AIDS
Issue: Volume 27(9), 1 June 2013, p 1403-1412
Copyright: © 2013 Lippincott Williams & Wilkins, Inc.
Publication Type: [CLINICAL SCIENCE]
DOI: 10.1097/QAD.0b013e32835f1db0
ISSN: 0269-9370
Accession: 00002030-201306010-00006
Keywords: adverse events, central nervous system toxicity, drug substitution, efavirenz, hepatotoxicity, hypersensitivity, nevirapine, rash, Stevens-Johnson syndrome

Hide Cover

[CLINICAL SCIENCE]

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

Shubber, Zara[a]; Calmy, Alexandra[b,c]; Andrieux-Meyer, Isabelle[c]; Vitoria, Marco[d]; Renaud-Théry, Françoise[d]; Shaffer, Nathan[d]; Hargreaves, Sally[e]; Mills, Edward J.[f]; Ford, Nathan[c]

Author Information

[a]Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College, London, UK

[b]HIV/AIDS Unit, Infectious Disease Service, Geneva University Hospital

[c]Médecins Sans Frontières, Geneva

[d]Department of HIV/AIDS, World Health Organization, Geneva, Switzerland

[e]The International Health Unit, Department of Infectious Diseases and Immunity, Hammersmith Hospital, Imperial College London, London, UK

[f]Faculty of Health Sciences, University of Ottawa, Ottawa, Canada.

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

Received 9 October, 2012
Revised 10 January, 2013
Accepted 17 January, 2013

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website (http://www.AIDSonline.com).

Abstract

Introduction: Since 2002, the WHO has recommended either nevirapine (NVP) or efavirenz (EFV) as part of first-line antiretroviral therapy. These two drugs are known to have differing toxicity profiles, but the risk of these toxicities overall is not well established.

Methods: We systematically reviewed adverse events among treatment-naive HIV-positive adults and children receiving either NVP or EFV as part of first-line antiretroviral therapy. The primary outcome was drug discontinuation as a result of any adverse event; specific toxicities were evaluated as secondary outcomes. Point estimates and 95% confidence intervals (95% CIs) were calculated and proportions and odds ratios (ORs) pooled using fixed-effects meta-analysis.

Results: We reviewed data on 26 446 adults and 3975 children from eight randomized trials and 26 prospective cohorts. Overall, adults on NVP were more than two times more likely to discontinue treatment due to any adverse event compared to patients on EFV (OR 2.2, 95% CI 1.9-2.6). Severe hepatotoxicity (OR 3.3, 95% CI 2.5-4.2), severe skin toxicity (OR 3.9, 95% CI 2.5-5.4), and severe hypersensitivity reactions (OR 2.4, 95% CI 1.9-2.9) were more likely to occur among patients on NVP. Patients receiving EFV were more likely to experience severe central nervous system events (OR 3.4, 95% CI 2.1-5.4). Similar associations were seen in children.

Discussion: Compared to NVP, EFV is associated with a lower frequency of severe adverse events, in particular treatment discontinuations. This finding supports a move toward EFV-based therapy as the preferred first-line treatment regimen for HIV treatment within a public health approach.

Introduction

Since 2002, the WHO has recommended either nevirapine (NVP) or efavirenz (EFV) as part of first-line antiretroviral therapy [1]. The current set of WHO treatment guidelines, published in 2010, state that these two drugs have comparable clinical efficacy but differing toxicity profiles. A higher incidence of rash, Stevens-Johnson syndrome, and hepatotoxicity has been associated with NVP compared to EFV [2], whereas EFV has been associated with a greater incidence of central nervous system (CNS) symptoms [3]. Furthermore, there have been concerns that EFV may be teratogenic [4].

More recent data, however, suggest that EFV may have superior clinical efficacy and decreased toxicity [5,6]. Moreover, recent systematic reviews have not found any evidence of increased risk of teratogenicity associated with EFV [7,8], supporting a move toward using EFV irrespective of pregnancy status [9,10]. To date, however, no

systematic evaluation of the differences in risks of adverse events between these two drugs has been carried out. In order to better inform future WHO and country treatment guidelines, we conducted a systematic review and meta-analysis of adverse events associated with NVP compared to EFV-based first-line antiretroviral therapy among treatment-naive HIV-positive adults and children.

Methods

We conducted this systematic review and meta-analysis according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group [11].

Eligibility criteria

We included randomized trials and prospective comparative cohorts that reported adverse events among treatment-naive HIV-positive patients on NVP or EFV-based first-line antiretroviral therapy according to a predefined protocol. Only studies that reported adverse events disaggregated by drug and in which at least 10 patients received each drug were included. Studies in which there was no clear denominator were excluded. We also excluded studies that only included patients with specific comorbidities that may influence drug outcomes such as hepatitis coinfection or liver transplant cohorts. No geographical, age, or language restriction was applied to the inclusion criteria.

Search strategy and study selection

We developed a sensitive search strategy that combined terms for adverse drug events [12] and NVP or EFV.

Initial searches were developed (N.F.) for the following databases (from inception to 01 July 2012): MEDLINE via PubMed, EMBASE, LILACS, Web of Science, Current Controlled Trials (www.controlled-trials.com), and the Cochrane Central Register of Controlled Trials. The MEDLINE search was subsequently updated to 01 October 2012. We also searched the searchable websites of all International AIDS Society conferences from July 2009 to July 2012 to identify recently completed studies that had not yet been published as full-text articles. Bibliographies of review articles were also screened. One of us (N.F.) did a preliminary search scanning all titles for eligibility according to predefined inclusion criteria. The full abstracts of potentially eligible studies were then reviewed by two reviewers (N.F., Z.S.) who worked independently to select potentially relevant full-text articles. Once all relevant full-text articles were reviewed, final agreement on study inclusions was determined through consensus (A.C., I.A.M., N.F., Z.S.).

Data extraction

We conducted data extraction independently, in duplicate, using a standardized data extraction form (N.F., S.H., I.A.M., Z.S.). The primary outcome was drug discontinuation as a result of any adverse event due to NVP or EFV; secondary outcomes were hepatotoxicity, skin rash, hypersensitivity reaction, CNS toxicity, other neurological toxicities, lipid changes, and toxicity-related mortality. The following definitions of outcomes were used in our analyses: drug discontinuation, any adverse event that resulted in a drug substitution or termination of treatment; hepatotoxicity, any instance of liver toxicity; skin toxicity, any instance of rash or adverse cutaneous reaction; hypersensitivity, any instance of severe hepatic or severe skin toxicity; CNS toxicity, any instance of adverse CNS sign or symptom (including neuropsychiatric disorders); neurology, any instance of adverse peripheral nervous system sign or symptom. Hepatic and skin events were categorized as either mild/moderate (grade 1 or 2) or severe (grade 3 or 4, or any cutaneous or hepatic event resulting in discontinuation of treatment) as defined by the studies. CNS events were considered severe if they resulted in drug discontinuation or death. Lipid-associated adverse events were classified as mild/moderate or severe according to study definitions. Where study definitions were lacking, and wherever possible, the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) was applied [13]. The overall occurrence of adverse events was calculated by summing up the mild/moderate and severe events; for studies that only reported severe adverse events, this figure was used for the overall estimate.

Data on study characteristics, the monitoring strategies implemented by the studies for the diagnosis and reporting of adverse drug events, and relevant indicators of potential risk of bias were also extracted. We used the GRADE system to assess the overall quality of the evidence [14].

Data analysis

Point estimates and 95% confidence intervals (95% CIs) were calculated for the proportion of patients experiencing each outcome. The variance of the raw proportions was stabilized using a Freeman-Tukey-type arcsine square-root transformation [15]. We calculated the odds ratios (ORs), risk differences, and corresponding 95% CIs for each outcome. In the event of zero outcome in one arm, we used the Haldane method and added 0.5 to each arm [16]. Data were pooled using a fixed-effects method, whereby the weight assigned to the estimated treatment effect for a given study is proportional to the amount of information provided by that study [17]. Because adverse drug reactions are generally rare events, and because no important differences in the reporting of these events have been observed between randomized trials and observational studies [18], we pooled together data from both clinical trials and prospective cohorts.

Heterogeneity was assessed using the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than due to chance [19]. The following predefined subgroups were used to

explore heterogeneity within our primary outcome of treatment discontinuation as a result of any adverse drug event: study design, the proportion of female patients within the study (<50 versus >=50%), the proportion of patients with a high CD4 cell count (defined as <250 versus >=250 cells/μl), the proportion of patients coinfected with tuberculosis (TB) or hepatitis B or C (<20 versus >=20%), the use of intensive monitoring within the first 3 months of treatment (defined as monthly monitoring versus less frequent monitoring), geographical region (as defined by WHO region), and level of economic development of the study setting (low or lower-middle income country versus middle or high-income country, as defined by the World Bank [20]).

All analyses were conducted using Stata version 12.0 (StataCorp. LP, College Station, Texas, USA) and GRADE Pro (www.gradeworkinggroup.org).

Results

Characteristics of included studies

Our initial search identified 2139 titles, of which 34 studies reporting data on 26 446 adults and 3975 children (age <15 years) met our inclusion criteria and were taken through for full review (Fig. 1). These included 30 studies reporting data for adults [2,3,21–48], and four studies reporting data for children [49–52]. The studies reporting outcomes in adults consisted of eight randomized trials [2,27,35,38,41,45–47], and 22 prospective cohort studies; all four studies involving children were prospective cohorts. One conference abstract included updated data for drug discontinuations from a cohort that had previously published adverse event data [53]. The sample size of the included studies ranged from 54 patients [32] to 3481 patients [39] and over half of the adult studies (19 studies) were conducted in low and low-middle income countries. All four studies reporting outcomes in children were cohort studies carried out in low-middle income countries (India [49], South Africa [52], Uganda [50], and Uzbekistan [51]). Study characteristics are summarized in Table 1. The type and frequency of adverse drug event monitoring was inconsistently reported and differed between the studies. Most studies, however, reported doing routine laboratory assessments of both renal and liver functions (Supplementary Table S1, http://links.lww.com/QAD/A309). Study duration ranged from 6 months to 9 years.

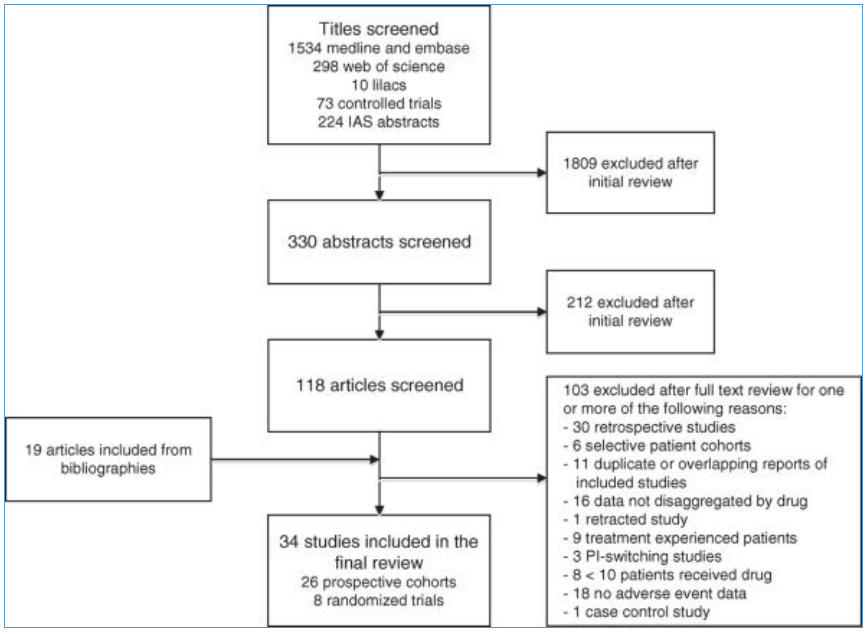

Fig. 1. Flow diagram of study selection process.

Study	Country	Sample size	Study duration	Design	Age (years)	% Female	Comorbidities	Viral load (copies/ml)	CD4 (cells/μl)	Backbone
Boulle et al. [21]	South Africa	3970	6 months	Prospective cohort	32	69	TB: 32%	5.1	94	2 NRTI
Bruck et al. [22]	Germany	296	88 weeks	Prospective cohort	38	20	HCV: 10.1%; HBV: 4.1%	2.8	354	NRTI +/- PI
Castelnuovo et al. [23]	Uganda	559	33 months	Prospective cohort	38	70		5.4	98	NVP: d4T+3TC; EFV: ZDV+3TC; TDF+FTC
Elzi et al. [24]	Switzerland	611	1 year	Prospective cohort	NR	NR	NR	NR	NR	NVP: TDF+FTC; EFV: TDF+FTC; ZDV+3TC, ABC+3TC
Ferradini et al. [25]	Malawi	1308	8.3 months (median)	Prospective cohort	35	64	NR	NR	132	NVP: D4T+3TC; ZDV+3TC; EFV: D4T+3TC; ZDV+3TC
Forna et al. [26]	Uganda	1029	20 months 11.2 months (median)	Prospective cohort	38	74	13.1% preexisting neuropathy	2.1	126	D4t+3TC
Gaytan et al. [27]	Mexico	58	48 weeks	RCT	34	19	NR	5.1	143	ZDV+3TC
George et al. [28]	India	142	6 months	Prospective cohort	38	36	NR	NR	NR	NVP: ZDV+3TC; d4T+3TC; EFV: d4T+3TC
Haddow et al. [29]	England	268	103 weeks (median)	Prospective cohort	37	49	NR	NR	NR	ZDV+3TC; ZDV+ddI; ABC+NRTI
Ibadova and Atakhodjieva [31]	Uzbekistan	160	2 years	Prospective cohort	Children	30	NR	NR	NR	NR
Jena et al. [30]	India	100	24 weeks	Prospective cohort	38	33	NR	NR	114	d4T+3TC; ZDV+3TC
Kampire et al. [32]	South Africa	3290	3 years	Prospective cohort	Children (46 months)	48	NR	NR	NR	NR
Kityesuhula et al. [33]	Uganda	202	14 weeks	Prospective cohort	36	67	HBV 3.5%, HCV 3%, TB 4%	NR	107	NVP: d4T +3TC; EFV: d4T +3TC or ZDV+3TC
Khalili et al. [32]	Iran	150	2 years 6 months (minimum)	Prospective cohort	36	18	26% HCV, 15% HBV, 14%TB, 8% hemophilia	NR	NR	NVP: ZDV+3TC; EFV: d4T +3TC or ZDV+3TC
Kumarasamy et al. [33]	India	3154	1 year	Prospective cohort	35 years	23		NR	105 at initiation of HAART (130 at baseline)	d4T +3TC; ZDV+3TC
Kumarasamy et al. [49]	India	147	>18 months	Prospective cohort	Children (6.3)	39	TB: 13.4%	NR	290	NR
Manfredi and Calza* [34]	Italy	742	>12 months (duration of study)	Prospective cohort	NR	NR	HCV: 14%	4.3	337	NR
Mankhatitham et al. [35]	Thailand	134	24 weeks	RCT	36.8	33	100% TB, 5.2% HBV, 23.9% HCV	5.75	69	d4T +3TC
Messou et al. [36]	Ivory Coast	1900		Prospective cohort	36	73	TB: 9%	NR	125	NVP+d4T+3TC; EFV+d4T+ 3TC; ZDV+3TC
Modayil et al.[b] [37]	India	400	9 months	Prospective cohort	98% aged 16–59 years	44	TB: 39.7%	NR	73% <200	d4T+3TC; ZDV+3TC
Nunez et al. [38]	Spain	67	48 weeks	RCT	35	22	HCV: 40%	2.2	374	d4T+ddI
Obiako et al.[c] [39]	Nigeria	3481	9 years (total duration of study)	Prospective cohort	39.2	68	NR	NR	NR	d4T +3TC; ZDV+3TC; NRTI+PI (4.4%)

Table 1-a Study characteristics.

Assessment of methodological quality

Patel et al. [3]	India	1111	24 months	Prospective	36	23	NR	NR	108	d4T+3TC; ZDV+3TC
Ritchie et al. [40]	USA	423	5 years (duration of study)	Prospective	NR	NR	NR	NR	NR	NR
Sanne et al. [41]	South Africa	NR	NR	RCT	NR	NR	NR	NR	NR	3TC/FTC + d4T
Sivadasan et al. [42]	India	230	48 weeks	Prospective cohort	37	25	NR	NR	112.5	ZDV/d4T + 3TC
Sreenivasan and Dasegowda [43]	India	100	48 weeks	Prospective cohort	>18 years	NR	NR	NR	NR	ZDV/d4T + 3TC
Sulkowski et al. [44]	USA	568	NVP: 314 days; EFV: 259 days	Prospective cohort	37	71	43% HCV	4.6	160	NR
Swaminathan et al. [45]	India	116	24 weeks	RCT	36	19	69% TB	3.2	84	ddI+3TC
Tukeiser et al. [30]	Uganda	378	170 weeks (median)	Prospective cohort	Children (7)	48	TB: 10.3%	NR	10.4%	NVP: ZDV/d4T+3TC; EFV: ZDV/d4T+3TC
van den Berg-Wolf et al. [46]	USA	228	5 years (median)	RCT	37	23	HCV: 18%	5.0	186	NRTI +/- PI
Van Leth et al. [2]	Australia, Europe, South Africa, Thailand	1007[e]	48 weeks	RCT	34	63	HCV: 10%	4.7	184	d4T+3TC
Wester et al. [47]	Botswana	650	2 years	RCT	33	69	TB: 9.1%	1.95	199	Various NRTI
Zhou et al.[a] [48]	Asia	1548[f]	24 weeks	Prospective cohort	36	28		3.9	291	ZDV+3TC +EFV; d4T+3TC + NVP

3TC, lamivudine; ABC, abacavir; ddI, didanosine; EFV, efavirenz; NR, not reported; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RCT, randomized controlled trial; TB, tuberculosis; TDF, tenofovir; ZDV, zidovudine.
[a]Naive patients only included in analysis.
[b]Intensive monitoring group only (treatment-naive).
[c]Includes some patients who were treatment-experienced.
[d]Does not include patients who received both NVP+EFV.
[e]Additional data from an updated report from the same cohort [53] was used for some analyses.
[f]29% previously treatment with other regimens.

Table 1-b Study characteristics.

Risk of bias was considered overall to be low-to-moderate (Table S2, http://links.lww.com/QAD/A309). The methods used for reporting adverse events were considered to be at low of risk of bias for most studies (25), and for those studies in which loss-to-follow-up could be ascertained, it was less than 20% for the majority of studies (23 out of 25 studies). Most studies (26) did not report differential follow-up by drug. Similarly, the majority of the studies (22 studies) did not apply a minimal follow-up time to their eligibility criteria, which if applied, can potentially result in a biased exclusion of early treatment discontinuations. However, among the randomized controlled trials (RCTs), only one study stated that allocation concealment was performed [2]. Most studies did not report clear inclusion/exclusion criteria. Three studies excluded women with higher CD4 cell counts (>250 cells/μl) and five studies excluded men with higher CD4 cell counts (>250 cells/μl). All but one study used a lead-in dose for NVP, among studies in which this was reported.

Our GRADE assessment of the adult studies found that the evidence base for most outcomes of critical importance (defined as discontinuations or severe adverse events) was determined to be of moderate quality, except for severe skin toxicity, for which the evidence base was determined to be of low quality (Supplementary Table S3, http://links.lww.com/QAD/A309). For children, the evidence base was determined to be of very low quality. This was mainly due to the limited number of studies, each of which reported different outcomes, resulting in imprecision of the estimated frequency for specific adverse drug outcomes (Supplementary Table S4, http://links.lww.com/QAD/A309).

Frequency and risk of adverse events among adults

The frequency of occurrence of all adverse events among adults receiving NVP and EFV-based regimens is summarized in Fig. 2. ORs and the risk differences for these events are provided in Fig. 3 and Supplementary Table S3, http://links.lww.com/QAD/A309, respectively.

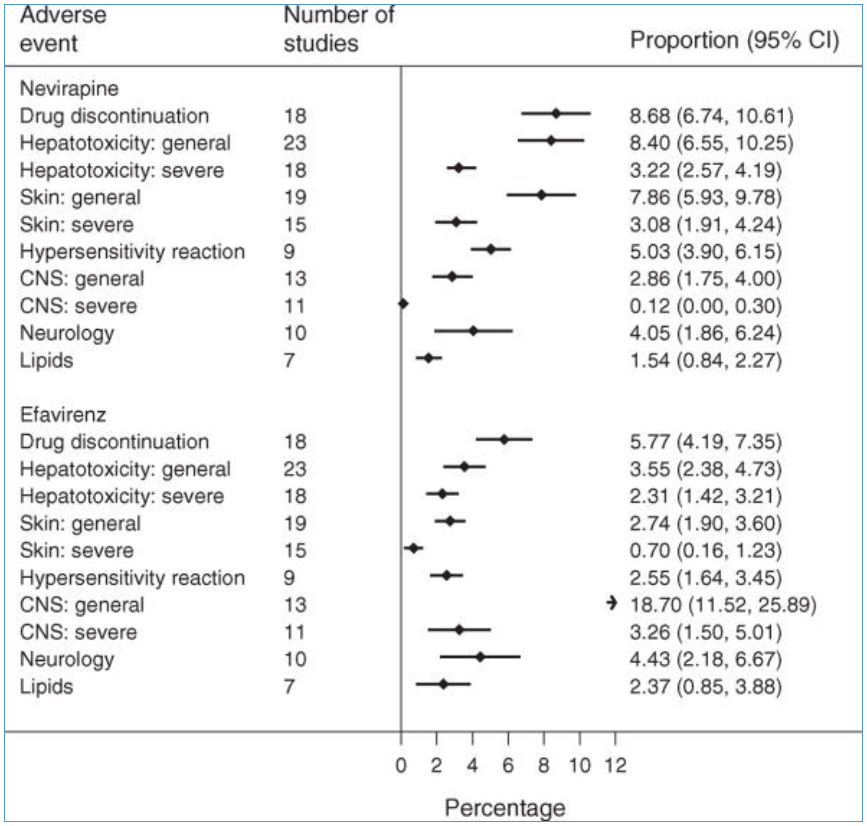

Fig. 2. Pooled proportion of adverse events by drug.

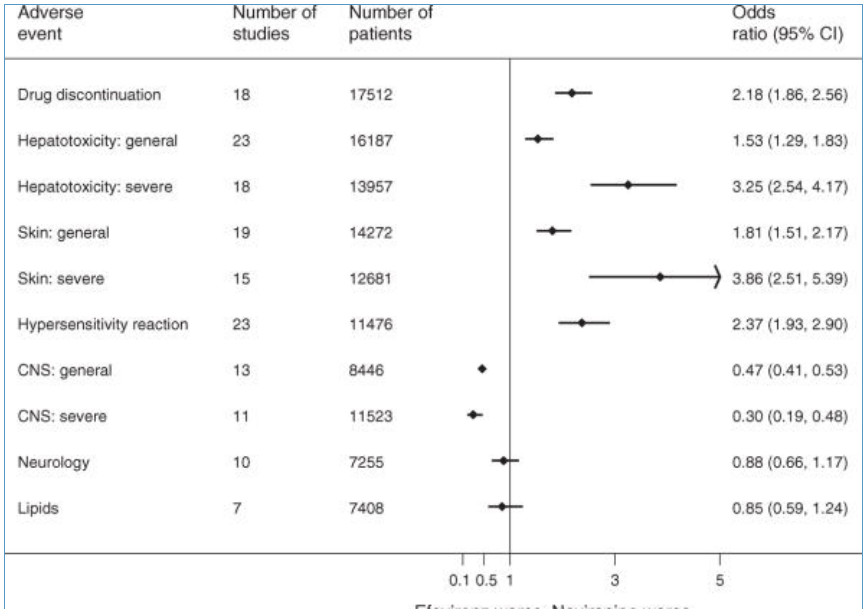

Fig. 3. Pooled odds ratios of adverse events by drug.

Primary outcome: drug discontinuation

Drug discontinuations due to adverse events were reported by 18 studies (17 512 patients). For patients on NVP, the proportion of patients discontinuing treatment due to any adverse event ranged from 1.3% (95% CI 0.9-1.7) [39] to 30.5% (95% CI 21.3-40.5%) [54], with an overall pooled proportion of 8.7% (95% CI 6.7-10.6%). For patients receiving EFV, this proportion ranged from 0.18% (95% CI 0.16-1.5%) to 22.6% (95% CI 16.7-29.2%), with a pooled proportion of 5.8% (95% CI 4.2-7.4%). Patients on NVP were more than two times more likely to discontinue treatment due to any adverse event compared to patients on EFV (OR 2.2, 95% CI 1.9-2.6, I^2 70.5%).

There was a tendency toward a higher frequency of discontinuations among patients on NVP with a higher CD4 cell count (16.9% at CD4 >=250 cells/μl versus 7.2% at CD4<250 cells/μl, P = 0.08); this association was not seen for EFV. A higher frequency of treatment discontinuations was also reported by studies with a follow-up time of greater than 1 year compared to studies with a follow-up time of less than 1 year (P <0.001), and for studies carried out in upper-income countries compared to lower-income countries (P = 0.02). All other subgroup findings were not statistically significant. No differences were found in the frequencies of treatment discontinuations reported by cohort studies and RCTs.

Secondary outcomes

Patients receiving NVP were more likely to experience any grade of hepatotoxicity (OR 1.5, 95% CI 1.3-1.8) or severe hepatotoxicity (OR 3.3, 95% CI 2.5-4.2) compared to patients on EFV. They were also more likely to experience any grade of skin toxicity (1.8, 95% CI 1.5-2.2), severe skin toxicity (OR 3.9, 95% CI 2.5-5.4), and severe hypersensitivity reactions (OR 2.4, 95% CI 1.9-2.9) compared to patients receiving EFV. Seven studies [2,26,32,33,39,42,45] reported 64 cases of Stevens-Johnson syndrome among 7391 patients exposed to NVP, giving a pooled proportion of 0.7% (95% CI 0.5-0.9%).

In contrast, patients receiving EFV were more likely to experience any CNS-related adverse event (OR 2.1, 95% CI 1.9-2.4) and severe CNS-related adverse events (OR 3.4, 95% CI 2.1-5.4). There were no differences between the two drugs in the occurrence of other neurological events (OR 0.9, 95% CI 0.6-1.2) and lipid-associated adverse events (OR 0.9, 95% CI 0.6-1.2). Deaths attributed to toxicity were rare (<1%) for both NVP (14 deaths among 5835 patients) and EFV (three deaths among 1380 patients).

Frequency and risk of adverse events among children

Four prospective cohort studies reported adverse drug outcomes in children. In the first study, from India [49], the frequency of rash was found to be higher for NVP (20%, 95% CI 13.1-30.0%) compared to EFV (14%, 95% CI 5.8-26.7%); differences in hepatotoxicity were not statistically significant. In the second study, from Uganda [50], 11 patients on NVP (6.4%, 95% CI 3.3-11.2) developed lipodystrophy resulting in antiretroviral drug substitution; no patients on EFV developed this adverse event. The occurrence of CNS-associated adverse events was lower among patients on NVP (7.6%, 95% CI 4.1-12.6%) compared to EFV (14.1%, 95% CI 9.4-20.1%); one patient on EFV changed treatment for this reason. The third study, a conference abstract from Uzbekistan [51], reported a greater frequency of rash among children receiving NVP (7.5%) compared to EFV (3.8%). The final study, from South Africa, found that children were seven times more likely to discontinue NVP-based first-line antiretroviral therapy compared to EFV-based therapy (OR 7.1, 95% CI 3.3-15.4) [52].

Discussion

Adverse drug events are an important concern in the provision of antiretroviral therapy. They can cause significant patient morbidity and are potentially fatal, are a common cause of drug discontinuations [55], and are associated with poorer patient adherence to treatment [56]. Poor adherence to treatment and regimen changes complicate patient management, decrease future treatment options, and may increase costs.

This systematic review supports prior findings of individual studies reporting a greater frequency of both liver and skin toxicities associated with NVP compared to EFV, and a greater frequency of CNS toxicity associated with EFV compared to NVP. Importantly, the number of deaths attributed to toxicity was rare for both drugs.

Drug discontinuation due to any adverse drug event was chosen as our primary outcome as a measure of the frequency of both clinically important and potentially life-threatening adverse drug events. We found that patients on NVP-based first-line ART were more than twice as likely to switch regimens due to any adverse drug event compared to patients on EFV-based therapy. Although CNS events were more frequent for EFV, these events infrequently led to a drug substitution.

We used a broad search strategy that allowed us to retrieve data for over 26 000 patients. A strength of such a sensitive search strategy is that a more precise estimate of both the frequencies and the risks of occurrence of a broad range of adverse events were obtained from a diversity of settings. There was moderate-to-high statistical heterogeneity across studies, and subgroup analyses highlighted some differences in outcomes reported by different studies. Higher income settings reported a higher frequency of treatment discontinuations compared to

low-income settings, which may be due to more intensive laboratory monitoring in higher income settings, more frequent switching in specific situations of suspected risk (e.g., high CD4 cell counts), and increased therapeutic options for drug substitutions. Drug discontinuations were also more common in studies with a longer duration of follow-up suggesting that not all clinically important adverse events occur early. Our exploration of potential sources of heterogeneity was limited by the inconsistent reporting by the studies. Higher toxicity-driven discontinuations appeared to be associated with higher CD4 cell counts, a finding that is consistent with other reports [57,58]. Other variables that may explain heterogeneity in adverse drug outcomes but which were not adequately reported by studies include baseline disease status (as defined by the CD4 cell count or viral load), or the contribution of other drugs in the regimen. Only a minority of studies reported the average time to occurrence of adverse event, but those that did report this found that adverse events generally occurred within the first 5 months. Finally, this review sought to compare adverse events between the two most commonly used nonnucleoside reverse transcriptase inhibitors. Because EFV has been contraindicated in pregnancy, our search strategy did not include pregnant women. As NVP toxicity remains a concern for pregnant women [59], this question has been reviewed separately [60]. Finally, we pooled data from RCTs and observational studies, both of which have limitations in the reporting of adverse events. Although adequately conducted RCTs provide stronger evidence of outcomes compared to cohort evaluations, observational studies are more likely to identify events that are rare in occurrence as well as events within populations that may not be represented in RCTs (for example, children, those with comorbidities, and the elderly).

Our review highlights several areas for future research. First, the diversity of monitoring strategies implemented among the studies for the diagnosis of adverse drug events (both the type and the frequency of monitoring) highlights the need for research to better rationalize toxicity monitoring. Second, a better ascertainment of the timing of clinically important adverse events would help better define monitoring requirements. Third, the exclusion of a large number of studies from this review due to a lack of or incomplete adverse drug event data is a missed opportunity. Finally, the scarcity of reports of adverse events among children underscores the need for more consistent reporting of adverse drug events in children.

NVP will likely continue to be an important drug for the management of HIV-infected individuals, and CNS-associated side-effects associated with EFV remain a concern, particularly for specific patient groups such as postnatal women and patients with psychiatric comorbidities. Nevertheless, the overall benefit in terms of reduced toxicity-driven drug substitution, better compatibility with TB drugs, and potentially superior efficacy of EFV compared to NVP, supports the move toward tenofovir, lamivudine or emtricitabine, and EFV as the preferred first-line regimen for scale up of ART.

Acknowledgements

The authors would like to thank Jonathan Ainsworth, Xavier Anglaret, Kathryn Chu, Mary-Anne Davies, Lewis Haddow, Robert Kalyesubula, Laetitia Kampiire, Nagalingeswaran Kumarasamy, and Roberto Manfredi for providing additional data. Finally, they thank Teri Roberts for assistance with data verification.

N.F., Z.S., I.A.M., and A.C. designed the review. N.F. and Z.S. undertook literature searches, extracted data from the studies, and contacted authors for data verifications. I.A.M. and S.H. undertook additional data extractions. N.F. and Z.S. performed the statistical analyses and wrote the first draft. All authors supported the interpretation of results, provided comments on subsequent drafts, and approved the final version.

This work was supported by funds from the WHO.

Conflicts of interest

There are no conflicts of interest.

References

1. Anon. Scaling up antiretroviral therapy in resource-limited settings. Guideline for a public health approach. 2002. Geneva; WHO, [Context Link]

2. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. **Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study**. Lancet 2004; 363:1253-1263. **Bibliographic Links** | [Context Link]

3. Patel AK, Pujari S, Patel K, Patel J, Shah N, Patel B, et al. **Nevirapine versus efavirenz based antiretroviral treatment in naive Indian patients: comparison of effectiveness in clinical cohort**. J Assoc Physicians India 2006; 54:915-918. **Bibliographic Links** | [Context Link]

4. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. **Myelomeningocele in a child with intrauterine exposure to efavirenz**. AIDS 2002; 16:299-300. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

5. Tang MW, Kanki PJ, Shafer RW. **A review of the virological efficacy of the 4 World Health Organization-recommended tenofovir-containing regimens for initial HIV therapy**. Clin Infect Dis 2012; 54:862-875. **Bibliographic Links** | [Context Link]

6. Amoroso A, Etienne-Mesubi M, Edozien A, Ojoo S, Sheneberger R, Obiefune M, et al. **Treatment outcomes of recommended first-line antiretroviral regimens in resource-limited clinics**. J Acquir Immune Defic Syndr 2012; 60:314-320. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

7. Ford N, Mofenson L, Kranzer K, Medu L, Frigati L, Mills EJ, et al. **Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts**. AIDS 2010; 24:1461-1470. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

8. Ford N, Calmy A, Mofenson L. **Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis**. AIDS 2011; 25:2301-2304. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

9. Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, et al. **British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012**. HIV Med 2012; 13 (Suppl 2):1-6. [Context Link]

10. WHO. *Use of efavirenz during pregnancy: a public health perspective*. Technical update on treatment optimization. 2012. Geneva; WHO, Available http://extranet.who.int/iris/bitstream/10665/70920/1/9789241503792_eng.pdf. [Context Link]

11. Moher D, Liberati A, Tetzlaff J, Altman DG. **The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement**. PLoS Med 2009; 6:6. [Context Link]

12. Golder S, Loke Y. **Search strategies to identify information on adverse effects: a systematic review**. J Med Libr Assoc 2009; 97:84-92. **Bibliographic Links** | [Context Link]

13. **Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health.**Table for Grading the Severity of Adult and Pediatric Adverse Events. 2004. Bethesda, Maryland: National Institutes of Health; [Context Link]

14. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. **GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**. BMJ 2008; 336:924-926. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

15. Freeman MF, Tukey JW. **Transformations related to the angular and the square root**. Ann Inst Stat Mathematics 1950; 21:607-611. [Context Link]

16. Sheehe PR. **Combination of log relative risk in retrospective studies of disease**. Am J Public Health Nations Health 1966; 56:1745-1750. **Bibliographic Links** | [Context Link]

17. Fleiss JL. **The statistical basis of meta-analysis**. Stat Methods Med Res 1993; 2:121-145. **Bibliographic Links** | [Context Link]

18. Golder S, Loke YK, Bland M. **Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview**. PLoS Med 2011; 8:e1001026. **Bibliographic Links** | [Context Link]

19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. **Measuring inconsistency in meta-analyses**. BMJ 2003; 327:557-560. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

20. Country and lending groups [Internet]. 2011. Washington: World Bank; Available from: http://data.worldbank.org/about/country-classifications/country-and-lending-groups. [Context Link]

21. Boulle A, Van Cutsem G, Cohen K, Hilderbrand K, Mathee S, Abrahams M, et al. **Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy**. JAMA 2008; 300:530-539. **Bibliographic Links** | [Context Link]

22. Bruck S, Witte S, Brust J, Schuster D, Mosthaf F, Procaccianti M, et al. **Hepatotoxicity in patients prescribed efavirenz or nevirapine**. Eur J Med Res 2008; 13:343-348. Bibliographic Links | [Context Link]

23. Castelnuovo B, Kiragga A, Kamya MR, Manabe Y. **Stavudine toxicity in women is the main reason for treatment change in a 3-year prospective cohort of adult patients started on first-line antiretroviral treatment in Uganda**. J Acquir Immune Defic Syndr 2011; 56:59-63. Ovid Full Text | Bibliographic Links | [Context Link]

24. Elzi L, Marzolini C, Furrer H, Ledergerber B, Cavassini M, Hirschel B, et al. **Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008**. Arch Intern Med 2010; 170:57-65. Bibliographic Links | [Context Link]

25. Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambo L, et al. **Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment**. Lancet 2006; 367:1335-1342. Bibliographic Links | [Context Link]

26. Forna F, Liechty CA, Solberg P, Asiimwe F, Were W, Mermin J, et al. **Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda**. J Acquir Immune Defic Syndr 2007; 44:456-462. Ovid Full Text | Bibliographic Links | [Context Link]

27. Gaytan JJA, de la Garza ERZ, Garcia MC, Chavez SBV. **Nevirapine or efavirenz in combination with nucleoside analogues in patients infected with HIV without previous treatment**. Med Int Mex 2004; 20:24-28. [Context Link]

28. George C, Yesoda A, Jayakumar B, Lal L. **A prospective study evaluating clinical outcomes and costs of three NNRTI-based HAART regimens in Kerala, India**. J Clin Pharm Ther 2009; 34:33-40. Bibliographic Links | [Context Link]

29. Haddow LJ, Wood CW, Ainsworth JG. **Discontinuation of nonnucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy due to nucleoside analogue reverse transcriptase inhibitor-related metabolic toxicity**. Int J STD AIDS 2007; 18:343-346. Bibliographic Links | [Context Link]

30. Jena A, Sachdeva RK, Sharma A, Wanchu A. **Adverse drug reactions to nonnucleoside reverse transcriptase inhibitor-based antiretroviral regimen: a 24-week prospective study**. J Int Assoc Physicians AIDS Care (Chic) 2009; 8:318-322. [Context Link]

31. Kalyesubula R, Kagimu M, Opio KC, Kiguba R, Semitala CF, Schlech WF, et al. **Hepatotoxicity from first line antiretroviral therapy: an experience from a resource limited setting**. Afr Health Sci 2011; 11:16-23. Bibliographic Links | [Context Link]

32. Khalili H, Dashti-Khavidaki S, Mohraz M, Etghani A, Almasi F. **Antiretroviral induced adverse drug reactions in Iranian human immunodeficiency virus positive patients**. Pharmacoepidemiol Drug Saf 2009; 18:848-857. Bibliographic Links | [Context Link]

33. Kumarasamy N, Venkatesh KK, Cecelia AJ, Devaleenal B, Lai AR, Saghayam S, et al. **Spectrum of adverse events after generic HAART in southern Indian HIV-infected patients**. AIDS Patient Care STDs 2008; 22:337-344. Ovid Full Text | Bibliographic Links | [Context Link]

34. Manfredi R, Calza L. **Nevirapine versus efavirenz in 742 patients: no link of liver toxicity with female sex, and a baseline CD4 cell count greater than 250 cells/microl**. AIDS 2006; 20:2233-2236. Ovid Full Text | Bibliographic Links | [Context Link]

35. Mankhatitham W, Lueangniyomkul A, Manosuthi W. **Hepatotoxicity in patients co-infected with tuberculosis and HIV-1 while receiving nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy and rifampicin-containing antituberculosis regimen**. Southeast Asian J Trop Med Public Health 2011; 42:651-658. Bibliographic Links | [Context Link]

36. Messou E, Anglaret X, Duvignac J, Konan-N'dri E, Komena E, Gnokoro J, et al. **Antiretroviral treatment changes in adults from Cote d'Ivoire: the roles of tuberculosis and pregnancy**. AIDS 2010; 24:93-99. Ovid Full Text | Bibliographic Links | [Context Link]

37. Modayil RR, Harugeri A, Parthasarathi G, Ramesh M, Prasad R, Naik V, et al. **Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART centre**

in India. Pharmacoepidemiol Drug Saf 2010; 19:247-255. **Bibliographic Links** | [Context Link]

38. Nunez M, Soriano V, Martin-Carbonero L, Barrios A, Barreiro P, Blanco F, et al. **SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals**. HIV Clin Trials 2002; 3:186-194. **Bibliographic Links** | [Context Link]

39. Obiako R, Muktar H, Garko S, Tobi-Ajayi E, Olayinka A, Iyanda M, et al. **Adverse reactions associated with antiretroviral regimens in adult patients of a university teaching hospital HIV program in Zaria, northern Nigeria: an observational cohort study**. J Antivir Antiretrovir 2012; 4:1. [Context Link]

40. Ritchie MD, Haas DW, Motsinger AA, Donahue JP, Erdem H, Raffanti S, et al. **Drug transporter and metabolizing enzyme gene variants and nonnucleoside reverse-transcriptase inhibitor hepatotoxicity**. Clin Infect Dis 2006; 43:779-782. **Bibliographic Links** | [Context Link]

41. Sanne I, Mommeja-Marin H, Hinkle J, Bartlett JA, Lederman MM, Maartens G, et al. **Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects**. J Infect Dis 2005; 191:825-829. **Bibliographic Links** | [Context Link]

42. Sivadasan A, Abraham OC, Rupali P, Pulimood SA, Rajan J, Rajkumar S, et al. **High rates of regimen change due to drug toxicity among a cohort of South Indian adults with HIV infection initiated on generic, first-line antiretroviral treatment**. J Assoc Physicians India 2009; 57:384-388. **Bibliographic Links** | [Context Link]

43. Sreenivasan S, Dasegowda V. **Adverse effects after HAART initiation in resource-limited settings: a prospective study from Mysore, India**. J Infect Dev Ctries 2010; 4:750-753. [Context Link]

44. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. **Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections**. Hepatology 2002; 35:182-189. **Bibliographic Links** | [Context Link]

45. Swaminathan S, Padmapriyadarsini C, Venkatesan P, Narendran G, Ramesh Kumar S, Iliayas S, et al. **Efficacy and safety of once-daily nevirapine- or efavirenz-based antiretroviral therapy in HIV-associated tuberculosis: a randomized clinical trial**. Clin Infect Dis 2011; 53:716-724. **Bibliographic Links** | [Context Link]

46. van den Berg-Wolf M, Hullsiek KH, Peng G, Kozal MJ, Novak RM, Chen L, et al. **Virologic, immunologic, clinical, safety, and resistance outcomes from a long-term comparison of efavirenz-based versus nevirapine-based antiretroviral regimens as initial therapy in HIV-1-infected persons**. HIV Clin Trials 2008; 9:324-336. [Context Link]

47. Wester CW, Thomas AM, Bussmann H, Moyo S, Makhema JM, Gaolathe T, et al. **Nonnucleoside reverse transcriptase inhibitor outcomes among combination antiretroviral therapy-treated adults in Botswana**. AIDS 2010; 24 (Suppl 1):S27-S36. [Context Link]

48. Zhou J, Phanupak P, Kiertiburanakul S, Ditangco R, Kamarulzaman A, Pujary S. **Highly active antiretroviral treatment containing efavirenz or nevirapine and related toxicity in the TREAT Asia HIV Observational Database**. J Acquir Immune Defic Syndr 2006; 43:501-503. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

49. Kumarasamy N, Venkatesh KK, Devaleenol B, Poongulali S, Mothi SN, Solomon S. **Safety, tolerability and effectiveness of generic HAART in HIV-infected children in South India**. J Trop Pediatr 2009; 55:155-159. **Bibliographic Links** | [Context Link]

50. Tukei VJ, Asiimwe A, Maganda A, Atugonza R, Sebuliba I, Bakeera-Kitaka S, et al. **Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda**. J Acquir Immune Defic Syndr 2012; 59:274-280. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

51. Ibadova G, Atakhodjieva K. **Evaluation of frequency of ARVT side effects in children of Uzbekistan.**AIDS 2010 - XVIII International AIDS Conference:Abstract CDB0233 [Context Link]

52. Kampiire L, Garone D, Giddy J, Rabie H, Wood R, Moultrie H, et al. **Substitutions to initial antiretroviral therapy in children in South Africa: the international epidemiological database to evaluate AIDS, Southern Africa (IeDEA-SA) Collaboration**. 2012. XVIV International AIDS Conference, Washington, Abstract TUPE092. [Context Link]

53. Lee L, Lim P, Fahey P, Yunihastuti E. **Predictors of nevirapine and efavirenz toxicity in HIV infected patients: updated analysis from the TREAT Asia HIV Observational Database (TAHOD)**. 6th IAS Conference on HIV

updated analysis from the TREAT Asia HIV Observational Database (TAHOD). 6th IAS Conference on HIV Pathogenesis and Treatment: Abstract no. CDB486. [Context Link]

54. Hartmann M, Witte S, Brust J, Schuster D, Mosthaf F, Procaccianti M, et al. **Comparison of efavirenz and nevirapine in HIV-infected patients (NEEF Cohort).** Int J STD AIDS 2005; 16:404-409. **Bibliographic Links** | [Context Link]

55. Elzi L, Erb S, Furrer H, Ledergerber B, Cavassini M, Hirschel B, et al. **Choice of initial combination antiretroviral therapy in individuals with HIV infection: determinants and outcomes.** Arch Intern Med 2012; 70:1-9. [Context Link]

56. Al-Dakkak I, Patel S, McCann E, Gadkari A, Prajapati G, Maiese EM. **The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis.**AIDS Care 2012. [Epub ahead of print] [Context Link]

57. Phanuphak N, Apornpong T, Teeratakulpisarn S, Chaithongwongwatthana S, Taweepolcharoen C, Mangclaviraj S, et al. **Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women.** HIV Med 2007; 8:357-366. **Bibliographic Links** | [Context Link]

58. Aaron E, Kempf MC, Criniti S, Tedaldi E, Gracely E, Warriner A, et al. **Adverse events in a cohort of HIV infected pregnant and nonpregnant women treated with nevirapine versus nonnevirapine antiretroviral medication.** PLoS One 2010; 5:e12617. **Bibliographic Links** | [Context Link]

59. Jamisse L, Balkus J, Hitti J, Gloyd S, Manuel R, Osman N, et al. **Antiretroviral-associated toxicity among HIV-1-seropositive pregnant women in Mozambique receiving nevirapine-based regimens.** J Acquir Immune Defic Syndr 2007; 44:371-376. **Ovid Full Text** | **Bibliographic Links** | [Context Link]

60. Ford N, Calmy A, Andrieux-Meyer I, Hargreaves S, Mills EJ, Shubber Z. **Adverse events associated with nevirapine use in pregnancy: a systematic review and meta-analysis.**AIDS 2013. [Epub ahead of print] [Context Link]

Keywords: adverse events; central nervous system toxicity; drug substitution; efavirenz; hepatotoxicity; hypersensitivity; nevirapine; rash; Stevens-Johnson syndrome

---

IMAGE GALLERY

Select All

Export Selected to PowerPoint

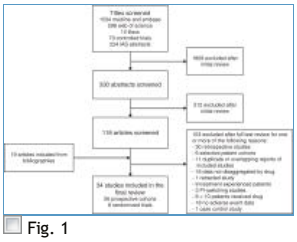

Fig. 1

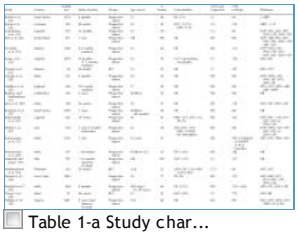

Table 1-a Study char...

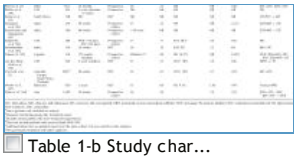

Table 1-b Study char...

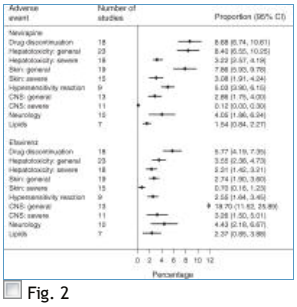

Fig. 2

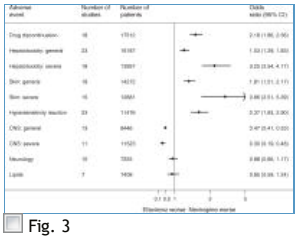

Fig. 3

Back to Top

Copyright (c) 2000-2012 Ovid Technologies, Inc.

Terms of Use | Support & Training | About Us | Contact Us

Version: OvidSP_UI03.08.01.105, SourceID 57688