Strengthening the Nevirapine Safety Signal by Using the Electronic Dispensing Tool in Namibia

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Key Words

Signal, Nevirapine, Electronic Dispensing Tool, Protease Inhibitor, Substitution

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ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
AMR	adverse medicine reaction
AR	adverse reaction
ART	antiretroviral therapy
ARV	antiretroviral
CI	confidence interval
DHHS	Department of Health and Human Services
EDT	Electronic Dispensing Tool
FTC	emtricitabine
HAART	highly active antiretroviral therapy
HCW	health care workers
HIV	human immunodeficiency virus
MOHSS	Ministry of Health and Social Services
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
OR	odds ratio
PI	protease inhibitor
SD	standard deviation
TDF	tenofovir
TIPC	Therapeutics Information and Pharmacovigilance Centre
WHO	World Health Organization

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EXECUTIVE SUMMARY

Introduction: When nevirapine (NVP) was approved for treatment of HIV, it was recommended that it should not be prescribed for females and males with baseline CD4 counts ≥250 cells/mm^3 and ≥400 cells/mm3, respectively. This was a safety measure taken to reduce severe and life-threatening reactions. Over the years, this safety measure has been countered by a number of clinical studies showing that the incidence of NVP-related skin and liver reactions in patients with high[1] baseline CD4 counts was no different than the incidence in patients with low[2] baseline CD4 counts. As a result, the World Health Organization (WHO 2010) and Namibia's antiretroviral therapy (ART) Guidelines (MOHSS 2010) recommended that NVP-based antiretroviral therapy (ART) could be initiated in females with baseline CD4 counts >250 but ≤350 cells/mm^3. The Therapeutics Information and Pharmacovigilance Centre (TIPC) detected a signal of an increased number of severe and life-threatening reactions to NVP. The clinical importance of the reactions required that the incidence of these reactions be determined to address thoughts that the increase in reports was simply an improvement in reporting, not an increase in actual adverse outcomes.

Objectives: The primary objective of this signal strengthening activity was to estimate the frequency of substitution of NVP with a protease inhibitor (PI) during the period 2008 to 2011 and to determine if any increase detected was statistically significant.

Methods: Antiretroviral (ARV) medicine dispensing records for all adult patients newly started on ART from 2008 to 2011 were extracted from the Electronic Dispensing Tool (EDT). Patients were said to have encountered a grade 3 or 4 adverse reaction associated with NVP if their records showed that their NVP was substituted with a PI within 24 weeks of the start of ART, and the nucleoside reverse transcriptase inhibitor (NRTI) backbone was unchanged. The proportions of grade 3 and 4 reactions were calculated per quarter, and between and within gender comparisons were done using odds ratio (OR).

Findings and Discussion: 84,742 dispensing records of patients newly started on ART from 2008 to 2011 were extracted from the EDT. Of these, 290 fit the criteria for inclusion in the group that changed from NVP to a PI due to stage 3 and 4 reactions. Of the 290 patient records examined, 211 were females and 79 males. There was a statistically significant increase in the number of NVP-to-PI substitutions for females in the third quarter of 2010 (odds ratio [OR] 2.4; 95% confidence interval [CI] 1.8 – 3.1), which occurred at the same time as the implementation of Namibia's 2010 ART Guidelines. Also, there was a statistically significant increase in the number of NVP-to-PI substitutions for males (OR 2.4; 95% CI 1.4 – 3.8), which occurred three months after the change observed in the females. The odds of needing a NVP-to-PI substitution due to grade 3 or 4 reactions to NVP in females compared to males before the launch of Namibia's 2010 ART Guidelines was the same as those after the publication of the Guidelines (before, OR 1.6; 95% CI 1.1 – 2.5; after, OR 1.6; 95% CI 1.2 – 2.2). Prescribers of antiretroviral medicines complied with the Guideline's preferred first line ART regimen: tenofovir/ lamivudine/nevirapine. This implies that they complied with the recommendation of starting

[1] CD4 counts ≥250 cells/mm^3 in females and ≥400 cells/mm3 in males.
[2] CD4 counts<250 cells/mm^3 in females and <400 cells/mm3 in males.

NVP-based antiretroviral therapy in females with baseline CD4 counts >250 cells/mm^3. It is possible that the increase in the number of grade 3 and 4 reactions among HIV-positive patients in Namibia is associated with the initiation of NVP-containing ART in females with baseline CD4 counts ≥250 cells/mm^3.

Conclusion: The incidence of NVP-related reactions of grade 3 and 4 increased with the implementation of Namibia's 2010 ART Guidelines. The NVP safety signal of increased reports of grade 3 and 4 reactions was indeed a true signal. It is possible that initiating NVP-containing ART in women with high baseline CD4 counts, that is >250 cells/mm^3, was the cause for the increase in the incidence of NVP-related grade 3 and 4 reactions. Therefore, the national HIV programme needs to review the use of NVP.

INTRODUCTION

From when nevirapine (NVP) was approved for the treatment of the human immunodeficiency virus (HIV) infection to this day (February 2013), a safety measure against its use in patients with high CD4 counts has been maintained in its prescribing information. This safety measure states that NVP should not be prescribed for women with CD4 counts ≥ 250 cells/mm^3, and for men with CD4 counts ≥ 400 cells/mm^3 (Boehringer Ingelheim Pharmaceuticals 2012). Over the years, this safety measure has been countered by a number of clinical studies showing that the incidence of NVP-related skin and liver reactions in patients with high[3] baseline CD4 counts was no different than the incidence in patients with low[4] baseline CD4 counts (Bonjoch et al. 2006; João et al. 2006; Kondo et al. 2007; Knobel et al. 2008; Lyons et al. 2006; Manfredi et al. 2006; Manfredi et al. 2007; Marazzi et al. 2006; Phanuphak et al. 2007; Phillips et al. 2007). On the other hand, there have been a number of studies showing that the incidence of NVP-related skin and liver reactions was higher in patients starting NVP-based antiretroviral therapy (ART) at high baseline CD4 counts than in patients with low baseline CD4 counts, thus confirming NVP's prescribing information (Hitti et al. 2004; Jamisse et al. 2007; Kiertiburanakul et al. 2008). The evidence from the latter group of studies was not considered to be strong enough to cause concern on the part of the reviewers of the ART guidelines of the World Health Organization (WHO) (WHO 2009). When the WHO recommended that ART should be initiated in patients with CD4 counts <350 cells/mm^3, NVP was included in the preferred first line regimens: meaning that NVP could be prescribed for women with CD4 counts >250 cells/mm^3 (WHO 2010).

In 2010, Namibia's Ministry of Health and Social Services (MoHSS) launched the Third Edition of the National Guidelines for Antiretroviral Therapy. Similar to the WHO's ART guidelines, Namibia's Guidelines state that the CD4 count threshold for initiation of ART is ≤350 cells/mm^3. According to Namibia's ART Guidelines, the preferred first line ART regimen is tenofovir (TDF)/lamivudine (3TC) and NVP (MoHSS 2010). During the first weeks of NVP-containing ART, close monitoring of liver function and careful examination of skin and mucosal surfaces of patients were recommended, especially for females with baseline CD4 counts greater than 250 cells/mm^3 (MoHSS 2010; WHO 2010).

One year after the implementation of Namibia's 2010 ART Guidelines, the Therapeutics Information and Pharmacovigilance Centre (TIPC) reviewed its database of adverse reaction (AR) reports with the purpose of evaluating the trends of NVP-related skin and liver reactions. The review showed that there was a statistically significant increase in the frequency of reports of severe and life-threatening skin and liver reactions associated with NVP in 2011 compared with previous years (2008 to 2010) ($p<0.0001$). By contrast, there was no difference in the frequency of mild and moderate reactions ($P=0.16$). The reviewers therefore concluded that the increase in frequency of NVP-related severe and life-threatening reactions was a NVP safety signal (Kalemeera et al. 2012). Nevertheless, recommendations to mitigate NVP-related reactions could not be made because it was not known whether there was indeed an increase in the incidence of the reactions. Moreover, it was thought that the signal could have been due to an

[3] CD4 counts ≥250 cells/mm^3 in females and ≥400 cells/mm3 in males.
[4] CD4 counts<250 cells/mm^3 in females and <400 cells/mm3 in males.

improvement in the reporting of adverse reactions by health care workers (HCW), meaning that the incidence of grade 3 and 4 reactions before and after prescribing NVP in accordance with Namibia's 2010 Guidelines was not any different than during the period 2008 to 2010.

Problem Statement

Since the signal was clinically important and the fact that NVP-containing ART was still in use in potentially high risk patients, it was essential to estimate the incidence of serious and life-threatening reactions associated with NVP to provide evidence of what really happened during the period in which the signal was detected. This evidence would be a potential source of information for decision making as regards the use of NVP-based ART.

LITERATURE REVIEW

Bera and Mia (2012) carried out a systematic review and meta-analysis with the objective of determining whether HIV-infected pregnant women initiating antiretroviral therapy at higher CD4 counts had greater toxicity to NVP than those who initiated NVP-based ART at lower CD4 counts. Fourteen studies were included in Bera and Mia's review, covering 2,663 patients. They found that the odds ratio (OR) for overall NVP toxicity among pregnant women with CD4 <250 cells/mm^3 was 0.61 (95% confidence interval [CI] 0.43 – 0.85). When the analysis was restricted to only prospective studies (seven studies, 1,318 patients), the results were consistent for overall NVP toxicity (OR 0.43; 95% CI 0.25 – 0.73) and severe hepatotoxicity (OR 0.45; 95% CI 0.22 – 0.90), but not for severe cutaneous reaction (OR 0.53; 95% CI 0.26 – 1.10). They concluded that initiating NVP-based ART during pregnancy at CD4 ≥250 cells/mm^3 increases the risk of toxicity and should be avoided.

Dhong et al. (2012) investigated the relationship between the pharmacokinetics of NVP and NVP-related cutaneous and hepatic reactions. The study population was HIV-positive non-pregnant women who were randomized to receive TDF/FTC[5]/NVP. NVP was administered as 200 mg once daily for two weeks and twice daily thereafter. Blood samples for pharmacokinetics analysis were collected at 14 and 28 days following randomization. Dhong et al. found that among the 359 women: 194 (54%) developed a rash of any grade; 82 (23%) had grade 2 and nine (3%) had grade 3 rash. Median clearance was 1.7 l/h for participants exhibiting grade 3 rash versus 2 l/h in women without grade 3 rash (P = 0.046). The odds of developing grade 3 rash were 50% higher for every 20% decrease in clearance (P = 0.046). They also found that NVP discontinuation due to rash/liver toxicity was significantly more common among women with a pretreatment CD4 cell count more than 250 cells/µl (P = 0.003). They concluded that HIV-positive African women starting a NVP-based antiretroviral regimen had a lower NVP clearance compared to previous reports. Severe rash, but not hepatotoxicity, was associated with higher NVP exposure. Although observed in a small number of women, a baseline CD4 cell count of at least 250 cells/mm^3 was significantly associated with NVP toxicity.

Aaron et al. (2010) carried out a retrospective study on a multisite cohort to determine the predictors of NVP-related adverse events. Out of 612 women in the cohort, 152 (24.8%) were initiated on NVP-based ART, and 86 (56%) of them were pregnant. They found that NVP initiation at a baseline of CD4 >250 cells/mm^3 was associated with rash (OR 2.68; 95% CI 1.19 – 6.02, p = 0.017), but not with hepatotoxicity. They concluded that the findings from their study had significant implications for women of child-bearing age initiating NVP-based ART, particularly in resource limited settings, and therefore emphasized the need to monitor for rash during NVP use.

Kiertiburanakul et al. (2008) carried out a case-control study aimed at determining the risk factors for NVP-related reactions. A total of 357 patients with a mean (standard deviation [SD]) age of 36.4 (7.5) years, and 52.1% males were included in the study. The mean body weight (SD) was 55.5 (10.5) kg. Of the group, 179 (49.0%) patients had a history of AIDS-defining illness and 57 (16.0%) patients had history of drug allergy. There were 115 patients in the case

[5] FTC is emtricitabine.

group and 242 patients in the control group. In the case group, 43.0%, 54.4%, and 2.6% of patients developed grade 2, 3, and 4 rash, respectively. The median time to develop rash was 12 days (95% CI 10.5 – 13.5). By logistic regression, CD4 cells counts (OR 1.20 per each 50 cells/mm^3 increment; 95% CI 1.12 – 1.30), among other variables, were significantly associated with rash.

OBJECTIVES AND METHODS

The primary objective of this signal strengthening activity was to estimate the incidence of substitution of NVP with a protease inhibitor (PI) during the period 2008 to 2011 and to determine if any increase detected was statistically significant.

The antiretroviral (ARV) medicine dispensing records for all adult patients who were newly started on ART during the period January 1, 2008 through November 30, 2011 were extracted from the Electronic Dispensing Tool (EDT) in an Excel format. Patients were said to have encountered a grade 3 or 4 adverse reaction associated with NVP if they were initiated on NVP-based ART and NVP was replaced with a PI within 24 weeks of the start of ART, and the nucleoside reverse transcriptase inhibitor (NRTI) backbone was unchanged. The assumption that was used was that all replacements of NVP with a PI within 24 weeks of initiating ART, without modification in the NRTI backbone, were due to grade 3 or 4 reactions associated with NVP. The proportions of grade 3 and 4 reactions were calculated per quarter from January 2008 to November 2011. Comparisons between and within gender were done using OR.

RESULTS

Frequency

According to the records extracted from the EDT, a total of 84,742 patients were newly initiated on ART from January 2008 to November 2011. Of these, 290 patient records were selected for patients who presumably encountered a grade 3 or 4 reaction associated with NVP, due to the NVP-to-PI substitutions (figure 1). The proportion (number) of NVP-to-PI substitutions that were made during the first six, seven to twelve, thirteen to eighteen, and nineteen to twenty-four weeks post-ART initiation were as follows:

- 46.9% (n=136) in the first six weeks
- 33.1% (n=96) during seven to twelve weeks
- 12.4% (n=36) during thirteen to eighteen weeks
- 7.6% (n=22) during nineteen to twenty-four weeks (table 1)

The majority of NVP-to-PI substitutions occurred in females (72.7%, n=211). The mean (and median) ages of the males and females were 41 (39) years and 36 (35) years, respectively.

Table 1. Number of Patients Changed from NVP to a PI Every Two Weeks

Period after starting HAART (number of weeks)	2008	2009	2010	2011	Total
2	3	7	2	12	24
4	1	6	23	12	42
6	6	8	24	32	70
8	4	6	11	26	47
10	1	4	7	12	24
12	2	4	9	10	25
14	3	5	6	3	17
16	3	2	3	4	12
18	0	1	2	4	7
20	1	4	3	4	12
22	1	1	1	2	5
24	0	0	2	3	5
Total	25	48	93	124	290

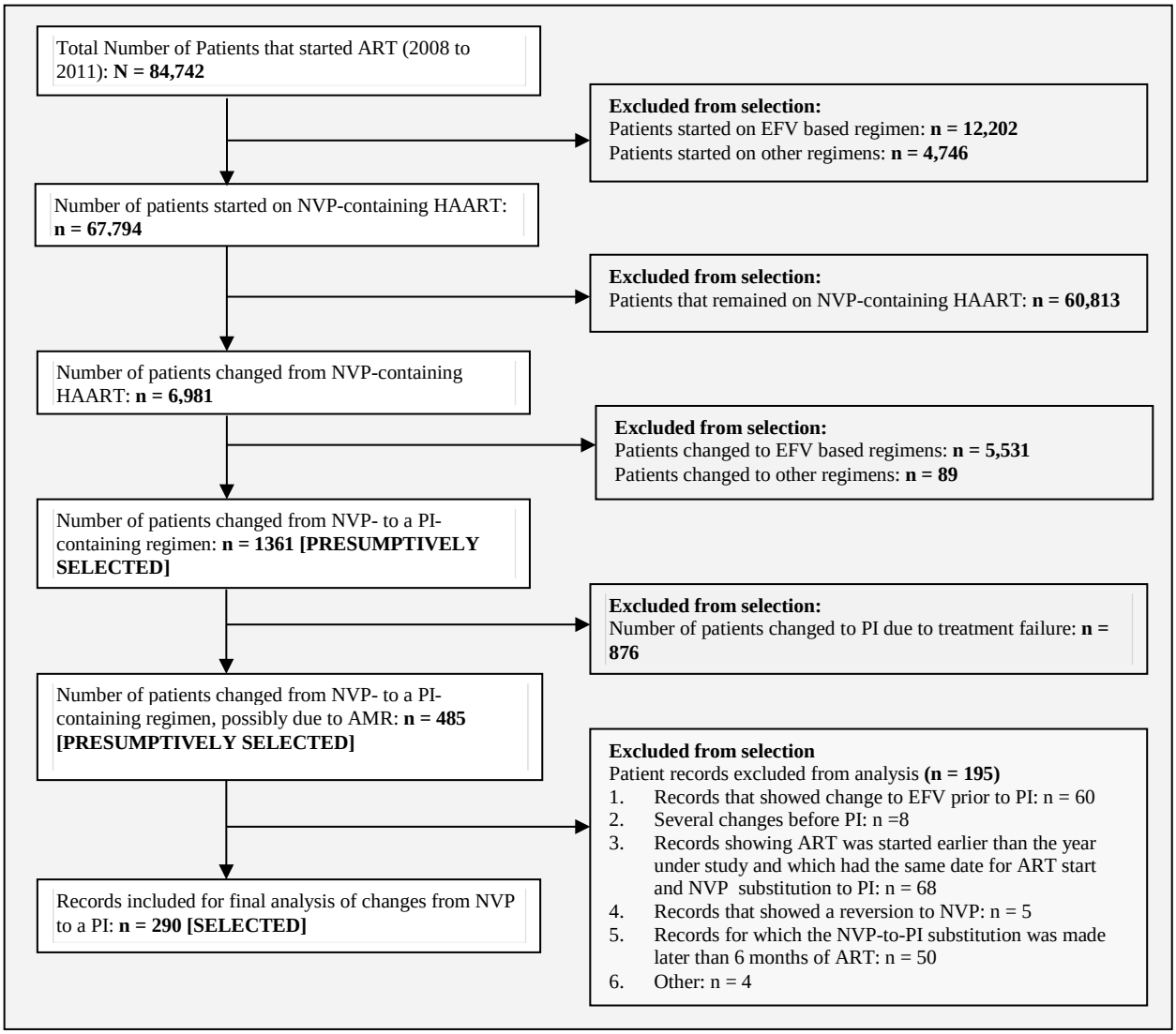

Figure 1. Algorithm for selection of records for patients with NVP-to-PI substitution

Increase in the Frequency of NVP-to-PI Substitutions

From the first quarter of 2008 to the third quarter of 2010 the average number of HIV- positive patients who were initiated on ART per quarter was 3,437 (figure 2). There was minimal variation in this number, ranging from 3,154 to 3,767. In the last quarter of 2010, the number rose (n=5,352) and peaked in the first quarter of 2011 (n=5,998). Despite a drop in the number of patients started on ART in the subsequent two quarters, the total per quarter was still higher than it was before October 2010 (n=4,513 and n=4,165, respectively). In the last quarter of 2011, the number of patients started on ART reverted to the earlier total level (n=3,025).

In the first three quarters of 2008, the frequency of NVP-to-PI substitutions averaged 0.14%. The frequency rose to 0.32% in the last quarter of 2008 and from then until the second quarter of 2009, the frequency increased from 0.26% and 0.54%, with an average of 0.37%. From the second quarter of 2010, the frequency of NVP-to-PI substitutions rose constantly to a peak of

0.95% in the second quarter of 2011. In the third quarter of 2011 the frequency dropped slightly to 0.70%, then sharply declined in the last quarter of 2011 to 0.20% (figure 2).

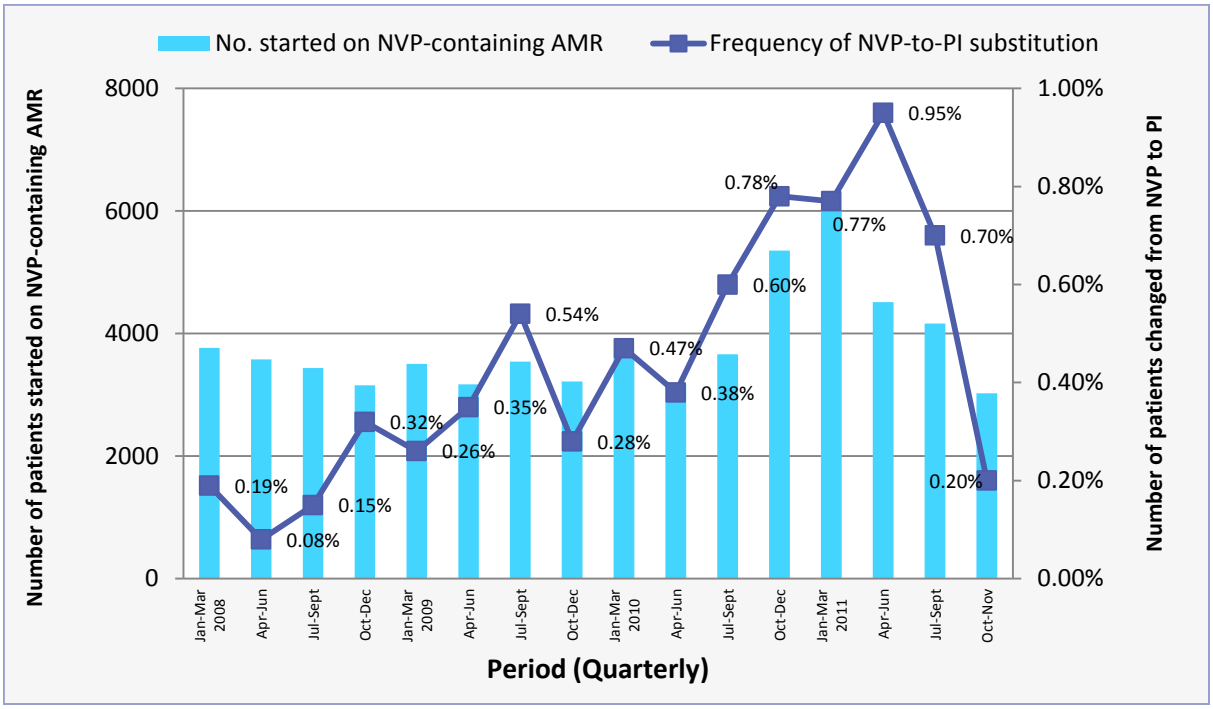

Figure 2. Trends in the use of NVP-containing ART and incidence of NVP-to-PI substitutions

Increase in the Use of TDF/3TC/NVP

From the first quarter of 2008 to the first quarter of 2010, an average of 400 patients were started on TDF/3TC/NVP per quarter (range: 346 to 619). In the third quarter of 2010, the number of patients started on this regimen rose to 963. In the fourth quarter of 2010, there was a sharp rise in the number of patients started on the TDF/3TC/NVP regimen. The number of patients was maintained at over 3,000 for the next four quarters, and then dropped substantially to just over 2,300 patients in the fourth quarter of 2011 (figure 3).

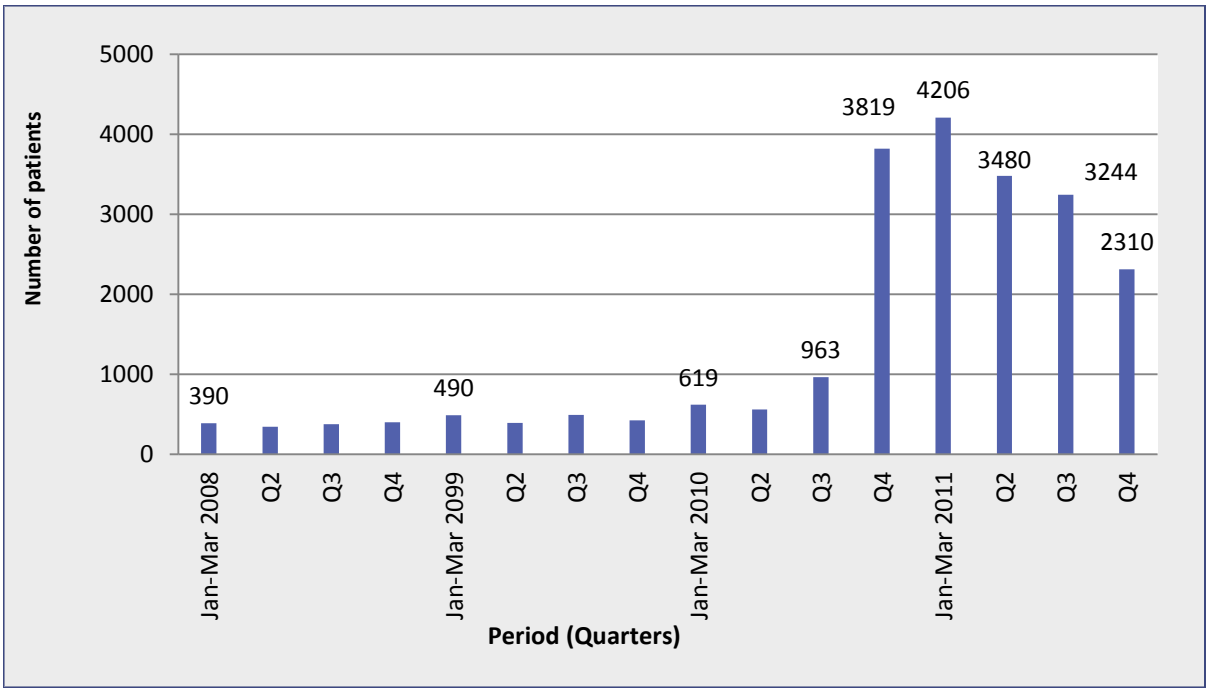

Figure 3. Trends in the use of TDF-based ART and the increase in NVP-to-PI substitutions from 2008 to 2011

Trends in the NVP-to-PI Substitutions

Females

There was a rise in the rate of NVP-to-PI substitutions from the third quarter of 2008 to the third quarter of 2009. Between the fourth quarter of 2009 and the end of the first quarter of 2010, the proportion of NVP-to-PI substitutions rose from 0.35% and 0.71%. The proportion of NVP-to-PI substitutions rose to higher levels in the third quarter of 2010, and stayed at a higher level until the third quarter of 2011. The proportion dropped sharply in the last quarter of 2011 (figure 4). The odds of getting a NVP-to-PI substitution in the third quarter of 2010 and afterwards was 2.4 times the odds of getting the same substitution in the earlier period (January 2008 to June 2010) (95% CI 1.8 – 3.1; $p<0.0001$) (table 2).

Males

From the first quarter of 2008 to the third quarter of 2010, the proportion of NVP-to-PI substitutions remained low (highest: 0.56%, lowest 0.07%). From the fourth quarter of 2010 to the third quarter of 2011, the proportion of NVP-to-PI substitutions was higher than in the previous period (quarter 1, 2008 to quarter 3, 2010). There was a sharp drop in the last quarter of 2011 (figure 4). The odds of needing a NVP-to-PI substitution from the third quarter of 2010 and afterwards was 2.4 times the odds of getting the same substitution in the earlier period (January 2008 to June 2010) (95% CI 1.4 – 3.8; $p=0.0002$) (table 2).

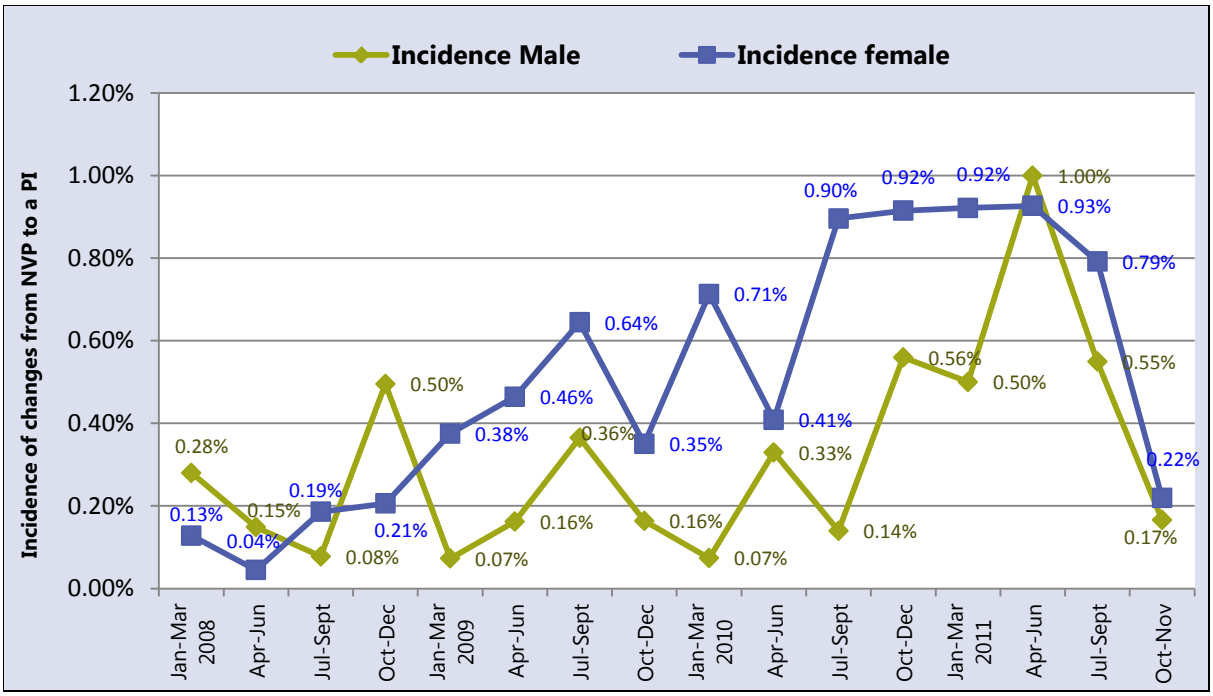

Figure 4. Incidence of NVP-to-PI substitutions for male and female patients

Table 2. Comparison of Frequencies of NVP-to-PI Substitutions Before and After July 2010: Results According to Gender

	No. started ART before Q3 2010	No. changed from NVP to PI	No. started ART in and after Q3 2010	No. changed from NVP to PI	Odds ratio (CI)	Z-statistic	P-value
Females	21,034	74	16,540	137	2.4 (1.8–3.1)	2.4	<0.0001
Males	13,012	28	9,987	51	2.4 (1.4–3.8)	3.7	0.0002

Comparison Between Males and Females Before and After the Launch of the ART Guidelines

Before and after July 2010, the odds of needing a NVP-to-PI substitution in females was 1.6 times that for males (P <0.03) (table 3).

Table 3. Frequencies of NVP-to-PI Substitutions Before and After the Launch of the 2010 ART Guidelines: Males vs. Females

	No.started on ART (males)	No. changed from NVP to PI	No. started on ART (females)	No. changed from NVP to PI	Odds ratio (CI)	Z-statistic	P-value
Females vs. males (after)	9,987	51	16,540	137	1.6 (1.2–2 .2)	2.9	0.003
Females vs. males (before)	13,012	28	21,034	74	1.6 (1.1–2.5)	2.2	0.03

DISCUSSION

Namibia's 2010 ART Guidelines (MoHSS 2010), the 2012 NVP prescribing information (Boerhinger Ingelheim Pharmaceuticals 2012), and WHO's 2010 guidelines (WHO 2010) were used to construct the assumption employed in this review. These sources of information were used as follows: First, Namibia's 2010 ART Guidelines recommend that a PI should replace NVP when "typical" NVP-related grade 3 and 4 reactions occur.[6] A substitution of NVP with a PI can be due to grade 3 or 4 reactions. Second, according to NVP prescribing information, most cutaneous and hepatic reactions occur within the first six weeks of NVP-based ART. Moreover, the prescribing information states that the first 18 weeks of NVP-based ART are critical for clinical and laboratory monitoring, but it also advises that monitoring should continue after 18 weeks. Third, the WHO guidelines recommend that treatment failure should be suspected if a patient encounters a new or persistent event of WHO clinical stage 3 or 4 at 24 weeks of ART. For such patients, PIs may be prescribed and their NRTI backbone is modified. For these reasons, patients who were changed from NVP to a PI after 25 weeks and longer on ART were not considered to be among those who may have experienced grade 3 or 4 reactions, despite the maintenance of the NRTI backbone. About half (46.9%, n=136) of the grade 3 and 4 reactions occurred in the first six weeks of NVP-based ART. This finding is consistent with the NVP prescribing information, which says that most skin and liver reactions occur in the first six weeks of NVP-based ART.

Based on this assumption, this review yields a number of essential findings. First, it provides evidence that the incidence of grade 3 and 4 reactions associated with NVP increased. Second, it has been shown that the increase in grade 3 and 4 reactions started in the third quarter of 2010, when Namibia's 2010 ART Guidelines were launched. The increase was maintained for a long period, 12 months. Third, the increase in the incidence of grade 3 and 4 reactions occurred in both male and female patients. Fourth, the review shows that health care workers complied with the 2010 ART Guidelines on the preferred first line ART regimen of TDF/3TC/NVP. The evidence of compliance with the Guidelines as regards the selection of the preferred first line ART regimen also means that prescribers complied with the recommendation to start NVP-based ART in females with baseline CD4 counts >250 cells/mm^3, but ≤350 cells/mm^3. The fact that TIPC received adverse reaction reports associated with NVP, revealing baseline CD4 counts >250 cells/mm^3 (52.1%, n=25) for females, is sufficient evidence that prescribers complied with the increased CD4 count threshold for the initiation of ART.

The NVP prescribing information states that NVP should not be used to treat HIV in females with baseline CD4 count >250 cells/mm3, and males with baseline CD4 counts >400 cells/mm3. Could the lifting of this safety measure be associated with the rise in the grade 3 and 4 reactions associated with NVP? Recent evidence shows that initiating NVP-based ART in females with CD4 counts greater than 250 cells/mm^3 is associated with increased risk of grade 3 and 4 reactions (Bera and Mia 2012; Dhong et al. 2012). WHO reports that the incidence of grade 3 and 4 reactions would increase in women treated with NVP-based ART if their baseline CD4 counts were >250 cells/mm^3 (WHO 2012). It is possible that the increase in the number of grade

[6] Typical NVP reactions include cutaneous and hepatic reactions.

3 and 4 reactions among HIV-positive patients in Namibia is associated with the initiation of NVP-containing ART in females with baseline CD4 counts ≥250 cells/mm^3.

Limitations

The EDT lacked baseline CD4 counts, which made it impossible for the reviewers to assess the effect of high baseline CD4 counts on adverse reaction outcomes. As a result, all arguments for restoration of the former precautionary measures that were imposed by the manufacturer of NVP strictly depend on recent evidence.

CONCLUSION

The incidence of NVP-related reactions of grade 3 and 4 increased with the implementation of Namibia's 2010 ART Guidelines, which lifted the restriction against the use of NVP in females with CD4 counts >250 cells/mm^3. Therefore, the NVP safety signal of increased reports of grade 3 and 4 reactions was indeed a true signal. It is possible that initiating NVP-containing ART in women with high baseline CD4 counts, that is >250 cells/mm^3, was the cause for the increase in the incidence of NVP-related grade 3 and 4 reactions. The national HIV programme should therefore review the use of NVP at higher CD4 counts, especially in women.

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