Adverse events associated with nevirapine use in pregnancy: a systematic review and meta-analysis

Adverse events associated with nevirapine use in pregnancy: a systematic review and meta-analysis

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Introduction: The risk of adverse drug events associated with nevirapine (NVP) is suggested to be greater in pregnant women. We conducted a systematic review and meta-analysis of severe adverse events in HIV-positive women who initiated NVP while pregnant.

Methods: We searched six databases for studies reporting adverse events among HIV-positive pregnant women who had received NVP-based antiretroviral therapy for at least 7 days. Data were pooled by the fixed-effects method.

Results: Twenty studies (3582 pregnant women) from 14 countries were included in the final review. The pooled proportion of patients experiencing a severe hepatotoxic event was 3.2% [95% confidence interval (CI) 2.1–4.3%], severe rash was experienced by 3.3% of patients (95% CI 2.1–4.5%) and 6.1% (95% CI 3.9–8.3%) of patients discontinued NVP due to an adverse event. These results were comparable to frequencies observed in the general adult patient population, and to frequencies reported in non-pregnant women within the same cohort. For pregnant women with a CD4 cell count above 250 cells/μl there was a non-significant tendency towards an increased likelihood of severe cutaneous adverse events (OR 1.4, 95% CI 0.8–2.4) and severe hepatotoxic events (OR 1.5, 95%CI 0.9-2.3) and consequently an increased risk of toxicity-driven regimen substitution (OR 1.7, 95% CI 1.1–2.6).

Discussion: These results suggest that the frequency of adverse events associated with NVP use in pregnant women, although high, is no higher than reported for NVP in the general adult population. Pregnant women with a high CD4 cell count may be at increased risk of adverse events, but evidence supporting this association is weak.

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Introduction

Current WHO guidelines for antiretroviral therapy (ART) recommend using either nevirapine (NVP) or efavirenz as part of combination ART [1]. NVP has been preferred for the treatment of HIV-positive pregnant women because of concerns about efavirenz safety in pregnancy. There have also been concerns that the frequency of occurrence of adverse drug events associated with NVP is greater in women, especially pregnant women with a higher CD4 cell count. This risk, however, is unclear as data are conflicting; some studies have reported an increased risk among pregnant women at higher CD4 cell count [2,3], whereas other studies did not find such an association [4,5].

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In resource-limited settings, NVP continues to be extensively used in pregnancy, both as part of ART for treatment-eligible women and for prophylaxis for prevention of mother-to-child transmission (PMTCT) of HIV. Current WHO guidelines for provision of antiretrovirals to pregnant women for both treatment and PMTCT urge caution in the use of NVP in women with CD4 cell counts of between 250 and 350 cells/μl, and recommend against the use of NVP at CD4 cell count above 350 cells/μl or in those women with unknown CD4 cell counts. These guidelines do, however, recognize that the benefits of using NVP in pregnancy in these circumstances can outweigh the risks of not initiating ART [6].

In order to help inform the revision of the 2013 WHO guidelines for ART, and given current considerations to extend access to ART regardless of CD4 cell count for all pregnant women for life [7], we conducted a systematic review and meta-analysis of adverse events in HIV-positive pregnant women initiating antiretroviral treatment including NVP, and reviewed the association between the occurrence of adverse events and CD4 cell count.

Methods

This systematic review and meta-analysis was conducted according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group [8].

Eligibility criteria

We initially sought randomized trials and prospective cohorts reporting adverse events among HIV-positive women who initiated NVP while pregnant. Anticipating a relative paucity of information, we also included retrospective cohorts as part of our search strategy. According to our predefined eligibility criteria (see protocol in Web Appendix), studies had to report outcomes among treatment-naïve women who initiated NVP while pregnant and had received NVP-based therapy for at least 7 days, either for their own health or as part of combination prophylaxis for PMTCT. Studies that included women who had initiated NVP preconceptionally or reported adverse events that occurred after delivery were excluded.

Search strategy and study selection

The following databases were searched from inception to 1 October 2012: MEDLINE via PubMed, EMBASE, LILACS, Web of Science, Current Controlled Trials, and the Cochrane database of systematic reviews. We also reviewed conference abstracts from the International AIDS Society conferences from July 2009 to July 2012 to identify potential studies that were recently completed but have not yet been published as full-text articles. Finally, bibliographies of relevant articles were screened. No date, geographical, or language restriction was applied.

Published articles identified by our search strategy were screened by one reviewer (N.F.), and the abstracts of potentially eligible studies were then assessed independently and in duplicate (N.F., Z.S.) to select potentially relevant full-text articles. Once a preliminary selection of articles was made, a list of these studies was sent to experts in the field to try to identify additional studies. Final agreement on study inclusions was determined through consensus (A.C., I.A.M., N.F. and Z.S.).

Data extraction

We conducted data extraction independently, in duplicate, using a standardized data extraction form (N.F., Z.S.). Once agreement was reached, completed data extraction forms were sent to authors of each study for verification and to seek additional data not reported by the published articles. We sought data on the number of pregnant women receiving NVP who experienced hepatotoxicity, rash or hypersensitivity reaction, which was defined as severe hepatotoxicity and/or severe rash (provided sufficient information was available to avoid double counting of patients). These adverse events were classified as mild/moderate or severe according to severity grading as defined by the studies; hepatic or cutaneous events that resulted in discontinuation of NVP were considered severe. When reported by the studies, the number of adverse events was disaggregated in order to compare outcomes among pregnant versus non-pregnant women, and pregnant women with CD4 cell count 250 cells/μl or less versus CD4 cell count above 250 cells/μl. Frequencies of adverse events in pregnant women receiving NVP were also compared against frequencies of adverse events for NVP in adults in general, based on data from a recent systematic review conducted by the same researchers [9]. Secondary outcomes included the number of any adverse events resulting in treatment discontinuation, termination of pregnancy due to adverse events, and mortality associated with adverse events.

Data on patient and study characteristics, monitoring strategies and adverse event classification used, and relevant indicators of potential risks of bias were also extracted. The quality of the evidence for each primary outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [10].

Data analysis

We calculated point estimates and 95% confidence intervals (95% CIs) for the proportion of patients experiencing each outcome using the Freeman Tukey approach [11]. The odds ratios (ORs), risk differences, and the corresponding 95% CIs for each outcome were calculated, applying the Haldane method in the event of zero outcomes in one arm [12], and data were pooled using a fixed-effects model [13]. Data from randomized trials and prospective cohorts were analysed together as no important differences have been found between designs

in the reliability of reporting of adverse events [14]. Heterogeneity was assessed using the I^2 statistic [15]. Recognizing that the I^2 statistic provides large estimates of heterogeneity when evaluating proportions, we examined the following predefined subgroups to explore heterogeneity within our primary outcomes of rash and/or hepatitis as a result of NVP: study design (prospective versus retrospective), 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; http://data.worldbank.org/about/country-classifications/country-and-lending-groups), gestational age at initiation of NVP (third trimester versus earlier) and concomitant use of other drugs associated with the outcomes of interest (rifampicin, co-trimoxazole or isoniazid).

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

Results

Study inclusions

After an initial review of 1031 titles, 411 abstracts were screened, 61 articles were assessed in full (Fig. 1) and agreement was reached on the inclusion of 20 studies. These studies comprised two randomized trials [2,4], five prospective cohorts [3,5,16–18] and 13 retrospective cohorts [19–31], and reported data from 14 countries including five countries in Africa, two countries in Latin America, one country in Asia, with the remainder carried out in Western (high income) settings. Most studies (10) used the United States Division of AIDS grading system for severity of adverse events. In all, 3582 women who initiated NVP while pregnant were included in this review. Study characteristics are summarized in Table 1 and monitoring strategies are detailed in Supplementary Table S1, http://links.lww.com/QAD/A300. Authors of 16 studies confirmed data extractions and provided additional data [3–5,16–19,21,22–24,25,27,30–32].

Assessment of methodological quality

Overall risk of bias for studies included in this review was considered to be moderate to high. The majority of studies were observational, and most (13) were retrospective in design. Few studies reported on potential confounding factors or attempted to adjust for these at baseline or analysis (Supplementary Table S2, http://links.lww.com/QAD/A300). The GRADE assessment for risk of adverse events comparing high and low CD4 cell counts rated the quality of evidence as being very low for all outcomes, mainly due to serious imprecision and risk of bias (Supplementary Table S3, http://links.lww.com/QAD/A300).

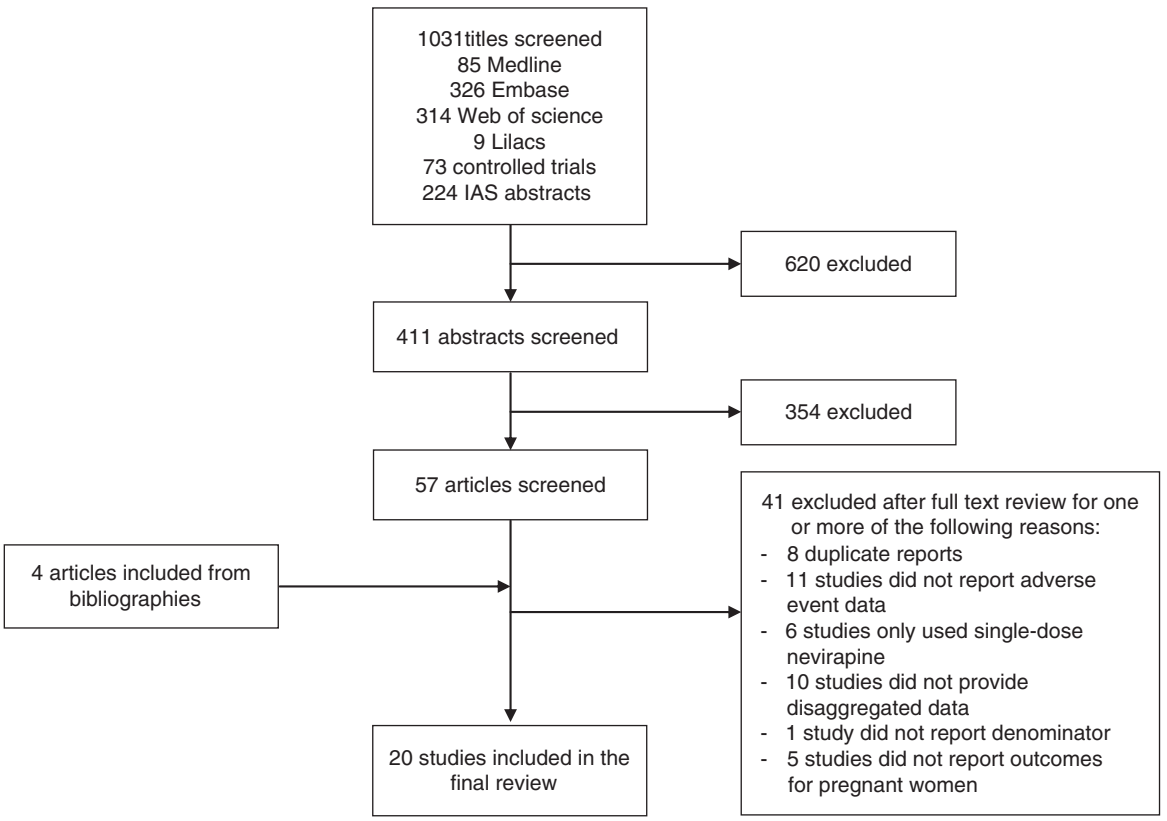

Fig. 1. Flow diagram of study selection process.

Table 1. Characteristics of included studies.

Study	Setting	Design	Period	Number on NVP	Age (years)	Median CD4 (cells/μl)	Median viral load (copies/ml)	Gestational age at initiation of NVP
Aaron	USA	Retrospective	01/1999–05/2005	79	28	401	NS	19 weeks
Bersoff-Matcha	USA	Retrospective	01/1995–05/2007	42	29	406	NS	NS
Black	South Africa	Retrospective	08/2004–02/2007	509	29	154	101 561	27 weeks
Bottaro[a]	Argentina	Retrospective	05/1997–03/2008	118	33	292	107 patients <400	NS
Coffie	Cote d'Ivoire	Prospective	08/2003–10/2006	125	29	186	NS	NS
Hitti	USA	RCT	2003	17	28	359	9772	20 weeks
Jamisse	Mozambique	Prospective	08/2004–06/2005	146	27	231	NS	26.5 weeks
Joao[b]	Brazil	Retrospective	01/1996–12/2003	197	26	298	NS	28 weeks
Joy	USA	Retrospective	07/2001–04/2005	23*	25	507	NS	44% 14–27 weeks
Kilewo	Tanzania	Prospective	04/2004–06/2006	429	26	414	14 621	34 weeks
Kondo	Brazil	Retrospective	01/2003–12/2006	133	30	456	24 192	23 weeks
Lyons[c]	Ireland	Retrospective	10/2000–02/2003	85	27	324	6600	NS
Marazzi	Italy	Retrospective	05/2002–07/2004	703	25	81% >250	84%>55 000	27 weeks
Natarajan[b]	UK	Retrospective	01/1997–12/2003	170	28	277	17 400	24 weeks
Peters[d]	Kenya	RCT	07/2003–02/2009	310	23	398	NS	NS
Phanuphak[e]	Thailand	Prospective	NS	244	NS	135 (therapy) 414 (PMTCT	NS	>28 weeks
Snijdewind	Netherlands	Retrospective	01/1997–02/2008	102	28	370	6.4	NS
Van Schalkwyk	Canada	Prospective	01/1997–02/2004	56	28	380	11 900	NS
Weinberg[f]	USA	Retrospective	08/1997–12/2005	19	NS	450	2657	NS
Zuk	USA	Retrospective	01/1997–03/2006	37	26	365	57 474	NS

[a]Women initiating NVP preconception excluded.
[b]Data for women with toxicities only.
[c]Mixed prospective and retrospective cohort.
[d]Analysis assumes that all patients provided with ART (as opposed to PMTCT) had CD4 below 200.
[e]In this study events were reported up to 6 months after delivery. We excluded all events after delivery in accordance with data provided by the study authors except two rash events, which occurred 6 days after delivery.
[f]Data for whole cohort.
*One patient started NVP preconceptionally (CD4 status not reported).

Frequency and risk of adverse events

Across all 20 studies, the pooled proportion of pregnant women experiencing a hepatotoxic event was 6.8% (95% CI 4.6–9.0%); the proportion of patients experiencing a severe hepatotoxic event was 3.2% (95% CI 2.1–4.3%). Rash was experienced by 7.2% of patients (95% CI 5.6–8.9%); severe rash was experienced by 3.2% of patients (95% CI 2.1–4.3%); hypersensitivity reaction was experienced by 6.5% of patients (95% CI 4.3–8.6%). Overall, 6.1% (95%CI 3.9–8.3%) of patients discontinued NVP due to NVP-associated adverse events. Mortality associated with adverse events was low, with four deaths reported attributed to NVP-associated adverse events: three deaths were reported from two retrospective cohorts [26,27] and the final death was reported from a prospective cohort [2]. All four deaths occurred among patients with a pretreatment CD4 cell count of more than 250 cells/μl.

In subgroup analyses, a higher proportion of hepatotoxic events was reported in prospective studies (8.9%, 95% CI 4.0–13.9%) compared to retrospective studies (5.8%, 95% CI 3.3–8.4%), and in studies in which the median gestational age at ART initiation was during the third trimester of pregnancy (8.5%, 95% CI 3.4–13.6%) compared to the first/second trimester (4.3%, 95% CI 1.6–7.0%). No other differences were observed.

We compared the frequency of adverse events among pregnant women included in this systematic review with the frequency of adverse events associated with NVP use in the general adult population reported by another recent systematic review using similar methodology [9]. These comparisons, which are summarized in Fig. 2, suggest that there are no differences in the frequencies of adverse events comparing pregnant women to HIV-positive adults overall.

Adverse events according to CD4 cell count among pregnant women

Fifteen studies reported data on outcomes comparing pregnant women with a lower CD4 cell count (≤250 cells/μl) and a higher CD4 cell count (>250 cells/μl) [2–5,16–19,22–25,27,28,31]. For women with a CD4 cell count greater than 250 cells/μl there was a non-significant tendency towards an increased likelihood of cutaneous events overall (OR 1.1, 95% CI 0.8–1.6), severe cutaneous adverse events (OR 1.4, 95% CI 0.8–2.4) and consequently an increased risk of toxicity-driven regimen substitution (OR 1.7, 95% CI 1.1–2.6). The likelihood of

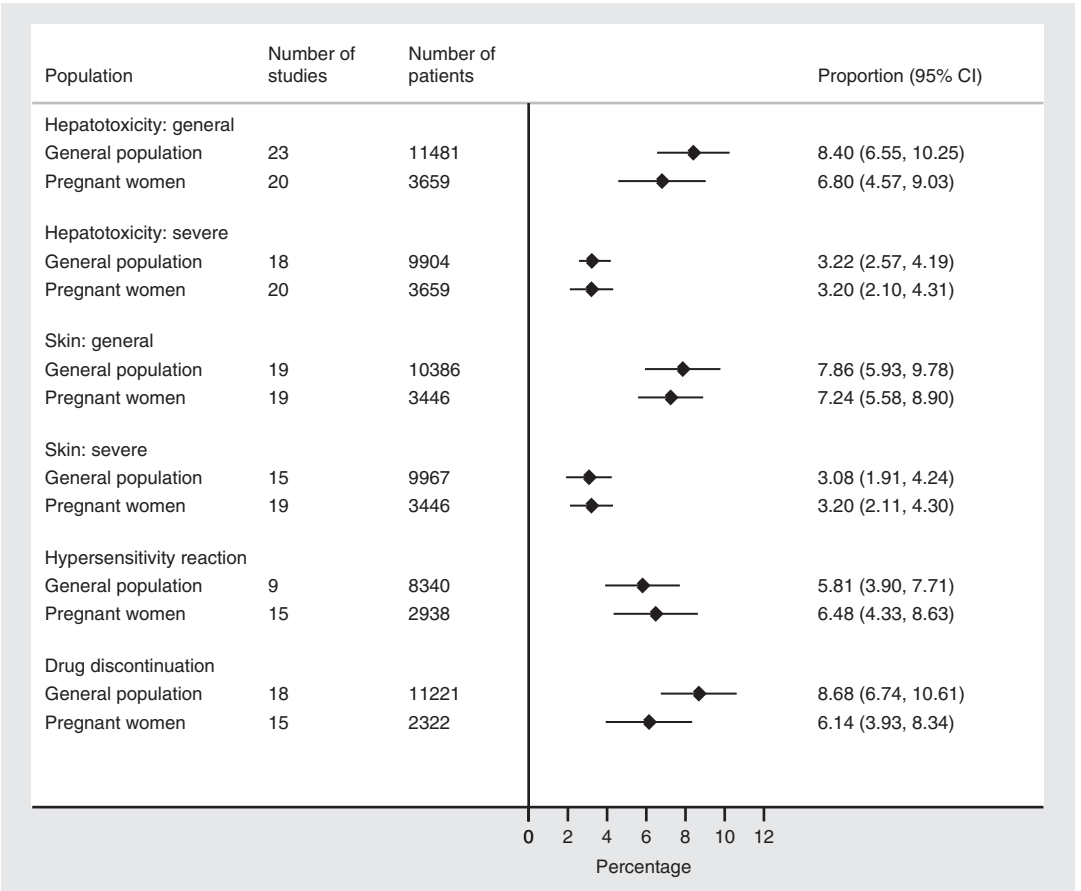

Fig. 2. Pooled proportion of adverse events comparing pregnant women to non-pregnant adults.

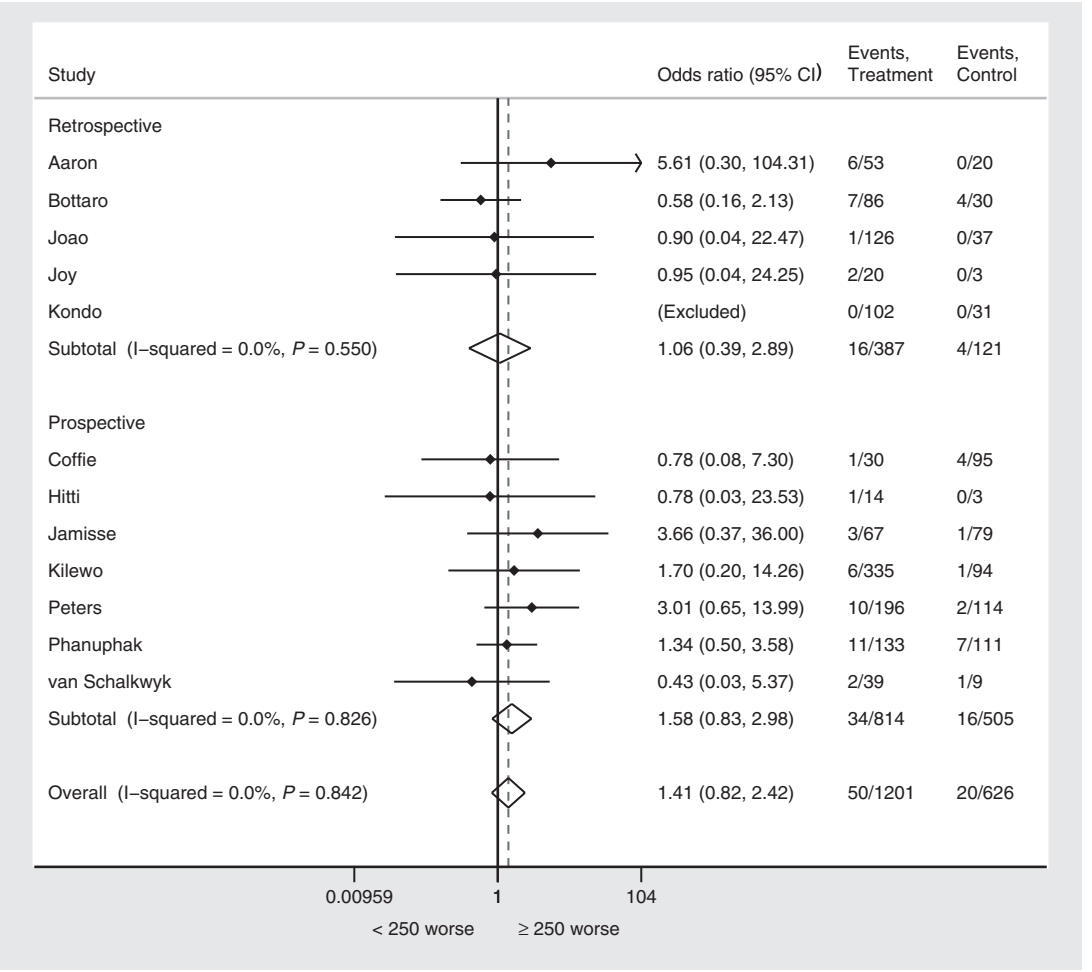

Fig. 3. Pooled odds ratio for severe rash by CD4 cell count.

severe cutaneous events was higher in prospective studies, although this was still non-significant (OR 1.6, 95% CI 0.8–3.0). Overall, no difference in the likelihood of hepatotoxic events was seen, but a greater risk of severe hepatic events was found when the analysis was restricted to prospective studies (OR 3.9, 95% CI 1.6–9.5) (Figs. 3 and 4).

Adverse events according to pregnancy status

Six studies reported adverse event data from cohorts that included both treatment-naive pregnant and non-pregnant women [5,17,19,20,22,29]. Among these studies, there was no evidence of an increased likelihood of developing any adverse outcome. The ORs for adverse events comparing pregnant and non-pregnant women were all non-significant: hepatotoxicity 1.3 (95% CI 0.8–1.9); severe hepatotoxicity 1.4 (95% CI 0.9–2.1); rash 1.2 (95% CI 0.8–1.9); severe rash 0.8 (95% CI 0.5–1.4); hypersensitivity 0.7 (95% CI 0.5–1.0). Discontinuations were not assessed, as this outcome was considered to be at high risk of bias (because of current concern regarding increased risk of NVP-associated adverse events in pregnant women and heightened concern about safety in pregnancy, treatment was more likely to be discontinued in pregnant women compared to non-pregnant women).

Discussion

Nevirapine is one of the most widely used antiretroviral drugs included in first-line triple ART, particularly in low- and middle-income countries. All antiretroviral drugs carry a risk of toxicity, and in the case of NVP a higher risk of hepatotoxicity and rash has been documented compared to efavirenz, the common non-nucleoside reverse transcriptase inhibitor alternative to NVP.

The risk of adverse events associated with NVP, in particular hepatic and cutaneous events, has been considered to be high in pregnant women generally, and in particular for those with a high CD4 cell count. Clinical guidelines have reflected this concern by advising NVP use only with careful toxicity monitoring and

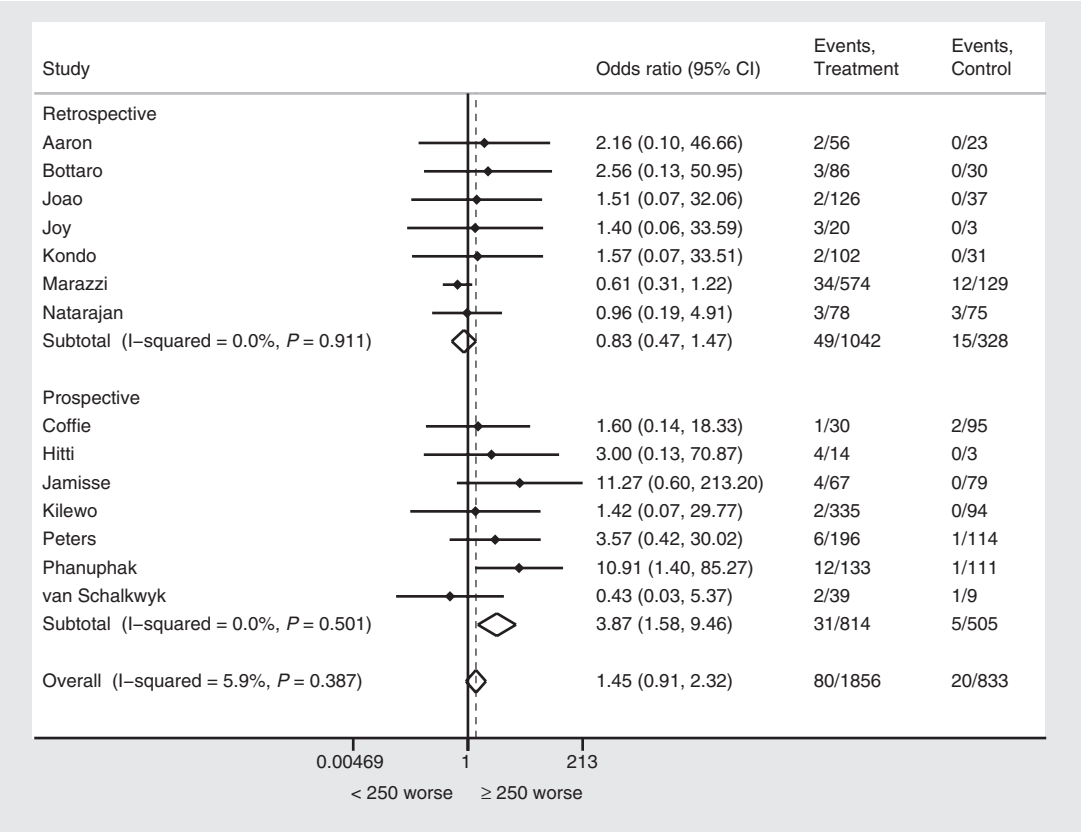

Fig. 4. Pooled odds ratio for severe hepatotoxicity by CD4 cell count.

recommending against the use of NVP in pregnant women with CD4 cell count above 350 cells/μl [6]. This has led to complex algorithms, particularly for PMTCT [6]. Efavirenz has recently been recommended by WHO as the preferred first-line option [33], but assessment of risk for NVP is still important since it remains widely used and is recommended as an alternative to efavirenz.

This systematic review found no evidence of increased risk of NVP-related adverse events associated with pregnancy compared to non-pregnant adults, and only weak evidence of elevated risk of cutaneous and hepatic events among pregnant women initiating a NVP-based ART at higher CD4 cell count. Nevertheless, the frequency of occurrence of adverse events was generally high, with almost 1 in 10 pregnant women experiencing a hepatotoxic event in prospective studies.

A recent systematic review specifically assessed the question of NVP safety in pregnancy according to CD4 cell counts, and concluded that there was a significantly higher risk of severe events at CD4 cell count above 250 cells/μl [34]. Our review differs from this review in several ways. First, our definition of severe adverse events included any grade of adverse event that resulted in a drug discontinuation. Second, we excluded data on patients in whom adverse events were reported after delivery (some studies followed up patients for up to 6 months after delivery). Finally, we were able to obtain additional information and clarifications from authors of three-quarters of all included studies, which allowed the inclusion of additional studies in the CD4 analysis.

There are several strengths and limitations to note. We used a broad search strategy that identified a number of published and unpublished studies, and included additional data provided by authors. We paid particular attention to data verification, extracting all outcome data independently, in duplicate, and verifying data with study authors. However, the overall meta-analysis dataset was small for some outcomes which may have limited the possibility to detect a difference for certain analyses. Some of the analyses presented in this review are based on retrospective data, which carry a higher risk of bias resulting in a possible over-estimation or under-estimation of events in these studies. We chose to include these studies despite the risk of bias in order to provide more complete information. This concern was assessed through subgroup analysis, and key results are presented stratified by study design. We could not assess the potential influence of other factors that may have influenced the overall findings such as co-infections and concomitant prophylaxis, backbone ART regimen, hepatitis co-infection or differences in laboratory

monitoring as these variables were not consistently reported. Another potential concern relates to the differences in adverse event grading systems used by different studies; however, these systems do not differ importantly in their grading of severity of hepatic and cutaneous adverse events. The evidence of adverse event risk according to low and high CD4 cell counts is based on study-level stratification of patients into two groups, with the result that all CD4 cell counts above 250 cells/μl are treated equally. A more nuanced investigation of adverse event risk at higher CD4 cell count would require individual patient-level data, which was not available for this review. Publication bias is an ever present concern for systematic reviews. This was not formally assessed due to the limited number of studies included in the review. Finally, the relatively limited number of patients and low event rate associated with all outcomes means that all data are fragile and the overall quality of evidence is very low.

This review points to several directions for future research. First, the potential association between NVP toxicity and later-stage pregnancy noted in subgroup analysis deserves further investigation. Second, not all severe adverse events led to treatment discontinuations, with up to 20% of patients in some studies continuing NVP despite experiencing severe hepatotoxicity; the reasons for this should be better understood in future studies. Finally, an individual patient data meta-analysis would allow a more precise determination of the association between adverse event risk at higher CD4 cell count.

In conclusion, the findings of this review suggest that there is little evidence to justify discrimination according to pregnancy status when using NVP as part of combination ART. An increased risk of rash among pregnant women at higher CD4 cell count is suggested but evidence for such an association remains very weak and this concern needs to be weighed against the limited adverse event monitoring capacity in many high-burden settings. The frequency of occurrence of adverse events associated with NVP in general suggests that, when possible, the use of alternative drugs with better overall toxicity profiles such as efavirenz should be considered [33]. Such considerations are all the more important in resource-limited settings in which capacity for toxicity monitoring remains limited.

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N.F., Z.S., I.A.M. and A.C. designed the review. N.F. and Z.S. undertook searches, extracted data and conducted authors for additional data. I.A.M. and S.H. undertook additional data extractions. N.F. 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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