

Prednisolone does not prevent hypersensitivity reactions in antiretroviral drug regimens containing abacavir with or without nevirapine

Ferdinand W.N.M. Wit, Robin Wood^a, Andrzej Horban^b,
Marek Beniowski^c, Reinhold E. Schmidt^d, Glenda Gray^e,
Adriano Lazzarin^f, Alain Lafeuillade^g, Dominic Paes^h, Hilde Carlierⁱ,
Liesbeth van Weert, Corry de Vries, Remko van Leeuwen and
Joep M.A. Lange

Objectives: To determine the effect of adjuvant prednisolone use on the development of abacavir (ABC)- and nevirapine (NVP)-associated hypersensitivity reactions (HSR).

Methods: Randomized open-label study in antiretroviral-naive adult HIV-1 infected patients using a factorial design in which NVP and/or hydroxyurea (HU) and/or prednisolone are added to a regimen of ABC, zidovudine and lamivudine. Prednisolone (40 mg once daily) was added for the first 2 weeks of treatment. As it was difficult to distinguish ABC-associated HSR from NVP-associated HSR, these events were treated as a composite endpoint. The odds ratio (OR) of developing HSR for prednisolone-use was calculated with and without stratification by NVP and/or HU. Logistic regression was performed to identify risk factors for developing HSR.

Results: Of the 229 patients 115 were randomized to prednisolone and 114 to no-prednisolone; 19 (17%) and 11 (10%) patients, respectively, developed HSR. The expected prevention of HSR by prednisolone use was not observed. In fact use of prednisolone showed an increased risk for HSR although this did not reach statistical significance [OR, 1.82; 95% confidence interval (CI), 0.82–4.03]. There was a higher incidence of HSR in the NVP group than in the non-NVP group (20% versus 6%; $P = 0.002$). An additional risk factor identified in a multivariate logistic model was a high baseline CD4 cell count (OR, 1.26 per 100×10^6 cells/l increase; 95% CI, 1.06–1.51).

Conclusions: The simultaneous start of ABC and NVP in first-line antiretroviral regimens should be avoided because of a high (20%) incidence of HSR. Short-term therapy with prednisolone did not prevent HSR in patients using ABC with or without NVP.

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From the International Antiviral Therapy Evaluation Center, Department of Human Retrovirology and Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands, the ^aDepartment of Medicine, Somerset Hospital, Cape Town, South Africa, ^bCentrum Diagnostyki i Terapii, Warsaw, ^cOceroдек Diagnostyki i Terapii AIDS, Szpital Specjalistyczny, Chorzów, Poland, ^dMedizinische Hochschule Hannover, Zentrum Innere Medizin, Department of Clinical Immunology, Hannover, Germany, ^eChris Hani Baragwanath Hospital, Perinatal HIV Research Unit, Johannesburg, South Africa, ^fClinica di Malattie Infettive, San Raffaele Scientific Institute, Milano, Italy, ^gHôpital Chalucet, Unité Infectiologie, Toulon, France, ^hAntivirals, GlaxoSmithKline Research & Development, Greenford, Middlesex, UK, and ⁱBoehringer Ingelheim Pharmaceuticals, Brussels, Belgium.

Requests for reprints to J. M. A. Lange, International Antiviral Therapy Evaluation Centre, room T0-120, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

E-mail: j.lange@amc.uva.nl

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Introduction

Antiretroviral therapy is often complicated by the occurrence of drug toxicity. Hypersensitivity reactions (HSR), which may include rash alone, are early side-effects of several antiretroviral drugs including all currently licensed non-nucleoside reverse transcriptase inhibitors [nevirapine (NVP), efavirenz and delavirdine], the nucleoside analogue reverse transcriptase inhibitor abacavir (ABC), and the protease inhibitor amprenavir [1]. Most HSR where rash is accompanied by other systemic symptoms usually occur within the first 6 weeks of treatment, are often dose limiting and can be life threatening [2–7].

Antiretroviral combination regimens containing NVP result in durable suppression of HIV-1 replication in therapy-naïve patients [8]. Rashes are the most frequent side-effect observed with NVP, and typically manifest themselves as maculopapular or urticarial eruptions with or without constitutional symptoms such as fever, arthralgia and myalgia. In early trials, when patients were started on the full dose of 200 mg NVP twice daily, incidences of rash as high as 48% were found [9]. Because NVP induces its own metabolism in the liver, patients nowadays are treated with 200 mg once daily during the first 2 weeks of dosing. This lead-in period results in an incidence of rash of 9–32% in clinical trials, leading to the discontinuation of the drug in 6–7% of patients [8,10–13]. Severe HSR like Stevens–Johnson syndrome and toxic epidermal necrolysis occur in 0.3–1% of patients [2–4]. NVP-associated rashes rarely occur in the first 7 days of treatment. Some data suggest that NVP-associated rashes may occur more often in women [14]. Severe hepatotoxicity occurs in a small number of patients in the first weeks after starting NVP [15,16]. It is unknown whether the hepatotoxicity and skin rashes share the same aetiology.

ABC is a guanosine analogue reverse transcriptase inhibitor with potent activity against HIV-1. Resistance of HIV-1 to ABC develops slowly. Its clinical value in antiretroviral combination regimens has been established in several trials [17,18]. The most frequent symptoms of ABC-associated HSR are rash, fever, and gastrointestinal symptoms. Other symptoms are malaise, fatigue, myalgia, arthralgia, and paraesthesiae. Less often respiratory symptoms such as cough and dyspnoea occur. HSR occur in about 3–7% of patients starting ABC [17–19]. Life-threatening reactions can occur, especially when patients who developed a HSR are rechallenged with ABC or continue dosing in the face of worsening symptoms, including hypotension and organ failure [5–7].

No information is available on the frequency and severity of HSRs when NVP and ABC are simultaneously introduced in the antiretroviral regimen of

HIV-1-infected patients. In clinical practice it is often difficult to make a reliable distinction between ABC-associated HSR and NVP-associated rashes due to overlapping signs and symptoms. This compromises the management of these patients. First of all, if no reliable distinction between the two types of HSR can be made, both ABC and NVP may need to be permanently stopped. Furthermore, if a HSR is attributed to the wrong drug and the use of the other drug is continued, this can cause life-threatening complications with NVP (e.g., Stevens–Johnson syndrome, toxic epidermal necrolysis), or ABC (severe hypotension with organ failure) [2–7].

Most mild rashes and HSR resolve spontaneously without specific treatment. For ABC and NVP, clinical management guidelines with detailed instructions when to discontinue therapy have been issued [20]. Antipyretics and antipruritics are widely used for the symptomatic treatment of mild rashes, but their effectiveness has not been studied. Adjunctive corticosteroid therapy for *Pneumocystis carinii* pneumonia in HIV-1-infected patients has been found to lower the incidence of cotrimoxazole associated HSR [21–24]. In analogy to these trials, several studies investigated the use of prednisolone for the prevention of NVP-associated HSR. Two studies found a lower risk of NVP-associated HSR [25–27], one study found no beneficial effect of adjuvant prednisolone use [28], and one study even found a higher incidence of NVP-associated HSR [29]. The use of prednisolone for the prevention of ABC-associated HSR has not been studied previously.

Materials and methods

Study design

The Charm Study is an ongoing randomized open-label study designed to evaluate the effect of adding hydroxyurea (HU) and/or NVP to nucleoside-based antiretroviral combination therapy, in terms of efficacy and tolerance in antiretroviral naïve HIV-1 infected subjects. A secondary objective of the Charm study (and the primary objective of this paper) is to explore the effect of short-term immunosuppressive therapy with prednisolone for prevention of ABC- and NVP-associated HSR. Enrolment of patients into the study is complete, and all patients have a potential follow-up of at least 6 weeks.

This open-label study has a factorial design (Fig. 1). All patients who entered the study receive zidovudine (ZDV), lamivudine (3TC) and ABC as the backbone of their antiretroviral regimen; ZDV and 3TC are combined when possible using Combivir. In a first randomization, patients are allocated to addition of NVP. Secondly patients are randomized to addition of

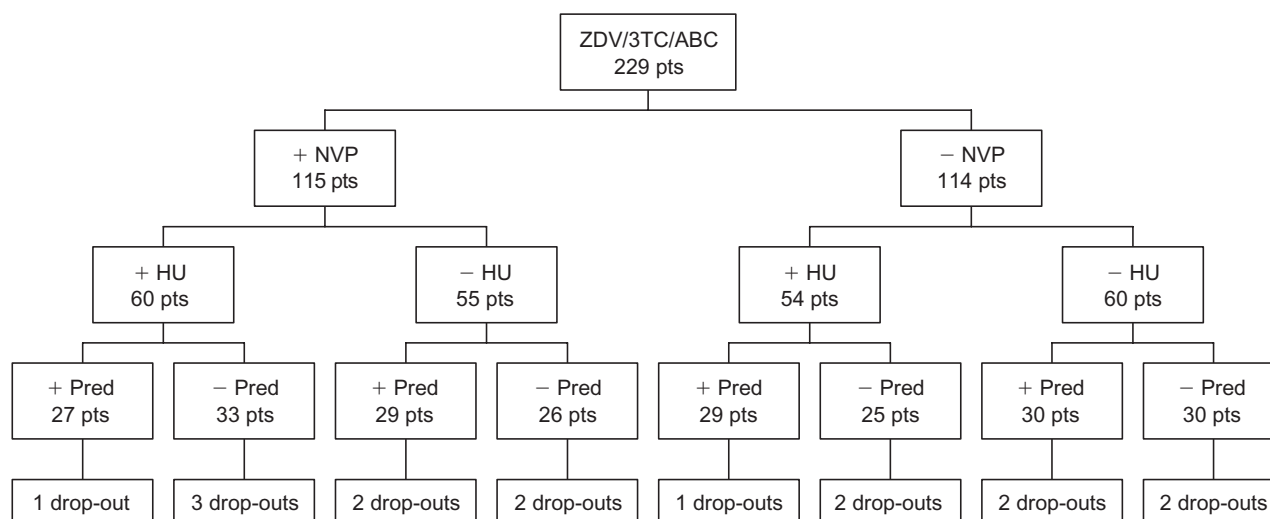


Fig. 1. Distribution of patients after randomization. Number of allocated patients and number of study discontinuations per study arm. Pred, prednisolone; pts, number of patients.

HU. Finally, there is a third randomization to addition of prednisolone during the first 2 weeks of treatment with the intent to prevent HSR within the first weeks of NVP and ABC treatment. All study drugs, except prednisolone, are dosed twice daily (b.i.d.). The dosing of the study drugs is: ZDV 300 mg b.i.d., 3TC 150 mg b.i.d., ABC 300 mg b.i.d., HU 500 mg b.i.d., NVP 200 mg once daily for 14 days, from day 15 onward 200 mg b.i.d., prednisolone 40 mg once daily during the first 14 days. During the first 6 weeks of treatment, the patients are evaluated every 2 weeks.

As clinical symptoms of NVP- and ABC-associated HSR overlap, a clear-cut distinction between the two can not be made in a reliable way. Furthermore, none of the study arms consisted of the use of NVP without ABC, making adequate comparisons between NVP- and ABC-associated HSR impossible. Therefore, these events were treated as a composite endpoint. In this text NVP-associated rashes of any grade, whether or not accompanied by clinical symptoms, and ABC-associated HSR will all be referred to as HSR.

Patient population

Patients were recruited in 21 centres in South Africa, Poland, Germany, France, the UK, Italy, Portugal and Canada from August 1999 until July 2000. For inclusion into the study patients had to be HIV-1 infected adults, who were antiretroviral therapy naive, with plasma HIV-1 RNA levels > 5000 copies/ml. There were no restrictions on the stage of HIV-1 infection or CD4 T-cell counts.

Statistical analysis

The analysis included all randomized patients. Time of analysis was 6 weeks after the start of treatment. Patients who discontinued study treatment early re-

mained in follow-up whenever possible. Data on these early terminators, as far as they could be collected, were included in this intention-to-treat safety analysis. Baseline characteristics were summarized by study group: age, sex, weight, body mass index, CD4 T-cell count, plasma HIV-1 RNA load, Centers for Disease Control and Prevention (CDC)-class, risk group for HIV-1 transmission and geographic region.

To make optimal use of the factorial study design and to enhance the power of statistical tests, the comparison in the analysis was based on study groups, categorized as follows: NVP use/non-use, HU use/non-use and prednisolone use/non-use. These groups have been denoted in this paper as 'study group' as opposed to 'study arm' which reflects the actual combination of all study drugs taken.

All HSR that, according to the clinical investigator, were possibly, probably or certainly related to either ABC or NVP were taken into account in this analysis. The number of HSR by study group and study arm were tabulated, as well as the reported type of rash and the frequency of clinical symptoms associated with the HSR. Of all patients who developed HSR the changes in allocated study medication after occurrence was described.

The effect of prednisolone use was measured by calculating the incidence of HSR as odds ratios (OR) of developing such an event comparing prednisolone use and non-use, using the Mantel-Haenszel analysis stratified for the use of NVP and HU. Only when no interaction between prednisolone use and use of other study medication was found, was a pooled estimate for the development of HSR presented. Furthermore, the median time to these events was compared for the two

study groups using ANOVA. Survival analysis using Kaplan–Meier estimates was presented and tested with a log-rank test.

A logistic regression model was used to examine possible risk factors for the development of HSR. Variables that were statistically significantly associated with HSR in the univariate analysis were used in the multivariate analysis. In addition, the variables sex, age and prednisolone use were fitted in the model, as these variables have been associated with HSR in previous studies [14,25,27,30]. The estimates of the variables which produce the best fitted multivariate model, as judged by the lowest Akaike's Information Criterion (AIC) score, were presented.

The level of significance was set at 5% throughout the analyses. All reported *P*-values are two-sided. Data were analysed with SAS version 8.0 (SAS Institute, Cary, North Carolina, USA).

Ethical review

The ethical review committees of all participating centres approved the protocol. All patients gave written informed consent.

Results

Baseline

The number of allocated patients in the randomization is presented in Fig. 1. Table 1 summarizes the baseline

Table 1. Baseline characteristics of the study population.

Characteristic	
Number of patients	229
Age (years), [mean (SD)]	34.8 (9.7)
Male sex (%)	70.7
Weight (kg) [mean (SD)]	67.7 (12.5)
CD4 cell count ($\times 10^6/l$) [median (IQR)]	269 (122–383)
HIV-1 RNA (\log_{10}) [median (IQR)]	4.61 (4.33–5.30)
BMI (kg/m^2) [mean (SD)]	23.1 (3.5)
CDC class (%)	
A	52.0
B	29.3
C	18.7
Risk group (%)	
MSM	32.4
Heterosexual	48.6
Injecting drug use	15.4
Blood products	0.0
Other risk factors	0.5
Unknown	3.1
Region (%)	
Western Europe	37.5
Eastern Europe	25.8
South Africa	36.7

IQR, Interquartile range; CDC, Centers for Disease Control and Prevention; MSM, men who have sex with men.

characteristics of all patients. The different study groups were equally balanced (data not shown).

Study discontinuations

Of the 229 randomized subjects, 15 discontinued the study before 6 weeks of follow-up. Seven of these 15 dropped out before they started randomized treatment, and one of these seven patients died of infectious meningitis. One other person died of a mesenteric artery infarct after 17 days of treatment with the nucleoside analogues backbone + NVP. Four patients were lost to follow-up after 14 (backbone + HU + NVP), 15 (backbone + HU + prednisolone), 16 (backbone + HU), and 29 days (backbone). An additional three patients withdrew informed consent after 10 (backbone + HU + NVP + prednisolone), 28 (backbone + HU + NVP), and 41 days (backbone + NVP + prednisolone), respectively. The 15 subjects were equally distributed over the different study groups (see Fig. 1).

HSR

Thirty patients developed HSR as summarized by study arm in Table 2 and study group in Table 3. As expected from the known relationship between the administration of NVP and HSR, there was a statistically significantly higher occurrence of HSR in the NVP group than the non-NVP group (20% versus 6%; $P = 0.002$). A higher incidence for HSR was seen for the prednisolone group than for the non-prednisolone group, but the difference was not statistically significant (17% versus 10%; $P = 0.12$). The study lacks power to calculate proper statistical measures when the events are divided over eight study arms.

For all rashes the clinical presentation and severity were recorded using the ACTG toxicity grading scale [31]. Skin rash was the most frequent symptom of the HSR, occurring in 21 out of 30 cases. One rash was classified as 'erythema', 12 rashes as 'diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation \pm pruritis without any additional constitutional

Table 2. Summary of the number of patients with hypersensitivity reactions (HSR) by study arm.

Study arm	Patients per study arm (n)	HSR [n (%)]
BB	30	2 (7%)
BB + Pred	30	2 (7%)
BB + NVP	26	4 (15%)
BB + NVP + HU	33	5 (15%)
BB + NVP + Pred	29	7 (24%)
BB + NVP + HU + Pred	27	7 (26%)
BB + HU	25	0 (0%)
BB + HU + Pred	29	3 (10%)

BB, Backbone (zidovudine + lamivudine + abacavir); Pred, prednisolone; NVP, nevirapine; HU, hydroxyurea.

Table 3. Summary of the number of patients with hypersensitivity reactions (HSR) by study group.

Study group	Patients per study group (n)	HSR [n (%; 95% CI)]	P
NVP –	114	7 (6%; 3–12%)	0.002
NVP +	115	23 (20%; 13–27%)	
HU –	115	15 (13%; 7–20%)	0.98
HU +	114	15 (13%; 7–20%)	
Prednisolone –	114	11 (10%; 4–15%)	0.12
Prednisolone +	115	19 (17%; 10–24%)	

NVP, Nevirapine; HU, hydroxyurea; CI, confidence interval

findings', five as 'extensive erythematous or maculopapular rash or moist desquamation' and one as 'diffuse rash and serum sickness-like reaction'. No Stevens–Johnson syndrome, toxic epidermal necrolysis, or anaphylactic reactions were reported. Only two patients had mucosal lesions, these patients were taking backbone + NVP + HU and backbone + NVP + HU + prednisolone. For two patients no data were available about the type of rash. There were no significant differences in type of rash between the study groups. Other frequently occurring symptoms associated with HSR were fever (n = 14), fatigue (n = 14), headache (n = 12), malaise (n = 12), pruritis (n = 11), vomiting (n = 10), myalgia (n = 9), and nausea (n = 9). There were no significant differences between the study groups. The nine HSR without skin rash typically presented as fever, headache, malaise, and gastrointestinal symptoms. One case of toxic hepatitis occurred in a patient using backbone + NVP.

In 25 of the 30 patients with HSR the use of study medication was discontinued for at least several days. For all but six patients ABC was stopped shortly after the occurrence of the event. Five of these six cases were thought to be related to the use of NVP according to the investigators, one was a possible ABC-associated HSR that resolved after six days. The study protocol strongly advised against ABC rechallenges. None of the patients who discontinued ABC

were rechallenged with ABC after the HSR had resolved.

Of the 23 NVP patients with HSR all but five stopped NVP. Two of these five cases were thought to be unrelated to the use of NVP, but instead to be associated with ABC, and so ABC was stopped. The other three cases were related to NVP use according to the investigators and were treated with additional antihistamines and resolved after a few days. In the case of mild rashes without constitutional symptoms the protocol allowed rechallenges with NVP at the discretion of the investigator. Of the 18 patients who discontinued NVP, eight patients were safely rechallenged with NVP after the HSR had resolved. Desensitization procedures were not used.

Prednisolone effect

As shown in Table 4, the use of prednisolone was not associated with a decrease in the incidence of HSR. In fact an increase was shown although this difference was not statistically significant [OR, 1.82; 95% confidence interval (CI), 0.82–4.03]. As no interaction between prednisolone and the other two study medications was found (data not shown), OR of HSR in prednisolone users and non-users were pooled.

In Fig. 2 the Kaplan–Meier estimate of the time to HSR is depicted for patients who used prednisolone and for those who did not. The median lag between the start of antiretroviral treatment and an occurrence of a HSR was 14 (95% CI, 12–21) and 7 (95% CI, 5–27) days in the prednisolone group and non-prednisolone group, respectively ($P = 0.089$). Until day 14, the incidence of HSR in the prednisolone group was lower than that in the non-prednisolone group. However, after day 14 an opposite effect was seen. For the complete period of 6 weeks no difference in cumulative frequency was shown (log-rank test $P = 0.15$).

Of all possible risk factors that might explain the occurrence of HSR only concomitant use of NVP and CD4 cell count contributed significantly to the multivariate logistic model (Table 5). Inclusion of prednisolone

Table 4. Percentage of subjects with hypersensitivity reactions (HSR) comparing prednisolone use/non-use. Odds ratios (OR) with 95% confidence intervals (CI) for the use of prednisolone stratified by study group and pooled.

Stratum	Prednisolone non-use		Prednisolone use		Stratum OR	95% CI	P	Pooled OR ^a	Pooled 95% CI
	Patients (n)	HSR (%)	Patients (n)	HSR (%)					
Overall	114	10.1	115	17.0	1.82	0.82–4.03	0.14		
NVP +	59	16.1	56	25.5	1.78	0.70–4.55	0.22	1.93	0.85–4.37
NVP –	55	3.8	59	8.8	2.45	0.45–13.21	0.28		
HU +	58	9.1	56	17.9	2.17	0.69–6.84	0.18	1.82	0.82–4.03
HU –	56	11.1	59	16.1	1.53	0.51–4.64	0.45		
NVP/HU +	33	16.1	27	25.9	1.82	0.50–6.59	0.36	1.91	0.86–4.28
NVP/HU –	81	7.7	88	14.1	1.97	0.70–5.54	0.19		

^aPooled estimate presented when no statistical heterogeneity between stratum-specific OR was present. NVP, Nevirapine; HU, hydroxyurea.

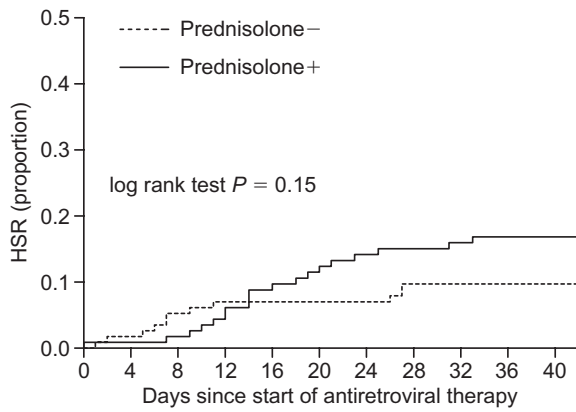


Fig. 2. Kaplan–Meier estimate of the time to HSR.

lone use in this model resulted in a significant improvement of the AIC score. All other parameters studied (sex, age, plasma HIV-1 RNA levels at baseline, CDC class, geographic region and HU use) were not statistically significantly associated with HSR. As all patients were exposed to ABC, ABC could not be studied as an independent variable.

Discussion

Because the events are divided over eight study arms, this study lacks power to calculate proper statistical measures. However, because the study has a factorial design, the power of the statistical test could be enhanced by basing the comparisons on study groups instead of study arms.

When systemic symptoms or internal organ involvement accompanies rash, it is not possible to make a reliable distinction between ABC- and NVP-associated HSR. Therefore both events were treated as a compo-

site endpoint. The concurrent use of ABC and NVP in this study resulted in a significantly higher risk for developing a HSR compared to other study groups in which the use of ABC was not combined with NVP: 20% versus 6%, respectively ($P = 0.002$). Currently, it is not known whether there is any synergetic effect between NVP and ABC on HSR. If it is assumed that the effects of NVP and ABC are strictly additive, the incidence of HSR attributable to the use of NVP would be $20 - 6 = 14\%$. The incidences of HSR of 6% for ABC and 14% for NVP are not dissimilar to incidences reported in the literature [8,10–13,18,19]. Furthermore, the open-label design of the study may have introduced a reporting bias, leading to an increased incidence of HSR.

The results of this study do not support the hypothesis that adjuvant prednisolone use has a preventive effect on the development of ABC- and NVP-associated HSR. Instead, patients using prednisolone even had a slightly higher incidence of HSR than patients not using prednisolone, 17% versus 10%, respectively ($P = 0.12$). However, use of prednisolone appears to delay the occurrence of HSR. A similar phenomenon has been observed with the use of adjuvant corticosteroids in the treatment of severe *Pneumocystis carinii* pneumonia with high-dose co-trimoxazole [22]. It might be argued that the discontinuation of prednisolone after 14 days, just at the moment when the dose of NVP is escalated from 200 mg once daily to 200 mg b.i.d., is too early. However, when prednisolone was discontinued at day 14 the incidence of HSR in the prednisolone group had already reached the same incidence as in the group of patients not using prednisolone. Thus it is unlikely that extending the use of prednisolone would have resulted in a lower incidence of HSR.

As shown previously [30], we found that a higher baseline CD4 T-cell count was associated with a higher

Table 5. Logistic regression analysis of predictors for hypersensitivity reactions (HSR).

Parameter	Univariate analysis			Multivariate analysis ^a		
	OR ^b	95% CI	P	OR	95% CI	P
Females compared to males	0.44	0.16–1.21	0.11			
Age ^c	0.99	0.95–1.03	0.56			
Baseline CD4 count ^d	1.24	1.05–1.47	0.011	1.26	1.06–1.51	0.010
Baseline HIV-1 RNA load ^e	0.94	0.53–1.68	0.84			
CDC class B ^f	0.63	0.24–1.71	0.37			
CDC class C ^f	1.47	0.58–3.73	0.42			
Eastern Europe ^g	1.11	0.44–2.83	0.83			
South Africa ^g	0.74	0.29–1.86	0.52			
Nevirapine use	3.82	1.57–9.31	0.003	4.75	1.79–12.65	0.002
Hydroxyurea use	1.01	0.47–2.18	0.98			
Prednisolone use	1.85	0.84–4.10	0.13	2.14	0.90–5.07	0.084

^aTwo events and data on eight patients missing due to incomplete data. ^bOdds ratio (OR) using no hypersensitivity reaction as baseline. ^cPer year increase. ^dPer 100×10^6 cells/l increase. ^ePer \log_{10} increase. ^fCompared to Centers of Disease Control and Prevention class A. ^gCompared to Western Europe; CI, Confidence interval.

incidence of HSR. In our study, females had a lower risk of HSR. Although this difference did not reach statistical significance, our results contradict previous findings [14,30].

We conclude that the simultaneous start of ABC and NVP in a first-line antiretroviral regimen leads to a high (20%) incidence of HSR. Simultaneous introduction of ABC and NVP into the antiretroviral regimen of HIV-1-infected patients should be avoided whenever possible, because of difficulties in distinguishing the reactions caused by these two drugs. The use of prednisolone did not protect against ABC- and NVP-associated HSR and should not be used prophylactically with these antiretroviral agents.

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