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

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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-naïve 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 3,975 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 [18]. 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.
Table 1-a Study characteristics.

<table>
<thead>
<tr>
<th>Country</th>
<th>Sample size</th>
<th>Study design</th>
<th>Age group</th>
<th>% females</th>
<th>% losses</th>
<th>% discontinuations</th>
<th>OR (95% CI)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>2044</td>
<td>Prospective</td>
<td>18-44</td>
<td>45%</td>
<td>12%</td>
<td>7.4%</td>
<td>1.03 (0.84-1.26)</td>
<td>Low</td>
</tr>
<tr>
<td>Germany</td>
<td>1701</td>
<td>Prospective</td>
<td>18-44</td>
<td>50%</td>
<td>0%</td>
<td>10%</td>
<td>1.07 (0.89-1.29)</td>
<td>Low</td>
</tr>
<tr>
<td>United States</td>
<td>1457</td>
<td>Prospective</td>
<td>18-44</td>
<td>50%</td>
<td>0%</td>
<td>10%</td>
<td>1.07 (0.89-1.29)</td>
<td>Low</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1831</td>
<td>Prospective</td>
<td>18-44</td>
<td>60%</td>
<td>0%</td>
<td>10%</td>
<td>1.07 (0.89-1.29)</td>
<td>Low</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1200</td>
<td>Prospective</td>
<td>18-44</td>
<td>45%</td>
<td>0%</td>
<td>10%</td>
<td>1.07 (0.89-1.29)</td>
<td>Low</td>
</tr>
<tr>
<td>Kenya</td>
<td>1100</td>
<td>Prospective</td>
<td>18-44</td>
<td>50%</td>
<td>0%</td>
<td>10%</td>
<td>1.07 (0.89-1.29)</td>
<td>Low</td>
</tr>
</tbody>
</table>

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.

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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 Table 3 and Supplementary Table S3, http://links.lww.com/QAD/A309, respectively.
### Ovid: Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis.

#### Table 1: Pooled proportion of adverse events by drug.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of studies</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>18</td>
<td>8.68 (6.74, 10.61)</td>
</tr>
<tr>
<td>Hepatotoxicity: general</td>
<td>23</td>
<td>8.40 (6.55, 10.25)</td>
</tr>
<tr>
<td>Hepatotoxicity: severe</td>
<td>18</td>
<td>3.22 (2.57, 4.19)</td>
</tr>
<tr>
<td>Skin: general</td>
<td>19</td>
<td>7.86 (5.93, 9.78)</td>
</tr>
<tr>
<td>Skin: severe</td>
<td>15</td>
<td>3.08 (1.91, 4.24)</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>9</td>
<td>5.03 (3.90, 6.15)</td>
</tr>
<tr>
<td>CNS: general</td>
<td>13</td>
<td>2.86 (1.75, 4.00)</td>
</tr>
<tr>
<td>CNS: severe</td>
<td>11</td>
<td>0.12 (0.00, 0.30)</td>
</tr>
<tr>
<td>Neurology</td>
<td>10</td>
<td>4.05 (3.16, 5.24)</td>
</tr>
<tr>
<td>Lipids</td>
<td>7</td>
<td>1.54 (0.84, 2.27)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>18</td>
<td>5.77 (4.19, 7.35)</td>
</tr>
<tr>
<td>Hepatotoxicity: general</td>
<td>23</td>
<td>3.55 (2.38, 4.73)</td>
</tr>
<tr>
<td>Hepatotoxicity: severe</td>
<td>18</td>
<td>2.31 (1.42, 3.21)</td>
</tr>
<tr>
<td>Skin: general</td>
<td>19</td>
<td>2.74 (1.90, 3.60)</td>
</tr>
<tr>
<td>Skin: severe</td>
<td>15</td>
<td>0.70 (0.15, 1.23)</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>9</td>
<td>2.55 (1.64, 3.45)</td>
</tr>
<tr>
<td>CNS: general</td>
<td>13</td>
<td>18.70 (11.52, 25.89)</td>
</tr>
<tr>
<td>CNS: severe</td>
<td>11</td>
<td>3.26 (1.50, 6.01)</td>
</tr>
<tr>
<td>Neurology</td>
<td>10</td>
<td>4.43 (2.18, 6.67)</td>
</tr>
<tr>
<td>Lipids</td>
<td>7</td>
<td>2.37 (0.85, 3.86)</td>
</tr>
</tbody>
</table>

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

#### Table 2: Odds ratio of adverse events.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug discontinuation</td>
<td>18</td>
<td>17512</td>
<td>2.18 (1.86, 2.56)</td>
</tr>
<tr>
<td>Hepatotoxicity: general</td>
<td>23</td>
<td>16167</td>
<td>1.53 (1.29, 1.83)</td>
</tr>
<tr>
<td>Hepatotoxicity: severe</td>
<td>18</td>
<td>19957</td>
<td>3.25 (2.54, 4.17)</td>
</tr>
<tr>
<td>Skin: general</td>
<td>19</td>
<td>14272</td>
<td>1.61 (1.51, 1.71)</td>
</tr>
<tr>
<td>Skin: severe</td>
<td>15</td>
<td>12681</td>
<td>3.88 (2.51, 5.39)</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>23</td>
<td>11476</td>
<td>2.37 (1.93, 2.90)</td>
</tr>
<tr>
<td>CNS: general</td>
<td>13</td>
<td>8446</td>
<td>0.47 (0.41, 0.53)</td>
</tr>
<tr>
<td>CNS: severe</td>
<td>11</td>
<td>11523</td>
<td>0.30 (0.18, 0.48)</td>
</tr>
<tr>
<td>Neurology</td>
<td>10</td>
<td>7255</td>
<td>0.88 (0.66, 1.17)</td>
</tr>
<tr>
<td>Lipids</td>
<td>7</td>
<td>7408</td>
<td>0.85 (0.59, 1.24)</td>
</tr>
</tbody>
</table>
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, I² 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 patients 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 lower-income settings, which may be due to more intensive laboratory monitoring in higher income settings, more treatment discontinuations compared to EFV-based therapy (OR 7.1, 95% CI 3.3–15.4).

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

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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.

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Conflicts of interest

There are no conflicts of interest.

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

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**IMAGE GALLERY**

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Fig. 1

Table 1-a Study char...

Table 1-b Study char...

Fig. 2

Fig. 3

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