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Assessment of Nevirapine-Related Adverse Reaction Reports Received from 2008 to 2011 in Namibia

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Abstract

Background

Nevirapine's (NVP) pharmaceutical manufacturer recommended the avoidance of NVP in females and males with baseline CD4 counts >250 and >400, respectively. This safety measure was challenged by research results that showed similar proportions of adverse events in high and low baseline CD4 count patients. WHO's antiretroviral therapy guidelines recommended the use of NVP in patients with CD4 counts <350. Whether this recommendation would result in increase of NVP-related adverse reaction reports in Namibia was not known. Consequently, the pharmacovigilance centre monitored the NVP-related reaction reports for change in number and severity.

Methods

We accessed adverse reaction reports in VigiFlow®. NVP-related skin and liver adverse reaction reports received in 2011 were compared with those received in the Previous Years. Also, NVP-related reaction reports were compared with the same reactions associated with other medicines. The comparisons were made by using reporting ratio, proportional reporting ratio, and the Students T-Test.

Results

1,074 adverse reaction reports were accessed. NVP-related liver and skin reactions were 208 (2011) and 99 (Previous Years). The proportions of reports related to ARV in 2011 and Previous Years were comparable (RR=1; p=0.87). The NVP-related reactions were greater in 2011 than in the Previous Years (43.2% vs. 16.7%: RR = 2.6; p <0.0001). Grade3 and 4 reactions related to NVP were greater in 2011 than in the Previous Years (SKIN: 22.7% vs. 5.6%: RR = 4.1; p <0.0001; LIVER: 8.5% vs. 2.2%: RR = 3.9; p <0.0001), but not for grade1 & 2 reactions (SKIN: 8.5% vs. 6.2%; RR = 1.4; p =0.16; LIVER: 2.7% vs. 2.4%; RR = 1.1; p = 0.73).The increase in reports was observed for both female and male patients (p<0.01). The increase ingrade 3 and 4 reactions were unique to NVP.

Conclusion

The significant increase in proportions of grade3 and 4 liver and skin reaction reports in patients on NVP was detected as a safety signal after shifting ART initiation to higher CD4 counts. The Ministry of Health halted the plan of initiating NVP-based ART in pregnant females, and recommended the avoidance of NVP in ART-naïve patients with high baseline CD4 counts. Through locally derived data, pharmacovigilance centres can protect patients from drug-induced harm.

Keywords: Nevirapine; CD4 count; Adverse reaction; Skin; Liver; Reaction ratio; Proportional reaction ratio

Abbreviations

ART: Antiretroviral Therapy; ARV: Antiretroviral; EFV: Efavirenz; HIV: Human Immunodeficiency Virus; HCW: Health Care Worker; NNRT1: Non-Nucleoside Reverse Transcriptase Inhibitor; NVP: Nevirapine; PRR: Proportional Reporting Ratio; RR: Reporting Ration; TIPC: Therapeutics Information and Pharmacovigilance Centre; WHO: World Health Organisation

Introduction

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with other antiretroviral (ARV) medicines for the treatment and prevention of transmission of the Human Immunodeficiency Virus (HIV) infection [1,2]. The approval of NVP for the management of HIV infection was made with safety precautions, namely: NVP was to be avoided in females and males with baseline CD4 T-lymphocyte counts ≥250 and ≥400/mm^3, respectively. This safety measure was devised to protect patients against serious NVP-related skin and hepatic reactions, based on the evidence that was generated during pre-approval clinical trials [1].

Despite the precautionary measure, during the post-approval period NVP was used in a clinical trial to test its effectiveness in the prevention of viral transmission to the child in utero during the intra-partum period, in women with a baseline CD4 count >250 cells/mm^3. In this case, a single dose of NVP was used [2]. Similar studies with comparable results were implemented in other settings. In addition to a significant reduction in Mother-to-Child Transmission, the proportion of patients that experienced NVP-related adverse effects (AE) in the study population was not different from that in females with baseline CD4 counts less than 250cells/mm^3 [3]. At this point, the precautionary measure that had been set by NVP's innovator came under scrutiny. Actually, some studies that involved patients of both gender yielded similar safety results with those of the single-dose-NVP study [4-7]. On the other hand, some studies reported that the frequency of NVP-related AEs in the high CD4 count group was significantly higher than the frequency in the low CD4 count group, thus affirming the precautionary measure [8-10]. Ameta-analysis by De Lazzari et al. [11] agreed with the former studies as they found no difference in the frequencies of NVP-related AEs between high and low baseline CD4 count patient groups. However, De Lazzari et al. concluded that their findings may not apply to ART-naïve patients with high baseline CD4 cell counts, because their study population was ART-experienced, clinically stable and virologically suppressed at the time of initiation of NVP-containing ART [11,12].

Nevertheless, the available evidence to the reviewers of the World Health Organisation's (WHO) ART guidelines led to the recommendation that NVP-containing ART can be used in the treatment of HIV infection in all patients with baseline CD4 counts <350 cells/mm^3 [13]. The Namibia ART guidelines of 2010 – launched in November 2010 – mirrored the WHO guidelines in regards to the preferred first line regimen (Tenofovir/ Lamivudine/ NVP) and in regards to the threshold CD4 count for initiation of ART (<350cells/mm^3)[14].

It was unknown whether higher starting CD4 count threshold would affect the rates and severity of NVP-related adverse reaction. Therefore, it was critical for the Therapeutics Information and Pharmacovigilance Centre (TIPC) to closely monitor the spontaneous reports of NVP-related adverse reactions with the purpose of detecting any increase, and to test if any increase was tantamount to a safety signal.

In this paper we discuss the findings of the review, and the associated policy outcomes.

Objectives

The purpose of this assessment was tofind out if there was a NVP safety concern following the upward change in the threshold CD4 count for initiation of antiretroviral therapy, from <200 to <350 cells/mm^3.

The specific objectives of the assessment were to:

- Find out if there was anincrease in thenumber and proportionof NVP related reaction reports in 2011compared with Previous Years
- Discover if there was a difference between the proportion of grade3 & 4 reactions related to NVPin 2011 and in the Previous Years
- Determine if there was a difference between the proportion of NVP-related reactions and the proportion of similar reactions related to other medicines

Methods and Materials

In VigiFlow®, we accessed the automated records of adverse medicine reaction reports that were received from January 1, 2008 to November 30, 2011. We selected all liver- and skin- related adverse reaction reports associated with NVP and other medicines. We divided the reports into group 1, which included NVP-related adverse reaction reports that were received from January 1, 2008 to December 31, 2010 and group 2, which contained NVP-related adverse reaction reports that were received in 2011: from January 1 to November 30. (In this paper, Group 1 is referred to as 'Previous Years', and Group 2 is referred to as 2011). We compared the proportion of NVP-related skin and liver adverse reaction reports received in 2011 with the proportion received in the Previous Years by using Reporting Ratio (RR) – a within medicine comparison method. The RR was calculated by dividing the proportion of NVP-related reports in 2011 with the proportion of the reports received in the Previous Years.

Next, we compared the proportion of NVP-related skin and liver reaction reports with the proportion of the same reactions associated with other medicines in 2011, and in the Previous Years by using the Proportional Reporting Ratio (PRR) – a between medicines comparison method. The PRR was calculated by dividing the proportion of NVP-related adverse reaction reports with the proportion of the same reaction for other medicines, and the same was done for efavirenz-related adverse reaction reports.We selected efavirenz (EFV) as the comparator medicine since it had a larger proportion of skin and liver-related reaction reports than other medicines. We used the Student's T-test to assess the difference in the proportions from the two groups, with the confidence interval and statistical significance set at 95% and a p-value <0.05, respectively.

Conclusion

We concluded that the extremely significant increase in grade 3 and 4 adverse reactions associated with NVP was a safety. Although spontaneous reports are not ideal for identification of risk factors, it was reasonable to suspect that the high baseline CD4 count was a risk factor, since the increase in grade 3 & 4 reaction reports started concurrently with the approval of the use of NVP-based ART in females with baseline CD4 counts >250 but <350 cells/mm^3. Based on these results the Technical Advisory Committee of the Ministry of Health and Social Services (MoHSS) decided to halt the plan of initiating NVP-based ART in all pregnant females with high CD4 counts, and awaited further information from TIPC on whether the increment in reports signified an increase in the number of grade 3 and 4 events. Also, TIPC had the responsibility to provide information regarding the factors associated with this safety signal.

The analysis of locally derived data by national pharmacovigilance centres can protect patients from impending drug-induced harm.

Results

Frequency

A total of 1,074 adverse reaction reports were accessed (Table 1). Of these 871 (81.1%) were related to antiretroviral medicines (Table 1). NVP-related liver and skin adverse reactions accounted for 307 reports, of which 208 were received in 2011, and 99 in the Previous Years (Table 1). For 2008, 2009 and 2010 the NVP-related reaction reports were 7.4%, 19.5% and 15.9%, respectively, of the total adverse medicine reaction reports (Figure 1).

NVP-Related Reactions in 2011 and Previous Years

The proportions of reports related to antiretroviral medicines in 2011 and the Previous Years were comparable (RR=1; p=0.87) (Tables 1 and 2). In regards to the total reports, the proportion of NVP-related reactions in 2011 was significantly greater than the proportion in the Previous Years (43.2% vs. 16.7%: RR = 2.6; p <0.0001) (Tables 1 and 2). The proportion of grade 3 & 4 skin reactions related to NVP was significantly greater in 2011 than in the Previous Years (22.7% vs. 5.6%: RR = 4.1; p <0.0001). On the other hand, there was no significant difference between proportions of grade1 & 2 skin reaction reports in 2011 and in the Previous Years (8.5% vs. 6.2%; RR = 1.4; p =0.16). Similarly, the proportion of grade3 and 4 liver reactions related to NVP was significantly greater in 2011 than in the Previous Years (8.5% vs. 2.2%: RR = 3.9; p <0.0001). However, there was no difference between proportions of mild/moderate liver reactions (2.7% vs. 2.4%; RR = 1.1; p = 0.73) (Tables 1 and 2). A significant increase in the proportions of grade3 and 4 liver and skin reaction reports was observed for both female and male patients (p<0.01) (Table 2).

Other medicines accounted for a lower proportion of the total adverse reactions reports in 2011 than in the previous years (RR = 0.7).Also, other medicines accounted for a lower proportion of skin and liver reports in 2011 than in the Previous Years (p = 0.002) (Table 2).

Comparison of Proportions of NVP- with EFV- Related Reactions

The RR for NVP was greater than that for EFV for both skin and liver associated reactions (Table 3).

Comparison of Proportions of NVP- and EFV- Related Reactions with Other Medicines

The PRR values for NVP were greater than those for EFV (Table 4).

Figure 1: Proportion of ARV- and NVP-Related Reaction Reports from 2008 to 2011

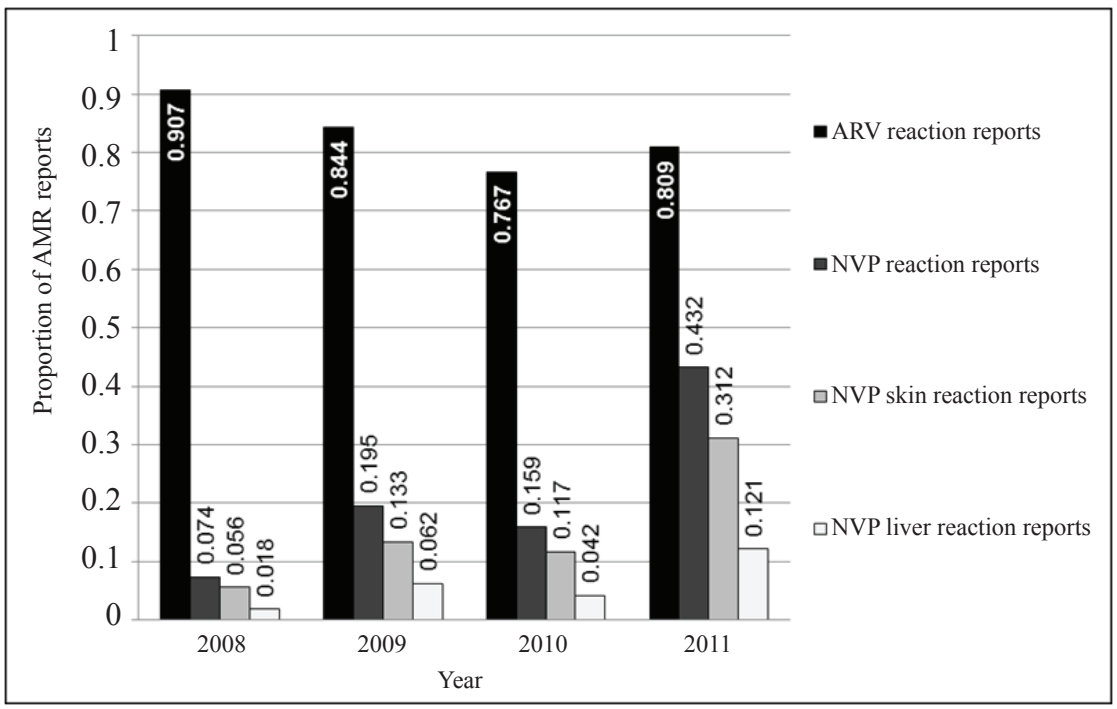

Table 1: Frequency of Adverse Reactions in 2011 and Previous Years (2008 to 2010)

Adverse Reaction Reports	2011 n = 481	2008–2010 (previous years) n = 593	RR
Adverse reaction related to antiretroviral medicines	389 (80.9%)	482 (81.3%)	1
Total NVP reactions (related to skin and liver)			
Adverse reactions attributed to NVP	208 (43.2%)	99 (16.7%)	2.6
NVP skin reactions			
All skin reactions	150 (31.2%)	70 (11.8%)	2.6
Severe	109 (22.7%)	33 (5.6%)	4.1
Mild/moderate	41 (8.5%)	37 (6.2%)	1.4
NVP-liver reactions			
All liver reactions	58 (12.1%)	29 (4.9%)	2.5
Severe	41 (8.5%)	13 (2.2%)	3.9
Mild/moderate	13 (2.7%)	14 (2.4%)	1.1
Unknown grade	4 (0.83%)	2 (0.34%)	-
Other antiretroviral medicine reactions			
Adverse reactions attributed to other medicines	273 (56.8%)	494 (83.3%)	0.7

Table 3: RRs for NVP- and EFV- Related Adverse Reaction Reports

Category of reaction	NVP	EFV
Skin	2.6	1.9
Liver	2.5	0.4

Table 4: PRR for NVP- and EFV- Related Adverse Reaction Reports

Category of reaction	PRR for NVP		PRR for EFV	
	2011	Previous years	2011	Previous years
Skin	3.8	1.5	0.06	0.06
Liver	9.7	2.2	0.03	0.17

Table 2: Comparison between Proportions of NVP-Related Adverse Reactions of Skin and Liver in 2011 with those in Previous Years

Adverse reaction type		% (95% CI) 2011	Previous years	P-value
ARV	Related reactions (all)	80.9% (77.4%-84.4%)	81.3% (78.1%-84.5%)	0.87
NVP-related	Skin and liver	43.2% (38.7%-47.7%)	16.7% (13.7%-19.7%)	<0.0001
	Skin (all)	31.2% (27.0%-35.5%)	11.8% (9.2%-14.4%)	<0.0001
	Skin: severe	22.7% (18.9%-26.5%)	5.6% (3.7%%-7.5%)	<0.0001
	Skin: mild/moderate	8.5% (6.0%-11.0%)	6.2% (4.2%-8.2%)	0.16
	Liver (all)	12.1% (9.2%-15.0%)	4.9% (3.1%-6.7%)	<0.0001
	Liver: severe	8.5% (6.0%-11.0%)	2.2% (1.0%-3.4%)	<0.0001
	Liver: mild/moderate	2.7% (1.0%-4.4%)	2.4% (1.2%-3.6%)	0.73
Other medicines	Skin and liver	5.0% (3.0%-7.0%)	9.9% (7.5%-12.3%)	0.002
NVP-related reactions for	Females	29.5% (25.4%-33.6%)	12.5% (9.8%-15.2%)	<0.0001
	Females: severe	21.6% (17.9%-25.3%)	5.6% (3.7%-7.5%)	<0.0001
	Females: skin-severe	17.3% (13.9%-20.7%)	4.0% (2.4%-5.6%)	<0.0001
	Females: liver-severe	4.3% (2.5%-6.1%)	1.5% (0.5%-2.5%)	0.0072
	Males	13.7% (10.6%-16.8%)	3.9% (2.3%-5.5%)	<0.0001
	Males: severe	9.6% (6.9%-12.3%)	2.2% (1.0%-3.4%)	<0.0001
	Males: skin-severe	5.4% (3.4%-7.4%)	1.5% (0.5%-2.5%)	0.0007
	Males: liver-severe	4.2% (2.4%-6.0%)	0.7% (0.0%-1.4%)	0.0003

Baseline CD4 Counts

Of the 150 skin reaction reports attributed to NVP, 55 had record of baseline CD4 counts. Of these, 48 were for females of which 62.5% (n =30) had CD4 counts above 250 cells/mm^3. For the high CD4 count group, the mean CD4 count was 309 cells/mm^3 (lowest count = 264; highest count = 356). The mean baseline CD4 count for the remaining 37.5% (n=18) was 156 cells/mm^3 (lowest count = 15; highest count = 248). In the high CD4 count group, 87% had severe and life-threatening reactions, while in the low CD4 count group, 72.2% (n=13) had severe and life-threatening reactions.

Discussion

The aggregation of the reports received by TIPC from 2008 to 2010 into one group for comparison with 2011 reports does not present any methodological or statistical shortcomings of this review for the following reasons. Firstly: The ART guidelines that were used to guide ART practice in the previous year's recommended the initiation of ART as soon as the CD4 count declined to <200cells/mm^3. It can be inferred that during this period ART was initiated in patients with a baseline CD4 count <200cells/mm^3, thus making the patient characteristics similar in this particular regard. Secondly: during the Previous Years, the NVP safety precaution that was set by NVP's innovator was being practiced. Lastly: Each of the individual previous years had approximately the same proportion of adverse reaction reports related to antiretroviral medicines (Figure 1). Therefore, the aggregation of the Previous Years reports into one group was justifiable.

If the analysis of the absolute numbers of adverse reaction reports had been done without categorizing them into their respective severity levels, the interpretation of the findings would have possibly swayed towards a misconception that the observed increase in the reports in 2011 was simply a result of improved reporting behaviour by the health care workers (HCW). The recommendation that would come out of such an analysis would be continued support for the use of NVP without noticing any safety-concerns. Therefore, the approach we took involved the categorization of individual reports into their respective severity levels; and the analysis of proportions of these reactions.

For both skin and liver reactions, the proportion of grade 3 & 4 reaction reports related to NVP in 2011 were more than two times the proportion in previous years (RR: 2.5 [skin] & 2.6 [liver]; p=0.0001). Unlike NVP-related results, for EFV the increase was observed for only skin reaction reports (RR=1.9) but not for liver reaction reports (RR=0.4).On comparison with other medicines, we found that the NVP-related skin reaction reports were about two times greater than those for other medicines in 2011 (PRR = 3.8) compared with the Previous Years (PRR = 1.5).Also, we found similar results for NVP-related liver reaction reports, but of a greater magnitude – that is, more than four times greater: (9.7 vs. 2.2). A similar analysis for EFV revealed that there was no difference between the proportion of skin reaction reports in 2011 (PRR =0.06) and the Previous Years (PRR = 0.06). Moreover, there was a reduction in EFV-related liver reaction reports in 2011

(PRR = 0.03) compared with Previous Years (PRR = 0.17). These results confirmed that the increment in number and proportion of skin and liver reaction reports was uniquely associated with NVP. Of more concern, the increment in NVP-related reaction reports was observed for grade3 and 4 reactions, but not for grade1 and 2 reactions.

We did not attempt to study the association between NVP-containing ART regimens and baseline CD4 counts due to the fact that the data we had was from spontaneous reports, and not from a conventional scientific study, such as a case-control study. Nevertheless, we had reasons to question the safety of NVP in patients with high baseline CD4 counts, which include: (1) The significantly high number and proportion of grade 3 and 4 reactions in females coincided with the period when NVP-containing ART could be initiated in ART-naïve females with a baseline CD4 count >250 but <350cells/mm^3; (2) A large proportion of grade 3 and 4 reaction reports were for females with a baseline CD4 count>250 cells/mm^3. (3) There was conflicting evidence regarding the safety of NVP at high baseline CD4 counts. On the other hand, there was a statistically significant increase in the proportion of similar reactions in males, yet for males NVP-containing ART was administered at baseline CD4 counts within the "safe margin" – that is, <400 cells/mm^3. But this may be explained by the fact that the higher the CD4 count the higher the risk for NVP-related reactions irrespective of gender.

Another factor that could have led to the increase in NVP-related adverse reactions could be genetic predisposition [15]. However, the genetic pool for patients in 2011 is most likely to be the same with that for the patients in the Previous Years.

Our findings were limited by the lack of sufficient data that could be used for allocation of severity for some of the reports. Our response was to consider all such reports to represent grade1&2 reactions. It is possible that amongst these were those that could have been grade 3 or 4 reactions, especially in 2011. In that regard, the proportion of grade 3&4 reactions may have been under-represented; nevertheless, a significant increase was observed. The other possible limitation may be that disproportionate measures have an inherent inability to detect medicine safety signals when the number of related adverse reaction reports is low [16]; however, the number of reports we had were in sufficient number for a signal to be detected. Lastly, the reactions that were reported against NVP are not new. This may obscure ones recognition of a safety signal. But the fact that there was a concern for patient's safety there were no better terms to use than 'a NVP safety signal', which was received as such by the MoHSS.

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