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Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy.

Short title: Risk factors for nevirapine toxicity.

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## Introduction

Nevirapine is frequently used as part of combination antiretroviral therapy (cART) regimens, and is currently listed as one of the alternative options for cART in treatment naïve patients [1]. Nevirapine may also be used in patients with prior cART experience for example to minimize diarrhea or to reduce cardiovascular risks associated with protease inhibitors, to avoid the neuropsychiatric side effects of efavirenz or to simplify the treatment regimen. However, nevirapine is occasionally associated with severe adverse events, typically hypersensitivity reactions that usually occur within the first 18 weeks of treatment (Viramune package insert). Six to seven percent of patients discontinue the use of nevirapine because of clinically significant hypersensitivity reactions [2-5]. Severe, life threatening and even fatal cases of hepatotoxicity [6, 7] and/or skin rashes [8-10] have occurred in patients taking nevirapine. HIV-1 seronegative adults using nevirapine for post-exposure prophylaxis appear at particularly high risk of life threatening hepatotoxicity [11]. Among HIV positive patients, the risk of hypersensitivity reactions is highest in patients with higher CD4 counts, with a lower CD4 threshold observed in women. Asians may also be at an increased risk [12]. This has led to the recommendation not to use nevirapine in HIV-1 infected patients starting nevirapine at higher CD4 counts (>400/mm<sup>3</sup> in males, >250/mm<sup>3</sup> in females) [13], unless the benefits clearly outweigh the risks. This recommendation is based on data from clinical trials in treatment-naïve HIV-1 infected patients. It is unclear, however, whether the risk of potentially fatal toxicities is increased similarly in other patient groups starting nevirapine-based cART (NVPc), for instance treatment-experienced patients starting NVPc for the first time with high CD4 counts. A recent study suggested that the risk of treatment-limiting toxicities for treatment-experienced patients who initiate NVPc with high CD4 counts may be similar to the risk in treatment-naïve patients with low CD4 counts [14], while another study suggested that antiretroviral-experienced patients with low nadir CD4 counts and an undetectable viral load had a similar risk for HSR compared to antiretroviral-naïve patients who started nevirapine with low CD4 counts [15]. Although these were large studies, the number of females included was relatively small. The risk of potentially fatal toxicities in treatment-experienced patients compared to treatment-naïve patients cannot easily be studied within the

setting of a randomized clinical trial. This collaboration of 7 established cohort studies therefore aimed to retrospectively evaluate the safety of nevirapine-based cART in treatment-experienced patients with high CD4 counts.

## Methods

### Participants

Patients from the ATHENA (n=3,906), British Columbia (n=367), EuroSIDA (n=1,035, Hospital Clinic Barcelona (n=750), Southern Alberta (n=61), Swiss HIV (n=795) and UK CHIC (n=3,272) cohort studies were included. [16-22]. Information on socio-demographic characteristics, reasons for discontinuation of antiretroviral drugs where available, cause of death, laboratory markers and treatment history were collected from each cohort. We included all patients over 16 years of age, who started nevirapine-based cART (defined as nevirapine plus 2 nucleosides/nucleotides) after 1 January 1998 with CD4 and viral load measurements in the 6 months before starting cART. Women who started nevirapine-based cART during pregnancy were excluded from the analyses. Duplicate patients, i.e. those who were included as part of a national cohort and also as part of EuroSIDA were included only once.

### Endpoints

We identified all patients who 1) discontinued nevirapine due to a hypersensitivity reaction (skin rash and/or hepatotoxicity) in cohorts with detailed information on reasons for discontinuation and 2) discontinued nevirapine due to all-cause toxicity and/or patient or physician choice. If a patient stopped another antiretroviral drug at the same time as nevirapine, the reported reasons for discontinuation of these drugs were also considered to apply to nevirapine. Some cohorts could provide the date of discontinuation of antiretroviral drugs, but not specific reasons for these discontinuations. From a total of 10,186 patients, 5269 patients discontinued nevirapine and the reason for discontinuation was unavailable for 1,645 patients (31.2%). Percentages varied per cohort: 111 out of 193 patients (57.5%) from British Columbia discontinued due to unknown reasons, for Barcelona this rate was 44/428 (10.3%), for EuroSIDA 102/702 (14.5%), Swiss HIV Cohort Study 28/482 (5.8%), Southern Alberta 0/41 (0%), UK CHIC 1,287/1,825 (70.5%) and Athena 73/1,539 (4.7%). For 5 cohorts (Barcelona, EuroSIDA, Swiss, Southern Alberta and Athena, n=6,547), specific information regarding reasons for discontinuation of antiretroviral therapy, including hypersensitivity reactions (skin rash and/or hepatotoxicity) was collected. By using hypersensitivity reactions as an endpoint in these 5 cohorts we may underestimate the occurrence of HSR in this population due to missing reasons for discontinuation or misclassification. To ensure we did not miss any treatment limiting toxicities associated with nevirapine we performed an additional sensitivity analysis considering discontinuations due to all treatment-limiting toxicities associated with nevirapine and/or patient or physician choice at any time and within 18 weeks of starting nevirapine. Toxicities occurring more than 18 weeks after starting cART are more likely to arise from other factors, for instance from the nucleosides/nucleotides backbone that are used together with nevirapine

For missing reasons for discontinuation, a standardized definition of discontinuation due to toxicity was used which takes the viral load at the time of discontinuation into account (C Sabin, personal communication). Discontinuation with viral loads below 1000 cp/ml are not likely because of virological failure. Using this definition, any discontinuation within the first 3 months of starting nevirapine was regarded as discontinuation due to all cause toxicity or patient/physician choice, as well as discontinuations in month 4-6 with a pre-discontinuation viral load <1000 cp/ml or no viral load available prior to the discontinuation of nevirapine.

## Definitions

Chronic hepatitis C was defined as a detectable plasma HCV-RNA, or in case HCV-RNA was missing presence of HCV-antibodies. Chronic hepatitis B was defined as positive hepatitis B surface antigen, positive core antigen or positive plasma HBV-DNA. Detectable HIV viremia was defined as viral load  $\geq 400$  cp/ml.

## Statistical analyses

The CD4 count at the start of nevirapine-based cART was classified as high ( $\geq 400$  cells/mm<sup>3</sup> in males and  $\geq 250$  cells/mm<sup>3</sup> in females) or low. Patients were further classified according to prior antiretroviral treatment experience and viral load ( $< 400$  vs  $> 400$  cp/ml) at starting NVPc. The proportions of patients discontinuing NVP therapy because of hypersensitivity reactions or all-cause toxicity and/or patient or physician's choice (TOXPC) were compared between patient groups using the chi squared test. Cox proportional hazards regression models were used to compare time to and risk factors for discontinuation of nevirapine in these patient groups due to hypersensitivity reactions (in patients where specific reasons for discontinuation were available) and TOXPC with missing reasons for discontinuation imputed using the methods described above.

All models were stratified by cohort. Individuals were followed from date of start of NVPc to the date of discontinuation of nevirapine, loss to follow up, death or 1 February 2008, whichever occurred first. Potential risk factors that were investigated included demographic factors (age, sex, HIV transmission category and ethnic group), nadir CD4 count, CD4 count and plasma HIV-1 RNA levels at the start of NVPc, calendar year of starting NVPc, AIDS diagnosis prior to starting nevirapine, chronic hepatitis virus co-infections, exposure to various combinations of nucleosides/nucleotides concurrently used with nevirapine, prior exposure to efavirenz, prior use of antiretroviral therapy and concomitant use of cotrimoxazole. Sensitivity analyses also further adjusted for body mass index in the cohorts where this information was available. Parameters identified by univariate analysis as significantly associated with HSR ( $p < 0.05$ ) were entered into a multivariate model for HSR with use of a stepwise selection of variables. Multivariate models for TOXPC within 18 weeks and TOXPC at any time were adjusted for significant variables identified in the multivariate model for HSR.

Mortality rates during the first 24 weeks after starting NVPc were compared between patients who discontinued nevirapine due to toxicities and those who did not. All analyses were performed using SAS, version 9.1 (SAS Institute, USA).

## Results

### Patient characteristics

Overall, 6,227 (61%) of the 10,186 patients who started NVPc were Caucasian, 274 (3%) were of Asian ethnicity and 2,791 (27%) were female. 391 patients (4%) were chronically HBV coinfecting, 732 (7%) had chronic hepatitis C, 1,011 (10%) were intravenous drug users. The median age was 38 years (IQR 33-45). 6,229 (62%) were treatment-experienced at the start of nevirapine. Median CD4 count in females was 259 cells/mm<sup>3</sup> (IQR 157-420), and 297 cells/mm<sup>3</sup> (IQR 180-481) in males. The NRTI backbone most often used in combination with nevirapine was zidovudine/lamivudine (4,620, 45%).

Table 1 shows baseline characteristics stratified by prior treatment experience, CD4 count and viral load. The majority of patients without prior treatment experience started nevirapine with low CD4 counts (3,051 patients, 79%). The majority of treatment experienced patients started nevirapine with high CD4 counts and undetectable viral load (2,272, 34%) or with low CD4 counts and detectable viral load (1,865, 29%).

## Reasons for discontinuation

The cohorts that collect the specific reasons for discontinuation of antiretroviral therapy contributed 6,547 patients to this study. A total of 1,535 out of these 6,547 (23%) patients discontinued nevirapine because of all-cause toxicity and/or patient/physician's choice at any time after the start of nevirapine. Of these 1,535 patients 458 (30%) discontinued due to hypersensitivity reactions: 334 (22%) due to skin rash and 124 (8%) due to hepatotoxicity without concomitant skin rash. Other reasons for discontinuation were gastrointestinal symptoms (n=402), pancreas-related (n=4), central nervous system disorders (n=23), renal disorders (n=2), endocrine disorders (n=1), lactic acidosis (4), other toxicities (n=38), or patient or physician's choice (603, 39%). 727 (11%) of the 6,547 patients for which specific reasons for discontinuation of antiretroviral therapy were collected, discontinued nevirapine because of all-cause toxicity and/or patient or physician's choice within 18 weeks: 375 of these (52%) discontinued nevirapine due to hypersensitivity reactions, as manifested by skin rash (n=299, 41%) or hepatotoxicity without concomitant skin rash (n=76, 11%). Other reasons were gastrointestinal symptoms (n=175), central nervous system disorders (n=5) and renal disorders (n=1). 29 patients discontinued due to other toxicities (n=29) or patient/ physician's choice (142, 20%).

## Deaths

Of all patients who started nevirapine, 87 (1%) died within 24 weeks of starting. There were five deaths from complications related to hepatitis. 27 deaths were HIV-related, 22 non-HIV related and the cause of death was unknown for 33 cases. Of the five patients who died from hepatitis, four had prior treatment experience, chronic hepatitis C and acquired HIV through intravenous drug use. Two of these five patients had switched to nevirapine with low CD<sub>4</sub> counts and detectable viral load (these patients both died within three months after starting nevirapine) and two of these had switched to nevirapine with high CD<sub>4</sub> counts and detectable viral load (one patient died after one month and one patient died five months after starting nevirapine). There was one treatment naïve patient who had started nevirapine with low CD<sub>4</sub> count and who was not chronically infected with hepatitis. This patient died 49 days after starting nevirapine. Two patients who experienced a nevirapine-associated HSR died within 24 weeks of starting nevirapine. Both of these deaths were reported to be unrelated to the use of nevirapine. Although none of the deaths were explicitly reported to be nevirapine-related, complete information on cause of deaths, such as by using the CoDe system ([www.cphif.df/CoDe/About/tabid/64/Default.aspx](http://www.cphif.df/CoDe/About/tabid/64/Default.aspx)), were not routinely available and we cannot be certain that the deaths were unrelated to nevirapine use.

## Discontinuation due to toxicities in treatment-naïve and experienced patients

The median time from starting NVPc to HSR and TOXPC was 30 days (IQR 17-60) and 162 days (IQR 31-737) respectively. 80 (5.9%) treatment-naïve patients who started NVPc with low CD<sub>4</sub> counts (the reference group) discontinued NVP due to HSR and 289 (9.5%) discontinued NVP due to TOXPC within 18 weeks. Table 2 shows the number of patients that discontinued nevirapine for the different endpoints. Of the treatment-experienced patients who initiated nevirapine with high CD<sub>4</sub> counts and undetectable viral load, 142 (7.9%) discontinued due to HSR and 226 (10%) discontinued nevirapine due to TOXPC within 18 weeks, while of the treatment experienced patients who initiated nevirapine with high CD<sub>4</sub> counts and detectable viral load, 75 (10.7%) discontinued due to HSR and 135 (15.8 %) due to TOXPC within 18 weeks.

## Risk factors for nevirapine-associated toxicity

In univariate analyses, current viral load and CD<sub>4</sub> count, nadir CD<sub>4</sub> count, ethnicity, calendar year of starting NVPc, nucleoside/nucleotide backbone used with nevirapine and HIV transmission category were associated with the risk of discontinuation due to HSR ( $p < 0.05$ ). The final adjusted Cox models for the endpoints of discontinuation due to (1) hypersensitivity reactions (2) TOXPC within 18 weeks, and (3) TOXPC at any time after starting nevirapine are presented in Figure 1.

All analysis were stratified by cohort and adjusted for current viral load and CD<sub>4</sub> count, nadir CD<sub>4</sub> count, region of origin, calendar year of starting nevirapine and HIV transmission category. The effect of having an undetectable viral load on all endpoints was considerable. Compared with treatment-naïve patients with low CD<sub>4</sub> count (and detectable viral load) as the reference group, treatment-experienced patients with low CD<sub>4</sub> count were at increased risk of HSR and TOXPC within 18 weeks (although the estimate for HSR was not significant) if nevirapine was started with detectable viremia, while the hazard for HSR and TOXPC within 18 weeks was significantly lower if NVP was started in patients with low CD<sub>4</sub> counts and undetectable viral loads. Compared to the reference group, the hazard for HSR and TOXPC within 18 weeks was significantly higher for treatment-experienced patients with high CD<sub>4</sub> counts who started nevirapine with detectable viremia while the hazards for all endpoints for treatment experienced patients with high CD<sub>4</sub> counts and undetectable viral loads were not significantly different from the reference group. Age, gender, Asian ethnicity, nadir CD<sub>4</sub>, year of starting cART and IDU were associated with an increased risk for HSR (Table 3).

## Discussion

### Findings

We found that the risk for developing hypersensitivity reactions in treatment-experienced patients starting nevirapine-based cART with high CD<sub>4</sub> counts strongly depends on whether patients have detectable viremia at the start of nevirapine. Treatment-experienced patients with high CD<sub>4</sub> counts and undetectable viral loads had comparable risks of discontinuation of nevirapine due to hypersensitivity reactions compared to antiretroviral-naïve patients with low CD<sub>4</sub> counts. Undetectable viral load also had a protective effect in treatment-experienced patients starting nevirapine with low CD<sub>4</sub> counts, with a risk of hypersensitivity reactions in this group of patients that was even lower than the risk in the reference group of treatment-naïve patients with low CD<sub>4</sub> counts.

### Rationale for different endpoints

One of the limitations of cohort studies and pooling cohort studies, are the different ways data are collected. In order to be sure we have not missed any nevirapine-associated toxicities, we also performed analyses considering all discontinuations due to toxicities within 18 weeks, or at any time point after starting nevirapine. Nevirapine-related hypersensitivity reactions are most likely to occur within 18 weeks after starting nevirapine (Viramune package insert). These additional analyses showed similar results compared to the HSR analysis. A limitation of using these broader endpoints is that we may have overestimated the proportion of patients that developed treatment limiting toxicities associated with nevirapine.

### Other studies

Recent data from EuroSIDA [14] showed that treatment-experienced patients starting NVPc with high CD<sub>4</sub> counts had a significantly lower risk of discontinuation of nevirapine due to toxicities or patient/physician choice compared to ARV-naïve patients starting NVPc with high CD<sub>4</sub> counts. A meta-analysis of randomised trials [23] found no evidence of an increased risk of hepatotoxicity, skin rash or death within the first 3 months after starting nevirapine in treatment-experienced patients who have an undetectable viral load at the start of nevirapine. In studies analyzing the safety and efficacy of switching to nevirapine in subjects experiencing long-term control of virus replication on PI-based cART, few cases of hypersensitivity (skin rash) were observed [24] [25]. Data from the Athena cohort study showed that treatment-experienced patients with low nadir

CD4 counts and an undetectable viral load and high CD4 counts at the time of switching to nevirapine, had a similar risk of developing HSR compared to treatment-naive patients who start nevirapine with low CD4 counts, while patients with low nadir CD4 counts, high current CD4 counts and detectable viral loads were at significantly higher risk of developing HSR [15]. However, these studies were limited by power. Our study, with its larger sample size, allowed for more precise estimation of the effects of the various risk factors, and also allowed more detailed analyses for some of the smaller subgroups of patients.

#### Immune-related mechanism

We found a strong association between nadir / current CD4 count and the risk of hypersensitivity reactions. Although the pathophysiology of nevirapine-associated hypersensitivity reactions remains unclear, the strong association with higher CD4 counts suggests the involvement of a CD4-dependent immune response directed to nevirapine-specific antigens. Several studies have described an association of HLA with a higher incidence of hypersensitivity reactions to nevirapine [26][27][28]. Nevirapine-associated skin rash appears to be immune-mediated by CD4 cells in an animal model of the female brown Norway rat [29].

#### Viral load effect

We found a strong effect of viremia on the occurrence of hypersensitivity reactions. A possible explanation for this finding might be that in a setting where HIV-1 replication is controlled, the lower antigenic HIV-1 load results in less hyper-activation [30], which in turn might lessen the tendency of the immune system to overreact to nevirapine. Patients with undetectable viremia were also less likely to discontinue nevirapine due to all-cause toxicity and/or patient or physician choice. These patients were more likely to substitute nevirapine for a single other drug, without simultaneously replacing the NRTI backbone (75%), and therefore we speculate that they experienced less toxicity related to the introduction of additional new antiretrovirals. Other studies have found a similar strong association between detectable viremia and the diagnosis of abacavir-associated hypersensitivity reactions (37).

#### Risk factors

Our finding that females and patients with Asian ethnicity had an increased risk for developing treatment-limiting hypersensitivity reactions confirmed results from other studies [31-34]. The mechanisms for these differences is not known. It is possible that body weight and pharmacokinetic differences may play a role [35] although pharmacokinetic parameters of nevirapine did not show a relationship with adverse events in the 2NN study [36]. We performed an additional analysis where we also adjusted for BMI (in a subset of patients for whom this information was available) and this did not explain the differences in the risk of discontinuation due to HSR observed for these patient groups (data not shown). Furthermore, we found no evidence that prior use of efavirenz, which induces the cytochrome p450 enzymes involved in the metabolism of nevirapine, lowers the risk of developing all-cause toxicity at any time, within 18 weeks or HSR (data not shown).

#### Limitations

This study has several limitations that are inherent to retrospective observational cohort studies in general. It was not fully possible to ascertain whether physicians who discontinued nevirapine because of skin rash and/or hepatotoxicity fully adhered to the toxicity management guidelines in the nevirapine package insert. One of the goals of this international collaboration was to examine the risk factors for nevirapine toxicity in more detail, especially in treatment experienced patients, females and patients with an Asian ethnicity. Unfortunately, although the sample size of this collaboration is large, there was a relatively small number of Asian patients. Our finding that

Asian patients have an increased risk for developing hypersensitivity reactions should be approached with caution. We encourage studies in Asia to further investigate the risk in Asian patients. As with all observational studies, we cannot rule out confounding by indication because it is impossible to retrospectively determine why doctors chose to start NVPc in any particular patient. For the participating cohorts with limited information on reasons for discontinuation, we used a standardized definition to estimate which of the discontinuations were due to toxicity.

However, in sensitivity analyses excluding those cohorts, we found the same risk factors (data not shown). It is possible that experienced patients with detectable viremia were more likely to be non-adherent and therefore more likely to discontinue treatment. However, this possible source of bias is less likely a problem with HSR as an endpoint. Although 793 patients used nevirapine in combination with abacavir, only nine of these patients simultaneously started nevirapine and abacavir and discontinued these drugs due to HSR at the same time.

## Recommendations

We found that having a detectable viral load, higher current and nadir CD<sub>4</sub> count, female gender, and Asian origin were each independently associated with an increased risk for treatment-limiting toxicities and hypersensitivity reactions associated with nevirapine. Our results suggest that it may be relatively safe to initiate nevirapine-based cART in antiretroviral-experienced patients with high CD<sub>4</sub> counts provided there is no detectable viremia.

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#### Author contributions

Anouk Kesselring helped develop the project, had access to the contributing data from each cohort, performed all statistical analyses and drafted the manuscript. Ferdinand Wit contributed to the development of the project, interpretation of analyses and writing the manuscript and cosupervised statistical analyses. Caroline Sabin, Jens Lundgren, John Gill, Jose Gatell, Andri Rauch, Julio Montaner, and Frank de Wolf provided data from their cohort study, and provided input into interpretation of analyses and contributed to writing the manuscript. Peter Reiss helped implement the study, contributed to study design, interpretation of analyses and writing the manuscript. Amanda Mocroft was responsible for overall supervision of this study, proposed the study and design, co-supervised the statistical analysis, provided data, and contributed to interpretation of statistical analysis and writing the manuscript.

#### Conflicts of interest

Anouk Kesselring none. Ferdinand Wit none. Over the past three years, Caroline Sabin has received fees for speaking, membership of advisory boards, organising education and consultancy from several companies, including Boehringer Ingelheim, Bristol Myers Squibb, Gilead Sciences and Tibotec. Jens Lundgren has received funding from a variety of pharmaceutical companies including Boehringer Ingelheim for research, travel grants, speaking engagements and consultancy fees. John Gill has received grants and/or served on advisory boards for GSK, Merck, Pfizer, Boehringer Ingelheim, Bristol Myers Squibb, Tibotec, Gilead Sciences and Abbott laboratories. Jose Gatell has received research grants and honoraria for participation in advisory boards or lectures from Boehringer Ingelheim. Andri Rauch none. Julio Montaner has received grants from, served as an ad hoc advisor to, or spoke at various events sponsored by: Abbott, Argos Therapeutics, Bioject Inc, Boehringer Ingelheim, BMS, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Janssen-Ortho, Merck Frosst, Panacos, Pfizer,

Schering, Serono Inc, TheraTechnologies, Tibotec (J&J), Trimeris. Frank de Wolf-none. Peter Reiss has received honoraria for speaking engagements, advisory board membership and consultancy, as well as research grants from companies including Boehringer Ingelheim, Hoffmann LaRoche, Merck, Tibotec, Gilead Sciences, GlaxoSmithKline, Pfizer, Bristol Myers Squibb and Theratechnologies. Amanda Mocroft has received funding from a variety of pharmaceutical companies including Boehringer-Ingelheim for research, travel grants, speaking engagements and consultancy fees.

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Table 1. Characteristics of 10369 patients starting nevirapine-based cART after 1 January 1998

Treatment naïve patients  
 Low CD4 count High CD4 count Low CD4 count  
 Detectable VL  
 Treatment experienced patients  
 Low CD4 count  
 Undet VL  
 High CD4 count  
 Det VL  
 High CD4 count  
 Undet VL  
 N 3051 796 1865 1349 853 2272  
 Female, N (%) 841 (28) 456 (57) 360 (13) 161 (6) 361 (13) 612 (22)  
 Age (years), median (IQR) 37 (32-43) 33 (29-39) 39 (34-45) 41 (36-49) 37 (32-44) 40 (35-47)  
 CDC-C prior to start  
 nevirapine, N (%)  
 617 (20) 127 (16) 720 (39) 580 (43) 243 (29) 653 (29)  
 HIV RNA load at start NVP  
 (log<sub>10</sub> c/mL, median (IQR))  
 4.9 (4.3-5.2) 4.3 (3.5-4.9) 4.5 (3.8-5.0) 1.7 (1.7-1.9) 3.7 (2.9-4.3) 1.7 (1.7-1.8)  
 BMI (kg/m<sup>2</sup>), median (IQR) 23 (20-25) 23 (21-26) 23 (20-25) 23 (21-25) 23 (21-25) 23 (21-25)  
 Start NVP after 2002 (n, (%)) 1209 (40) 251 (32) 398 (21) 566 (42) 131 (15) 853 (38)  
 Duration of pre-treatment  
 (days)  
 --1174 (525-2196) 761 (312-1645) 1071 (547-910) 1214 (610-2138)

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Country of origin/Race\*, N  
 (%)  
 Europe/USA/Australia 1543 (51) 354 (45) 1208 (65) 935 (69) 565 (66) 1622 (71)  
 Africa 1021 (34) 304 (38) 337 (18) 235 (17) 142 (17) 344 (15)  
 Asia 91 (3) 13 (2) 52 (3) 31 (2) 25 (3) 62 (3)  
 Other 48 (1.6) 14 (1.8) 22 (1.2) 9 (0.7) 4 (0.5) 15 (0.7)  
 Unknown 348 (11.4) 111 (13.9) 246 (13.2) 139 (10.3) 117 (13.7) 229 (10.1)  
 Exposure group, N (%)  
 Homosexual 1298 (43) 243 (31) 898 (48) 778 (58) 362 (42) 1263 (56)  
 Heterosexual 1200 (39) 435 (55) 477 (26) 316 (23) 316 (37) 687 (30)  
 Intravenous Drug User 222 (7) 59 (7) 325 (17) 128 (10) 108 (12.7) 169 (7.4)  
 Other 47 (1.5) 6 (0.8) 27 (1.5) 27 (2.0) 28 (3.3) 42 (1.9)  
 Unknown 284 (9.3) 53 (6.7) 138 (7.4) 100 (7.4) 39 (4.6) 111 (4.9)  
 HBV Status\*\*, N (%)  
 Negative 2070 (68) 506 (64) 1275 (68) 1044 (77) 639 (75) 1742 (77)  
 Positive 81 (3) 17 (2) 103 (5.5) 52 (3.9) 34 (4) 104 (4.6)  
 Unknown 900 (30) 127 (16) 720 (39) 580 (43) 243 (29) 653 (29)

## HCV Status\*\*, N (%)

Negative 2169 (71) 519 (65) 1198 (64) 1000(74) 583 (68) 1697 (75)

Positive 129 (4) 33 (4) 234 (13) 105 (7.8) 87 (10.2) 144 (6.3)

Unknown 753 (25) 244 (31) 433 (23) 244 (18) 183 (22) 431 (19)

## NRTI Backbone, N (%)

AZT/3TC 1750 (57) 506 (64) 590 (32) 544 (40) 315 (37) 915 (40)

TDF containing 445 (15) 48 (6.0) 225 (12.1) 222 (16.5) 69 (8.1) 322 (14)

Other 744 (24) 231 (29) 851 (46) 440 (33) 396 (46) 779 (34)

ABC containing 111 (3.6) 11 (1.4) 199 (11) 143 (11) 73 (8.6) 256 (11.3)

Table legend: CDC-C = AIDS diagnosis according to CDC classification. ART = antiretroviral therapy. BMI = body mass index. NRTI = nucleosideanalogue

reverse transcriptase. AZT = zidovudine. 3TC = lamivudine. TDF = tenofovir. ABC = abacavir.

\* Prior to starting nevirapine, chronic hepatitis C was defined as positive plasma HCV-RNA, or HCV-positive antibodies in case HCV-RNA was missing. Chronic hepatitis B was defined as positive hepatitis B surface antigen, positive core antigen or positive plasma HBV-DNA.

Table 2: Percentages of patients that discontinue due to hypersensitivity reactions, treatment-limiting toxicities within 18 weeks and at any time, according to prior antiretroviral treatment, CD4 count and viral load.

## Treatment naïve patients

Low CD4 count High CD4 count Low CD4 count

Detectable VL

## Treatment experienced patients

Low CD4 count

Undet VL

High CD4 count

Det VL

High CD4 count

Undet VL

Discontinuation due to hypersensitivity reactions, N (%)\*\*\*

Discontinuation due to TOXPC within 18 weeks, N (%) \*\*

Discontinuation due to toxicity at any time (TOXPC)\*, N (%)

80/1348 (6) 37/378 (10)

289/3051 (10) 139/796 (18)

690/3051 (23) 284/796 (36)

90/1265 (7)

222/1865 (12)

563/1865 (30)

34/1011 (3) 75/699 (11)

77/1349 (6) 135/853(16)

280/1349 (21) 269/853 (32)

142/1846 (8)

226/2272 (10)

524/2272 (23)

\* TOXPC is defined as discontinuation due to all-cause toxicity and/or patient/physician choice in which missing reasons for discontinuation were imputed. \*\* No. of patients from all cohorts. \*\*\* No. of patients from cohorts with detailed information on reasons for discontinuation  
High CD4 count is defined as >400 cells/mm<sup>3</sup> in males, >250 cells/mm<sup>3</sup> in females. Undetectable viral load is defined as HIV RNA below 400 copies/ml.

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Table 3: Risk factors gender, race, intravenous drug use, nadir CD4, year of starting cART and age according to endpoint.\*

Hypersensitivity reactions TOXPC within 18 weeks TOXPC

HR CI p HR CI p HR CI p

Age at start cART 0.98 0.89-1.09 0.75 0.97 0.91-1.03 0.31 0.91 0.87-0.95 <0.0001

Intravenous drug user 1.28 0.95-1.72 0.11 1.38 1.13-1.68 0.002 1.57 1.37-1.80 <0.0001

Asian Race 2.24 1.43-3.52 0.0005 1.93 1.44-2.59 <0.0001 1.30 1.04-1.64 0.02

Female gender 1.78 1.36-2.33 <0.0001 1.41 1.19-1.66 <0.0001 1.22 1.08-1.36 0.0008

Year of starting NVP-based cART 1.37 1.11-1.69 0.003 1.20 1.05-1.37 0.006 1.19 1.08-1.32 0.0004

Nadir CD4 1.08 1.03-1.12 0.0004 1.07 1.04-1.11 <0.0001 1.05 1.03-1.07 <0.0001

Table legend: HR=hazard ratio. TOXPC = discontinuation due to toxicity and/or patient/physician choice, includes estimate of toxicity in case of missing reason for discontinuation. HSR = hypersensitivity reaction.

\*Multivariate models are stratified per cohort, adjusted for CD4 count and viral load at start of nevirapine, prior treatment experience, gender, region of origin, mode of transmission, year of starting cART, age at start nevirapine. For hypersensitivity reactions, only cohorts with specific information regarding reasons for discontinuation were included (n=6,547).

Figure 1: Hazard ratios\* for toxicity and hypersensitivity reactions for treatment naïve and experienced patients stratified according to CD4 count and viral load.

Table legend: HR=hazard ratio. TOXPC=discontinuation due to toxicity and/or patient/physician choice, includes estimate of toxicity in case of missing reason for discontinuation. HSR=hypersensitivity reaction. \*Multivariate models are stratified by cohort and adjusted for gender, region of origin, mode of transmission, year of starting cART, age at start nevirapine. High CD4 count is defined as >400 cells/mm<sup>3</sup> in males, >250 cells/mm<sup>3</sup> in females. Undetectable viral load is defined as HIV RNA below 400 copies/ml.

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