to the pooled estimate; however, none of these were statistically significant. A further 3 studies reported odds ratios with confidence intervals consistent with either an increase or a decrease in the risk of adverse events.
[5] 4 of 16 studies reported odds ratios in the other direction to the pooled estimate; however, none of these were statistically significant.
[6] 1 study (138 patients) reported increased skin toxicity associated with EFV use; however, 8 studies reported odds ratios with confidence intervals consistent with either an increase or

a decrease in the risk of adverse events.
[7] 3 studies reported odds ratios in the other direction to the pooled estimate; only one of these was statistically significant. However, a further 6 studies included odds ratios for which the confidence intervals were consistent with either an increase or a decrease in the risk of adverse events.
[8] 1 study suggested a greater tendency towards HSR with EFV, but this was based on a single event. All other studies indicated either a statistically significant association or a strong tendency towards a statistically significant association between NVP use and a greater likelihood of severe hypersensitivity reaction.
[9] Rated down because lower bound is consistent with a 44% reduction in neurological complications.
[10] Non-overlapping confidence intervals for several studies.
[11] Different markers of lipid abnormalities were used by different studies.
[12] Result consistent with a 41% decrease or a 23% increase in risk of adverse events.

GRADE table– Children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nevirapine	Efavirenz	Relative (95% CI)	Absolute		
Hepatotoxicity (assessed with: Laboratory)												
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/393 (3.1%)	4/260 (1.5%)	not pooled	not pooled	⊕OOO VERY LOW	CRITICAL
								0%		not pooled		
Skin toxicity												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	24/262 (9.2%)	10/234 (4.2%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT
								0%		not pooled		
CNS												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/171 (7.6%)	25/177 (14.1%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT
								0%		not pooled		
Lipid abnormalities												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/171 (6.4%)	0/177 (0%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT
Discontinuation												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/259 (3.9%)	17/3031 (0.6%)	not pooled	not pooled	⊕⊕OO LOW	CRITICAL
								0%		not pooled		

[1] Confidence intervals around pooled estimate consistent with appreciable harm or benefit
[2] Data only available from 1 study