Antiretroviral therapy in Thai adults and children with HIV-1 infection
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Chapter 6:
Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs

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Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs

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**Objective:** To determine the incidence and risk factors for rash in Thai patients taking four different non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens.

**Methods:** HIV-positive, antiretroviral-naive patients enrolled in the 2NN study in Thailand and followed for at least 1 week were included. Patients were randomized to efavirenz (EFV) 600 mg once daily (OD) versus nevirapine (NVP) 200 mg twice daily (BD) versus NVP 400 mg OD versus NVP 400 mg OD + EFV 800 mg OD with stavudine/lamivudine.

**Results:** Of 202 patients, 95 (47\%) and 69 (34.2\%) developed a rash from all reasons and from NNRTI, respectively. For NNRTI-related rash the incidences were EFV (20\%), NVP BD (21\%), NVP OD (38\%) and NVP + EFV (67\%). The proportions of patients with grade I, II and III within the four treatment arms are as follows: EFV, 4.3, 13 and 2.9\%; NVP BD, 2.3, 15.9 and 2.3\%; NVP OD, 12.8, 19.1 and 6.4\%; and NVP + EFV, 11.9, 47.6 and 7.1\%. Multivariate analyses showed females with CD4 cell count $\geq 250 \times 10^6$ cells/l, high body mass index ($\geq 21.3$ kg/m\(^2\)), and a rise in CD4 ($\geq 53 \times 10^6$ cells/l) and alanine aminotransferase (ALT) ($\geq 34$ U/l) at week 4 to be risk factors for rash.

**Conclusions:** Thai patients had a high incidence of NNRTI-related rash when treated with NVP + EFV or NVP OD. NVP if used BD had the same rash incidence as EFV for rash of all grades. Females, and persons with earlier HIV disease or with a large rise in CD4+ cell count after starting therapy are at greater risk for NNRTI-related rash.

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**Keywords:** rash, non-nucleoside reverse transcriptase inhibitor, efavirenz, nevirapine, risk factors, incidence, antiretrovirals

**Introduction**

Nevirapine (NVP) and efavirenz (EFZ) are non-nucleoside reverse transcriptase inhibitors (NNRTI) most commonly used as components of first line antiretroviral (ARV) regimens worldwide. Rash is the most common adverse drug reaction associated with NVP, with an incidence of about 20\% [1–4]. Rash has also been associated with EFZ.
although to a lesser extent. Most patients develop rash between the first and third week of treatment [3–5].

How race affects the development of NNRTI-related rash is unknown. High incidence of rash in Asians has been reported [6]. In our clinical practice, we have also noticed that many of our patients have rash from NVP and EFV. An NNRTI-based ARV therapy is being used as the mainstay of therapy in Thailand and many other countries, the evaluation of the incidence and risk factors for NNRTI-related rash in the Asian population is critical.

Therefore, we conducted an evaluation in Thai patients enrolled and randomized to four different NNRTI regimens as part of the 2NN study. We investigated the incidence, characteristics, severity and treatment of rash and the outcome after continuing or switching to a different NNRTI. We looked for the risk factors that may predict the occurrence of rash.

**Methods**

HIV-positive ARV-naive patients (n = 210) were randomized into four treatment arms in the 2NN study in Thailand. The design and results of the 2NN study are described in detail elsewhere [7]. Briefly, the study compared the efficacy of EFV 600 mg once daily (OD) versus NVP 200 mg twice daily (BD) versus NVP 400 mg OD versus NVP 400 mg OD + EFV 800 mg OD in combination with stavudine and lamivudine. Nevirapine was given at half-dose (200 mg OD) during the first 2 weeks in all patients. Data from 202 patients were included in this analysis. Eight patients were excluded because they had less than 1 week of follow up. The 2NN study was approved by the Institutional Review Board at Chulalongkorn University.

For this analysis, the following baseline and weeks 2, 4, 8, 12, 24 data were used: demography, Centers for Disease Control (CDC) clinical classification, adverse events, CD4, HIV-RNA, liver enzymes [alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT)]. The outpatient charts of the six patients with serious adverse events were reviewed.

During the study, all cases of rash were documented in detail. According to the 2NN protocol, causality and severity of rash were determined as follows: (1) causality determined as relationship to NNRTI: unlikely, possible, probable, definite; (2) severity determined as Level I: erythema; Level IIA: diffuse maculopapular rash; Level IIB: urticaria; Level III: rash + constitutional symptoms, angioedema, serum sickness-like reactions, Stevens Johnson syndrome; Level IV: toxic epidermal necrolysis. Treatment for rash was recorded. NNRTI was documented as a cause for rash if it had at least a possible relationship to NNRTI.

The primary outcome was incidence of NNRTI-related rash. Secondary outcome was risk factors for NNRTI-related rash.

**Statistical analysis**

Analysis of variance (ANOVA) test and Kruskal–Wallis test were used to compare continuous outcomes while Student t-test and Mann–Whitney U-test were used to compare two groups. The percentage differences in each outcome were evaluated by chi-square test and Fisher’s exact test. Paired t-test and Wilcoxon signed ranks test were used for continuous outcomes and McNemar test for dichotomous outcomes. Logistic regression models were used to compare rates of rash between randomized treatment groups, both unadjusted and adjusted for other factors. To ensure that treatment comparisons are adjusted for any possible baseline imbalances, the multivariate analyses presented are adjusted for all other factors regardless of whether they were themselves statistically significant. Further analyses, only including variables in multivariate analyses that remained statistically significant, were also performed and gave similar results (not presented). Percentile and median values were used to group predictive factors. The odds ratio for each independent variable was determined from logistic regression coefficients. Our sample size gave 80% power to detect an increase of at least 28% in the NNRTI-related rash incidence between the arm predicted to have the least rash (EFV) and the arm predicted to have the most rash (NVP + EFV). Statistical Product and Service Solutions (SPSS) for Windows, version 9.0 software (SPSS Inc., Chicago, Illinois, USA) was used. All tests and confidence intervals (CI) were considered to be significant at \( P \leq 0.05 \) (two-sided).

**Results**

**Baseline characteristics**

Of the 210 patients enrolled in the 2NN trial in Thailand, 202 were included for this analysis. The eight patients excluded had less than 1 week of NNRTI: six did not start at all and two elected to stop after 3 days. Of the 202 patients included, the number of patients randomly allocated to the four arms were EFV 600 mg OD (n = 69), NVP 200 mg BD (n = 44), NVP 400 mg OD (n = 47), NVP + EFV (n = 42). Table 1 shows matched baseline characteristics between arms for number of patients, gender, mean body weight, height and body mass index (BMI). Patients randomized to the EFV OD and NVP BD arms had more advanced clinical HIV disease, lower CD4 cell count and higher ALT than the other two arms. The median HIV RNA was higher in the NVP BD and NVP OD arms.
Table 1. Baseline characteristics of all patients (n = 202*).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EFV 600 mg OD</th>
<th>NVP 200 mg BD</th>
<th>NVP 400 mg OD</th>
<th>NVP 400 mg + EFV 800 mg OD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>69 (34.2)</td>
<td>44 (21.8)</td>
<td>47 (23.1)</td>
<td>42 (20.8)</td>
<td>202 (100)</td>
</tr>
<tr>
<td>Gender (M : F)</td>
<td>39.30 (56.5-43.5)</td>
<td>26.18 (39.1-40.9)</td>
<td>21.26 (44.7-55.3)</td>
<td>25.17 (59.5-40.5)</td>
<td>111.91 (55.45)</td>
</tr>
<tr>
<td>Mean age (years) (SD)</td>
<td>32.3 (6.0)</td>
<td>36.0 (7.4)</td>
<td>33.2 (7.9)</td>
<td>31 (5.7)</td>
<td>33.0 (6.9)</td>
</tr>
<tr>
<td>Mean body weight (kg) (SD)</td>
<td>57.9 (10.8)</td>
<td>57.6 (11.1)</td>
<td>56.8 (11.7)</td>
<td>59.3 (10.2)</td>
<td>57.9 (10.9)</td>
</tr>
<tr>
<td>Mean height (cm) (SD)</td>
<td>164.4 (9.6)</td>
<td>163.6 (8.6)</td>
<td>161.5 (8.7)</td>
<td>164.4 (9.6)</td>
<td>163.6 (9.0)</td>
</tr>
<tr>
<td>Mean BMI (kg/m²) (SD)</td>
<td>21.4 (3.4)</td>
<td>21.4 (3.2)</td>
<td>21.7 (3.5)</td>
<td>21.8 (2.6)</td>
<td>21.6 (3.2)</td>
</tr>
<tr>
<td>CDC class n (%)</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>Median CD4 cell count (cells x 10³/µL) (IQR)</td>
<td>Median HIV-RNA (log₁₀ copies/ml) (IQR)</td>
</tr>
<tr>
<td>30 (43.5)</td>
<td>20 (29)</td>
<td>18 (40.9)</td>
<td>20 (42.6)</td>
<td>4 (9.5)</td>
<td>4.7 (4.4–5.5)</td>
</tr>
<tr>
<td>Median CD4 cell count (cells x 10³/µL) (IQR)</td>
<td>19 (27.5)</td>
<td>11 (25)</td>
<td>4.8 (6.1–5.7)</td>
<td>4 (4.6–5.3)</td>
<td>4.7 (4.4–5.5)</td>
</tr>
<tr>
<td>Biomarker</td>
<td>108 (35.0–244.9)</td>
<td>68 (22.2–146.6)</td>
<td>165.6 (42.9–276.4)</td>
<td>176.4 (121.5–303.9)</td>
<td>130 (42.5–255.1)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>28 (18–41)</td>
<td>32.5 (23.5–48.5)</td>
<td>21 (15–35)</td>
<td>25 (16–35.3)</td>
<td>27 (18–40)</td>
</tr>
</tbody>
</table>

EFV, efavirenz; BD, twice daily; BMI, body mass index; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; ALT, alanine aminotransferase. *Initially 210 patients enrolled in the study. Eight patients with less than 1 week on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based highly active antiretroviral therapy were excluded; six did not start treatment, two elected to stop nevirapine (NVP) 200 mg once daily (OD) after 3 days.

Incidence and characteristics of NNRTI-related rash
Ninety-five (47%) and 69 (34%) of 202 patients had rash from all reasons and from NNRTI respectively. Of these, 69 (34%) were considered to be due to NNRTI (Fig. 1). More patients in the NVP + EFV arm had rash regardless of cause. The EFV and NVP BD arms had similar but lower incidence of NNRTI-related rash than the other two arms. Reasons other than NNRTI for rash were HIV-related (n = 5), food allergy (n = 2), viral infection (n = 1), fungal

![Fig. 1. Incidence and grades of NNRTI-related rash within the four treatment arms. P-value represents the difference in percentage of patients with different grades of non-nucleoside reverse transcriptase inhibitor (NNRTI)-related rash within each treatment arm (by chi-square test). EFV, efavirenz; NVP, nevirapine; OD, once daily; BD, twice daily.](image-url)
infection (n = 1), contact dermatitis (n = 2), other drug allergy (n = 4) and other dermatitis (n = 1).

Table 2 shows the characteristics of NNRTI-related rash. No patient had grade IV rash and most had grade II (52.1%). Patients treated with NVP + EFV had significantly more urticaria. There were slightly more patients on EFV and NVP BD who had grade III rash than the other two arms. Grade III rash included Stevens Johnson syndrome (n = 2), angioedema (n = 1), extensive rash and constitutional symptoms (n = 4) and serum sickness-like reaction (n = 4). Prodomal symptoms were seen more with EFV and NVP OD. Median onset and duration of rash were not different between arms; however, it took slightly longer to develop a rash with NVP BD. Once a rash occurred, most patients were treated with antihistamines and only one received corticosteroids. After the initial rash, the decision to continue the same NNRTI or switch to a different NNRTI did not differ significantly between arms, although, there was a trend towards more patients on NVP being switched to EFV than vice versa. In one-third of the patients on NVP + EFV with rash, NVP was stopped and only EFV was continued. Histories of drug allergy and atopy were documented in 18 (26.1%) and nine (13%) patients, respectively, without any significant differences between arms. Of the 69 patients who had NNRTI-related rash, at week 4, 11 (16%) had ALT above five times the upper normal limits. Seven were taking NVP OD and four were taking NVP + EFV.

Fig. 2 shows the percentage of patients with and without recurrent rash, grouped according to whether they continued on the same NNRTI or switched to a different NNRTI. Recurrent rash was defined as a new rash that occurred after resolution of the previous rash. The median time between these was 16 days [interquartile range (IQR), 7–14]. Overall, most patients who continued the

<table>
<thead>
<tr>
<th>Type</th>
<th>EFV 600 mg OD (n = 14)</th>
<th>NVP 200 mg BD (n = 9)</th>
<th>NVP 400 mg OD (n = 18)</th>
<th>NVP 400 mg OD + EFV 800 mg OD (n = 20)</th>
<th>Total (n = 69)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I (erythema)</td>
<td>3 (21.4)</td>
<td>3 (33.3)</td>
<td>8 (44.4)</td>
<td>8 (28.6)</td>
<td>22 (31.9)</td>
<td>0.208</td>
</tr>
<tr>
<td>Grade II (diffuse maculopapular rash)</td>
<td>5 (35.7)</td>
<td>2 (22.2)</td>
<td>4 (22.2)</td>
<td>4 (14.3)</td>
<td>15 (21.7)</td>
<td>0.737</td>
</tr>
<tr>
<td>Grade III (urticaria)</td>
<td>2 (14.3)</td>
<td>1 (11.1)</td>
<td>5 (27.8)</td>
<td>13 (46.4)</td>
<td>21 (31.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Grade IV</td>
<td>4 (28.6)</td>
<td>3 (33.3)</td>
<td>1 (5.5)</td>
<td>3 (10.7)</td>
<td>13 (14.4)</td>
<td>0.631</td>
</tr>
<tr>
<td>Presence of prodomal symptoms (%)</td>
<td>5 (45.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11 (21.2)</td>
<td>0.037</td>
</tr>
<tr>
<td>Median onset of rash (days) (IQR)</td>
<td>10 (6–14)</td>
<td>21 (14–25)</td>
<td>15 (11–23)</td>
<td>10 (8–12)</td>
<td>11 (9–16)</td>
<td>0.126</td>
</tr>
<tr>
<td>Medication for rash treatment (%)</td>
<td>8 (7–26)</td>
<td>12 (9–17)</td>
<td>10 (8–18)</td>
<td>13 (6–19)</td>
<td>12 (7–19)</td>
<td>0.956</td>
</tr>
</tbody>
</table>

| Corticosteroids            | 0                      | 0                     | 0                      | 1 (3.6)                                | 1 (1.4)        | NS      |
| Antihistamines             | 9 (62.4)               | 5 (55.5)              | 12 (66.6)              | 25 (89.2)                              | 51 (73.9)      | 0.003   |

*Grade III is defined as grade I, II + constitutional symptoms or angioedema or serum sickness-like reaction or Stevens Johnson Syndrome. Of the 11 patients with grade III rash, two had Stevens Johnson syndrome (one each in nevirapine (NVP) twice daily (BD) and NVP once daily (OD) groups). 

#Toxic epidermal necrolysis. Prodomal symptoms are symptoms that occurred before the onset of rash. Examples are malaise, pruitus, fever and myalgia. EFV, efavirenz; IQR, interquartile range.

Fig. 2. Number of patients with and without rash when continued or switched to a different non-nucleoside reverse transcriptase inhibitor (NNRTI) stratified by treatment arms (n = 69). Recurrent rash: new rash that occurred after resolution of the previous rash (median time between rash was 16 days [interquartile range (IQR), 7–14]). Continued NNRTI: the same NNRTI regimens were continued with or without interruption. Switched NNRTI: For the elavires (EFV) once daily (OD), nevirapine (NVP) twice daily (BD), NVP OD arms, the NNRTI was switched to the other NNRTI. No delavirdine was used. For the NVP + EFV arm, NVP was stopped and only EFV was continued.
Table 3. Comparison of type of non-nucleoside reverse transcriptase inhibitor (NNRTI), demographic data, Centers for Disease Control and Prevention (CDC) class, CD4, log HIV RNA, liver function tests in patients with and without NNRTI-related rash.

<table>
<thead>
<tr>
<th>Factors</th>
<th>With rash (n = 69)</th>
<th>Without rash (n = 113)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV 600 mg OD</td>
<td>14 (20.3)</td>
<td>55 (41.4)</td>
<td></td>
</tr>
<tr>
<td>NVP 200 mg BD</td>
<td>9 (13)</td>
<td>35 (26.3)</td>
<td></td>
</tr>
<tr>
<td>NVP 400 mg OD</td>
<td>18 (26.1)</td>
<td>29 (21.8)</td>
<td></td>
</tr>
<tr>
<td>NVP 400 mg OD + EFV 800 mg OD</td>
<td>28 (40.6)</td>
<td>14 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Gender MF, n (%)</td>
<td>36.31 (52.2-47.8)</td>
<td>75.58 (56.4-43.6)</td>
<td>0.655</td>
</tr>
<tr>
<td>Mean age (years) (SD)</td>
<td>32.6 (5.9)</td>
<td>31.3 (7.4)</td>
<td>0.482</td>
</tr>
<tr>
<td>Mean BMI (kg/m²) (SD)</td>
<td>21.3 (3.06)</td>
<td>21.7 (3.3)</td>
<td>0.483</td>
</tr>
<tr>
<td>CDC class n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>40 (58)</td>
<td>52 (42.1)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>19 (27.5)</td>
<td>49 (36.8)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>10 (14.5)</td>
<td>21 (16.7)</td>
<td></td>
</tr>
<tr>
<td>CD4 (week 0)</td>
<td>128 (52.3–291.1)</td>
<td>131 (34.8–246.4)</td>
<td>0.274</td>
</tr>
<tr>
<td>CD4 increase (week 4)</td>
<td>79.8 (33.2–148.4)</td>
<td>47.6 (6.1–99.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Log HIV RNA (week 0)</td>
<td>4.7 (4.4–4.5)</td>
<td>4.7 (4.4–4.6)</td>
<td>0.480</td>
</tr>
<tr>
<td>Log HIV RNA change group/week 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2.55</td>
<td>27 (43.5)</td>
<td>34 (27.4)</td>
<td>0.370</td>
</tr>
<tr>
<td>&lt; 2.04</td>
<td>23 (31.9)</td>
<td>42 (33.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>ALT increase (week 4)</td>
<td>35 (26–77)</td>
<td>32 (20–47.5)</td>
<td>0.031</td>
</tr>
<tr>
<td>GGT (week 0)</td>
<td>29 (17.5–19.5)</td>
<td>33 (20.6–63)</td>
<td>0.196</td>
</tr>
<tr>
<td>GGT increase (week 4)</td>
<td>72 (44–346)</td>
<td>58 (38–109)</td>
<td>0.014</td>
</tr>
<tr>
<td>Total bilirubin (week 0)</td>
<td>0.39 (0.30–0.54)</td>
<td>0.38 (0.29–0.52)</td>
<td>0.538</td>
</tr>
<tr>
<td>Total bilirubin change (week 4)</td>
<td>–0.06 (–0.18 to 0.07)</td>
<td>–0.11 (–0.19 to –0.01)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

All laboratory results are expressed as median [interquartile range (IQR)]. Units expressed as are as follows: CD4 (cells x 10⁹/L), alanine aminotransferase (ALT) (U/L), γ-glutamyltransferase (GGT) (U/L), total bilirubin (μmol/L). BMI, body mass index; EFV, efavirenz; NVP, nevirapine; OD, once daily; BD, twice daily.

same NNRTI did not have a recurrent rash. However, for those who switched, the NVP OD and BD patients appeared to tolerate EFV better (rash in one of 12 patients) than the EFV patients who switched to NVP (rash in two of three patients). When only EFV was continued in the NVP + EFV arm, seven of 10 patients did not develop recurrent rash.

**Risk factors for NNRTI-related rash**

Factors that may contribute to NNRTI-related rash are explored and shown in Table 3. There were no differences in the gender, mean age and mean BMI between the patients with and without rash. Baseline CDC B, CDC C and low ALT were risk factors for rash but CD4 count was not. An interesting finding was seen after 4 weeks of treatment in that a larger rise in CD4 cell count, ALT and GGT predicted the occurrence of rash. A drop in HIV RNA by less than 2 logs at week 4 also predicted rash. These factors were evaluated for study weeks 2, 8, 16 and 24 and no statistical significant differences were seen in the patients who did and did not have rash.

In the univariate analysis (Table 4), with the EFV arm as the reference group, NVP OD and NVP + EFV treatments were significantly more likely to cause rash. The risk of rash was similar in the EFV and NVP BD arms. Patients with CDC A were more likely to have rash than patients with CDC B and CDC C disease. Gender, BMI and a baseline CD4 cell count greater or less than 250 x 10⁶ cells/L were not associated with the development of rash. Similar to findings in Table 3, a larger rise in CD4 cell count and a smaller drop in HIV RNA after 4 weeks of treatment were risk factors for rash. However, higher ALT was not a risk factor. We further investigated combinations of factors that have been shown by others to be risk factors for hypersensitivity due to NVP: CD4 ≥250 x 10⁶ cells/L, CDC A, female gender, we did not find these to predict rash.

The multivariate analysis (Table 4) confirmed that patients treated with NVP OD and NVP + EFV were at more risk for rash. The rise in CD4 (≥53 cells) and ALT (≥34 U/L), and the HIV RNA drop of less than 2 logs at week 2 were also risk factors. CDC A no longer achieved statistical significance in predicting rash. Interestingly, a higher risk was observed in those with higher BMI and in women with CD4 ≥250 x 10⁶ cells/L.

**Serious adverse events**

There were six patients (2.9%) who developed NNRTI-related serious adverse events, as defined by hospitalization or death. Four were women and five were treated NVP; namely three taking NVP OD and two taking NVP BD. All patients were hospitalized and one died. Two patients had Stevens Johnson syndrome (one each in the NVP OD and NVP BD arms) and three had a serum sickness-like reaction with fever and rash (One each in the NVP OD, NVP BD and EFV arms). One patient with underlying congenital heart disease (ventral septal defect) died of heart failure during hospitalization for rash and
Table 4. Univariate and multivariate analyses of risk factors for non-nucleoside reverse transcriptase inhibitor (NNRTI)-related rash (n = 202).

<table>
<thead>
<tr>
<th>Factors</th>
<th>NNRTI-related rash n (%)</th>
<th>Unadjusted OR (CI)</th>
<th>P value</th>
<th>Adjusted OR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>14 (20.3)</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td>9 (20.5)</td>
<td>1.010 (0.395–2.583)</td>
<td>0.983</td>
<td>1.017 (0.336–3.074)</td>
<td>0.843</td>
</tr>
<tr>
<td>NVP + OD</td>
<td>18 (38.3)</td>
<td>2.438 (1.063–5.596)</td>
<td>0.035</td>
<td>3.081 (1.138–8.495)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>CDC at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>29 (27.4)</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>B and C</td>
<td>36 (32.4)</td>
<td>1.097 (1.052–3.418)</td>
<td>0.033</td>
<td>1.211 (0.506–2.899)</td>
<td>0.701</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (32.4)</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (36.3)</td>
<td>1.185 (0.661–2.125)</td>
<td>0.568</td>
<td>0.611 (0.242–1.542)</td>
<td>0.256</td>
</tr>
<tr>
<td><strong>BMI</strong> (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21.3</td>
<td>40 (39.2)</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>≥21.3</td>
<td>29 (29.6)</td>
<td>1.580 (0.878–2.841)</td>
<td>0.126</td>
<td>2.565 (1.185–5.550)</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>CD4 count at baseline (cells x 10^3/l)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CD4 ≥250</td>
<td>21 (40.4)</td>
<td>1.440 (0.750–2.762)</td>
<td>0.273</td>
<td>0.214 (0.013–2.976)</td>
<td>0.236</td>
</tr>
<tr>
<td>CD4 &lt;500</td>
<td>25 (25.8)</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 increase at wk4</strong> (cells x 10^3/l)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 ≥500</td>
<td>41 (41.8)</td>
<td>2.072 (1.129–3.80)</td>
<td>0.018</td>
<td>2.160 (1.016–4.594)</td>
<td>0.034</td>
</tr>
<tr>
<td>CD4 &lt;500</td>
<td>14 (22.6)</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Log HIV RNA change at week 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−2.55 to −2.04</td>
<td>21 (33.3)</td>
<td>1.714 (0.776–3.789)</td>
<td>0.182</td>
<td>2.171 (0.782–6.025)</td>
<td>0.156</td>
</tr>
<tr>
<td>&lt; −2.04</td>
<td>27 (43.3)</td>
<td>2.723 (1.247–5.944)</td>
<td>0.031</td>
<td>3.644 (1.359–9.914)</td>
<td>0.011</td>
</tr>
<tr>
<td>ALT at week4 (U/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT ≥34</td>
<td>29 (29.9)</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>ALT ≥34</td>
<td>30 (36.4)</td>
<td>1.461 (0.806–2.646)</td>
<td>0.211</td>
<td>2.437 (1.082–4.97)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>CD4 ≥250 + female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT ≥34</td>
<td>18 (42.9)</td>
<td>1.603 (0.799–3.214)</td>
<td>0.183</td>
<td>1.374 (0.822–2.248)</td>
<td>0.184</td>
</tr>
<tr>
<td>ALT ≥34</td>
<td>8 (15.3)</td>
<td>2.361 (0.818–6.810)</td>
<td>0.112</td>
<td>0.121 (0.002–6.054)</td>
<td>0.290</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; EFV, efavirenz; NVP, nevirapine; OD, once daily; BD, twice daily; CDC, Centers for Disease Control and Prevention; BMI, body mass index; ALT, alanine aminotransferase. *The median values from 202 patients were used.
severe liver toxicity from NVP. All the other patients on NVP except one were switched to EFV and did not have recurrent rash. The single patient on EFV did well after having EFV temporarily stopped.

Discussion

The overall incidence of rash in our patient population was high in comparison with most reports [1,4,5,8]. Treatments with NVP + EFV and NVP OD were associated with the highest risk for rash with incidences of 67 and 38%, respectively. The former is the highest incidence ever reported to our knowledge. The latter is closer to the incidence when NVP was used without the 2-week half-dose lead-in period even though all our patients had a lead-in dosing period [2,9]. Both the EFV and NVP BD treatments had a similar incidence of rash of 20% which was not higher than most reported cohorts [1,3,10,11].

Most occurrences of rash were mild and required treatment with antihistamines only. There were more patients who had urticaria from NVP + EFV, otherwise, the severity did not significantly differ between treatment arms. Nevertheless, we were surprised that one-third of the patients with rash in the EFV and the NVP BD arms had a grade III rash. This poses some concerns as these two regimens are the most widely used. Hepatotoxicity (ALT five or more times the upper normal limits) was seen in 16% of patients with rash and only in those on NVP OD and NVP + EFV. Similar to other reports, serious adverse events were uncommon in our patients [3,12–14].

We evaluated the decisions taken at the time of development of rash and found that most patients continued on the same regimen and did well. Nevertheless, we found a trend towards more patients with NVP-related rash being switched to EFV than vice versa. This is probably due to physician’s beliefs that EFV-related rash is generally less common. There is little guidance on what to do when such events occur [3]. We found that only one of 12 patients who switched from NVP to EFV had rash whereas switching from EFV to NVP resulted in rash in two of three patients. Confirmation of this trend requires a larger cohort.

Treatments with NVP + EFV and NVP OD were risk factors for rash development. In the multivariate analysis in which all factors including type of treatments were controlled, we found that having BMI above the median value (21.3 kg/m²) posed a greater risk for rash from NNRTI. Persons of small stature such as Thais may be predisposed to having high drug levels during standard dosing of antiretroviral drugs. We have shown Thais patients to have higher levels of ritonavir-boosted saquinavir than Caucasians and Blacks [15,16]. Even if this holds true for NNRTI, it is still unknown whether higher NNRTI plasma concentrations correlate with rash occurrence [9,17]. The fact that our patients with higher BMI were at more risk for rash contradicts this.

An increased incidence and severity of NVP hypersensitivity in women, especially during pregnancy, has been reported (Viramune package insert; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA) [10,18,19]. Women also have a higher incidence of rash from other antiretroviral drugs [20]. In our study, women with baseline CD4 cell count ≥250 x 10⁶ cells/l were more likely to have rash, and four of six patients with serious adverse events were women. Whether this is due to a hormonal effect or gender-related differences in cytochrome P450 metabolism or body size is not known. Previous reports have suggested that persons with a higher baseline CD4 cell count are likely to develop rash from NVP [8,10,21]. In our analysis, a CD4 cell count ≥250 x 10⁶ cells/l was associated with a higher risk but only in women. However, persons with CDC A were more likely to have rash, and patients in the EFV and the NVP BD arms who overall had a much lower baseline CD4 cell count and more advanced HIV disease developed less rash. Essentially, the evidence points towards a greater risk of NNRTI-related rash in persons with better preserved immune function.

The mechanism of NNRTI-related rash is unclear. Current animal and human data suggest a cell-mediated immune mechanism [3,22]. The lower risk of rash in patients with lower CD4 cell count is consistent with other reports suggesting a mechanism of immune tolerance in those with a higher degree of immunodeficiency [10,20,21]. Our patients who had a rapid CD4 recovery were at a higher risk for developing rash. This is similar to those who are at risk for immune reconstitution syndrome [23]. We hypothesize that the rapid reversal of immune dysfunction caused an immune response towards NNRTI antigens and manifested itself in rash and elevated ALT.

Ethnicity has also been reported to be a risk factor, although this remains controversial. A higher incidence of NVP-associated rash was reported in Hispanics [24]. In a small cohort of Chinese, five of eight (62.5%) had rash from NVP [6]. Our patients had a higher incidence of NNRTI-related rash only if NVP OD and NVP + EFV were used. The importance of histocompatibility leukocyte antigens (HLA) in the pathogenesis of hypersensitivity has been demonstrated for abacavir and other drugs [25,26]. Further studies that carefully examine HLA and relevant epitopes would help determine the underlying mechanisms of NNRTI hypersensitivity.

In conclusion, our population had a higher incidence of NNRTI-related rash than most published cohorts did when treated with NVP OD and NVP + EFV but not
with NVP BD or EFV alone. If used, NVP BD did not cause more rash than EFV. Women with CD4 cell count ≥ 250 × 10^3 cells/l, and those with baseline CDC A and higher BMI were more likely to develop rash. A rise in CD4 cell count and transaminases 4 weeks after treatment were risk factors for NNRTI-related rash.

**Acknowledgement**

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**References**
