Journal of
AIDS & Clinical Research
ISSN: 2155-6113

Kudzi et al., J AIDS Clin Res 2017, 8:1
DOI: 10.4172/2155-6113.1000654

Research Article OMICS International

# Risk Factors of Nevirapine Hypersensitivity Reaction among Human Immunodeficiency Virus-1 Infected Treatment Naïve Patients at Korle-Bu Teaching Hospital

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## Abstract

**Objective:** Ghana like most African countries, still carry the communicable disease burden. The introduction of antiretroviral drugs in Ghana has improved survival rates amongst HIV patients. According to the National Guidelines for antiretroviral treatment in Ghana, administration of nevirapine, a frontline antiretroviral drug leads to hypersensitivity reactions in some patients. This study examines the clinical risk factors and specific genotypic alleles associated with nevirapine hypersensitivity reactions.

**Methods:** Seventy (70) antiretroviral naïve HIV patients, initiating nevirapine-based HAART therapy were enrolled in this cohort study and monitored clinically over a period of 24 weeks from July 2013 through to June 2014. Blood samples were evaluated for aminotransferase activity and DNA genotyped for specific *ABCB1* and *CYP2B6* markers.

**Results:** Eleven (15.7%) patients were identified as cases and 59 (84.3%) patients classed as comparisons out of the study population at the end of the 24 week-monitoring periods. Eight out of the observed cases were categorized as nevirapine hypersensitivity rash and 4 as hepatotoxicity. The concentration of AST was much higher in the cases (119.44 ± 155.86) compared to the comparisons group (68.80 ± 42.65), p=0.056. The Concentration of ALT was also higher in the cases (136.44 ± 165.99) compared to the control (56.72 ± 33.02) p=0.003. The *CYP2B6* 516 G>T, variant allele frequency observed in the study was 62 (44.3%). However, there was no variant allele detected for the three SNPs in *ABCB1* gene genotyped.

**Conclusion:** The observed NVP HSR outcome suggests an adverse reaction among the cohort of HIV-1 infected patients within the Ghanaian population studied. The effect of this outcome although not statistically significant, might be clinically traced to non-adherence to medication and hospitalization of patients which seem to be a major factor to treatment failure in resource-limited countries.

**Keywords:** Nevirapine; Hypersensitivity; Antiretroviral therapy; Adverse drug reactions; Genetic polymorphisms

**Abbreviations:** ABCB1: Antigen Binding Cassette Beta globin I; ADRs: Adverse Drug Reactions; ART: Antiretroviral Therapy; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HIV: Human Immunodeficiency Virus; HAART: Highly Active Antiretroviral Therapy; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NVP: Nevirapine; UNAIDS: United Nations Programme on HIV/AIDS; KBTH: Korle-Bu Teaching Hospital; ANRS: French National Agency for Research on AIDS and Viral Hepatitis; ULN: Upper Limit Normal

## Introduction

Human Immunodeficiency Virus (HIV) is one of the communicable diseases in Ghana being controlled and prevented through treatment with antiretroviral therapies (ARTs). The use of Highly Active Antiretroviral Therapy (HAART) as standard care in the health care system has greatly improved the survival of HIV-infected patients. There are over 20 antiretroviral agents available; however, variability in efficacy and toxicity of these drugs has been a major limitation for HIV management [1].

Nevirapine (NVP), a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) is widely used as the first-line treatment for HIV-1 infections in developing countries [2]. It is the preferred NNRTI antiretroviral regimen in pregnancy because of its proven efficacy in reducing mother-to-child transmission [3]. Although NVP is generally well tolerated and effective, its use is limited by potentially fatal immune-mediated hypersensitive reactions. The most common NVP hypersensitivity usually presents within the first few weeks of therapy and include flu-like symptoms (fever, fatigue, malaise, nausea, and vomiting), and development of skin rash amongst up to 15% of patients initiating NVP. Severe forms of the rash such as the Stevens - Johnson syndrome have been reported in some studies. There are reports of increased serum transaminase concentrations in about 20% of patients and hepatotoxicity manifesting as fever and immune-mediated hypersensitive reactions [4,5].

Ghana like other resource-limited countries use NVP in fixed dose combinations of two drugs from other classes within the triple drug regime, due to its availability and cost [4]. NVP is usually given

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**Received** November 24, 2016; **Accepted** January 07, 2017; **Published** January 14, 2017

**Citation:** Kudzi W, Aboagye ET, Dzudzor B, Nartey ET, Achel DG (2017) Risk Factors of Nevirapine Hypersensitivity Reaction among Human Immunodeficiency Virus-1 Infected Treatment Naïve Patients at Korle-Bu Teaching Hospital. J AIDS Clin Res 8: 654. doi: 10.4172/2155-6113.1000654

in combination with either stavudine and lamivudine or zidovudine and lamivudine which are nucleoside reverse-transcriptase inhibitors (NRTIs) [6]. Approximately 35% of HIV patients receiving HAART in Ghana are put on NVP [7]. Response to ART is often limited by the occurrence of ADRs or by the emergence of HIV drug resistance [8]. Multiple factors that affect the variability of ARTs response include host factors (gender, age and body weight), physiological conditions (pregnancy, renal or liver function impairment), drug-drug and drug-food interactions together with the genetic variations [9]. Genetic background of patients has been increasingly linked to susceptibility to adverse reactions especially among Africans [10].

The prevalence of this NVP hypersensitive reactions has been reported as 4–6% in Caucasians [11], 8% in South Africa's [12] 5.1% in Malawians and 3% in Cameroonians [13]. There also exist limited literature on NVP hypersensitivity and its associated risk factors in West African AIDS patients on the drug [14]. In addition, literature on the incidence of NVP hypersensitivity and its related risk factors among Ghanaian HIV patients is scanty.

The aim of this study was to identify potential risk factors which predispose NVP hypersensitivity reactions in HIV- 1 infected treatment naïve Ghanaian patients at the Korle-Bu Teaching Hospital (KBTH). The information may be useful in maximizing effective drug response, particularly for life-long medications.

## Methodology

### Study patients

This was a cohort study of HIV/AIDS conducted at the Fever's Unit of Korle-Bu Teaching Hospital (Accra, Ghana) from July 2013 through June 2014. There are approximately 19,000 registered People Living with HIV (PLHIV) attending this clinic and 7,000 of these patients were on various regimes of HAART recruitment. The study was approved by Ethical and Protocol Review Committee of the School of Medicine and Dentistry, University of Ghana (MS-Et/M.8–P4.2/2012-2013) and all participating patients provided written informed consent. All participating patients were HIV-1 infected treatment naïve adults who were 18 years and above, initiating NVP-based triple drug HAART regimen. NVP naïve HIV/AIDS patients recommended by the attending clinician for NVP based triple HAART regime were recruited for the study. The eligibility criteria was use to exclude patients presenting with jaundice, HIV-1 pregnant women, patients with elevated serum transaminase levels as well as CD4 T-cells >350 cells/μL in females and >400 cells/μL from the study. Seventy-four (74) antiretroviral naïve HIV patients, initiating nevirapine-based HAART therapy were enrolled in this cohort study. Seventy (70) patients were monitored clinically over a period of 24 weeks. One patient died and 3 patients were lost to follow-up after recruitment.

### Clinical and laboratory monitoring

Baseline laboratory clinical investigations including $CD4^+$T- cell count, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum concentrations were determined before initiation of NVP–HAART treatment. $CD4^+$ T-cell count was determined with BD FACSCount™ CD4/CD3 reagent kits (BD Bioscience, San Jose, USA), using BD FACSCount System analyzer (BECTON DICKINSON, USA) following the manufacture's protocol. For each subject sample, 20 uL of MultiTEST CD3/CD8/CD45/CD4 reconstituted working reagent was added to anti-coagulated whole blood (50 uL) in a test tube, gently vortexed and incubated at room temperature for 15 min. FACS lysing solution (450 uL) was then added to the mixture, gently vortexed and incubated in the dark at room temperature before reading from the analyzer.

Clinical evaluations for skin rash and jaundice in subjects were performed both at the beginning of the study and on scheduled follow-up visits (2, 4, 8, 16 and 24 weeks) by qualified dermatologist.

Hepatotoxicity was identified and graded by attending clinician using the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) toxicity scale; ALT or AST level of 1.25-2.5 times greater than the ULN defines grade 1; ALT or AST greater than 2.5-5 times the ULN defines grade 2; ALT or AST greater than 5-10 times the ULN defines grade 3 and ALT or AST greater than 10 times the ULN defines grade 4. Hypersensitivity rash equally identified by the dermatologist with reference to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table").

Serum (500 uL) from patient samples was used to determine AST and ALT level, using the RXmonza Semi-Automated Chemistry Analyzer (Randox Laboratories Ltd, United Kingdom). Briefly, reagents were reconstituted following supplier's protocol (Randox Laboratories Ltd, United Kingdom). Fifty microliters (50 uL) of the serum was added to working reagent (500 uL), vortexed for few seconds and results determined using an analyzer. Three absorbance readings were recorded at one minute interval and ALT serum concentration computed using manufacturer's protocol. The same procedure was followed to determine serum AST concentration with the AST reagent kits.

Weight was recorded in kilograms with the patient wearing light clothing and height was measured in meters with the patient standing upright without shoes using a stadiometer and height rod respectively (Secagmbh & Co. Kg, Germany). Body Mass Index (BMI) was calculated as height (m)/weight (kg) square.

These clinical evaluations along with physical examination were used to determine reaction rash (allergic reaction due to NVP), fever, anemia, Steven Johnson Syndrome or Toxic Epidermal and necrolysis due to NVP on all follow-up visits. Patients with hypersensitivity reactions were characterized as cases while those without symptoms were classed as comparisons. Individuals with a fever, rash or elevated AST and ALT levels equal to or greater than 3 times the "upper limit of the normal" were also grouped as cases while patients without a fever, rash and with normal aminotransferase values were comparisons.

### Identification of genetic variants

Whole blood samples were collected from patients in each group. Genomic DNA was extracted from whole blood samples using Quick-gDNA TM MiniPrep Kits (Zymo Research, South Africa) according to the manufacturer's instructions. Subjects were genotyped for *ABCB1* c.1236C>T (rs1128503), c.2677G>T/A (rs2032582) and c.3435C>T (rs1045642) variants using polymerase chain reaction – restriction fragment length polymorphism (PCR-RLFP) technique previously described [15]. The presence of *CYP2B6* c.516G>T (rs3745274) was determined by direct sequence analysis of PCR products which amplified exons 4, 5, 7 and 9 as previously described with minor modifications [16].

### Statistical analysis

All data were entered into Statistical Packaging for Social Science (ver. 17.0; SPSS, Chicago, IL) and imported into Stata™ version 10 (StataCorp, College Station, Texas, United States) for statistical analysis.

Data were summarized as frequencies and proportions. Continuous data were reported as mean ± standard deviation (if normally distributed) or median with interquartile range (if not normally distributed). Statistical differences between proportions were determined using the chi-square test. Incidence rates were calculated as per intention treat approach (i.e., In the statistical analysis, the time in weeks, for subjects falling out before the end of 24 weeks which may be due to either lost to follow-up or competing risk was considered in the incidence rate calculation). Each subject period of monitoring was factored in the calculation of incidence rate and reported as person-weeks. Observed allelic frequencies in Hardy-Weinberg equilibrium were consistent but not significant in the study population. All reported p-values were two - sided and $p<0.05$ was considered statistically significant.

## Results and Discussion

### Study population

Out of the 70 patients studied, 16 (22.9%) were males and 54 (77.1%) were females. The study participants' ages were between 21 and 62 years. At the end of the 24 weeks of monitoring, 11 (15.7%) were categorized as cases and 59 (84.3%) as comparisons. One patient died within one month after NVP initiation and 3 patients were lost to follow-up after recruitment. Out of the 11 cases observed, 8 were categorized as NVP hypersensitivity rash and 4 as hepatotoxicity. One patient had both NVP rash and hepatotoxicity. The average time in weeks for the incidence of rash and hepatotoxicity development was 6.25 and 13 person-weeks respectively. There was no significant difference between the age of cases and comparisons. The concentration of AST was much higher in the cases (119.44 ± 155.86) compared to the comparisons group (68.80 ± 42.65), p=0.056. The Concentration of ALT was also higher in the cases (136.44 ± 165.99) compared to the control (56.72 ± 33.02) p=0.003 (Table 1). All study participants were genotyped for three SNPs within *ABCB1* and *CYP2B6* 516 G>T. The frequencies of each polymorphism are summarized in Table 2. All polymorphisms were in Hardy-Weinberg equilibrium. No variant allele was detected for the three SNPs in *ABCB1* gene, while that for *CYP2B6* G>T allele, recorded 0.56% G and 0.44% T variant frequencies.

This study also investigated the risk factors associated with the development of cutaneous and hepatic adverse effects linked with NVP hypersensitivity reaction in HIV-1 treatment naïve Ghanaian subjects at the Korle-Bu Teaching Hospital.

Our findings did not seem to implicate any of the SNPs genotypes found to be associated with the development of NVP hypersensitivity reactions as reported in other studies [17]. There was no significant association between subjects for the *ABCB1* 1236 C>T linked with 2677

| Characteristic | | Cases N=11 | Comparison N=56 | p-value |
|---|---|---|---|---|
| **Age (mean ± SD)** | | 38.45 ± 11.28 | 38.09 ± 9.37 | 0.909 |
| **Gender** | | | | |
| | **Female** | 10 (19.61%) | 41 (80.39%) | 0.208 |
| | **Male** | 1 (6.25%) | 15 (93.75%) | 0.208 |
| **AST concentration (mean ± SD) (U/L)** | | | | |
| | **Baseline** | 39.70 ± 27.89 | 51.31 ± 47.51 | 0.459 |
| | **Study endpoint** | 119.44 ± 155.86 | 68.80 ± 42.65 | 0.056 |
| **ALT concentration (mean ± SD) (U/L)** | | | | |
| | **Baseline** | 27.05 ± 22.91 | 32.84 ± 21.43 | 0.442 |
| | **Study endpoint** | 136.44 ± 165.99 | 56.72 ± 33.02 | 0.003 |
| **CD4+ count (cells/mL)** | **Baseline** | 113.27 ± 100.45 | 141.00 ± 135.14 | 0.522 |
| **BMI** | **Baseline** | 19.31 ± 2.71 | 21.62 ± 3.92 | 0.066 |

**Abbreviations:** N: number of subjects; BMI: Body Mass Index; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; SD: Standard Deviation

**Table 1:** Demographic and phenotypic data for the nevirapine induced hypersensitivity reaction in study population.

| Genetic characteristic | | | Frequency, % |
|---|---|---|---|
| ***ABCB1*c. 1236 C>T (N=60) rs 1128503** | **Gene** | CC | 60 (100) |
| | | CT | (0) 0 |
| | | TT | (0) 0 |
| | **Allele** | C | 120 (100) |
| | | T | 0 (0) |
| ***ABCB1*c. 2677 G>T/A (N=67) rs 2032582** | **Gene** | GG | 67 (100) |
| | | GT | 0 (0) |
| | | TT<br>GA<br>AA | 0 (0)<br>0 (0)<br>0 (0) |
| | **Allele** | G | 134 (100) |
| | | T<br>A | 0 (0)<br>0 (0) |
| ***CYP2B6*c. 516 G>T (N=70) rs 3745274** | **Gene** | GG | 26 (37) |
| | | GT | 26 (37) |
| | | TT | 18 (26) |
| | **Allele** | G | 78 (55.7) |
| | | T | 62 (44.3) |

**Abbreviations:** G: Guanine; A: Adenine; T: Thymine; C: Cytosine

**Table 2:** Genotypic and allelic frequency distribution of *ABCB1* 1236C>T, *ABCB1* 2677 G>T/A and CYP2B6 516 G>T observed among study population.

G>A allele differences. This observation may be due to individual SNPs within the *ABCB1* gene not linked to the NVP rash/hepatotoxicity, but rather the haplotype (CA/TC) inherited together could be significantly associated with the reaction as suggested in other reports [18]. However, all genotype subjects were homozygous of the wild type. This was consistent with earlier findings among Ghanaian population [19]. The 1236T allele within exon 4, often associated with a decreased activity in the P-gp activity, detected in populations of Caucasian [20,21] and Asian origin [22,23] was absent in our study population. In addition, the 2677A variant allele in exon 21 reported in 1 % from Benin [24] was also absent in our population.

The low prevalence of implicated SNPs in the sub-region could be due to evolutionary positive natural selection for the wild type, which plays a vital role against gastrointestinal-tract infections [25]. This is because the *ABCB1* 3435C allele, in particular, leads to increased P-gp activity, which confers immunity to the intestinal epithelium against pathogens. Moreover, biochemical analysis on these MDR1 alleles points to the view that, the 2677T/A could alter drug transport by influencing its ATPase activity [26]. The 3435 C>T combined with 2677 T/A have an impact on the three dimensional structure of the gene product leading to reduced effect by some inhibitors [27].

The genotypic frequencies observed for the *CYP2B6* 516 G>T showed no significant difference between cases and comparisons to the development of the reaction in this study. This suggests that, other alleles may be linked to the NVP HSR in our study population contrary to *CYP2B6* 516 G>T implicated in other population [17]. The allele frequencies of 0.56% G and 0.44% T recorded in this study almost replicate studies involving Ghanaians that recorded 0.52% G and 0.48% T [28] and 0.55% G and 0.45% T [29] respectively. Alternatively, a secondary metabolic pathway for NVP such as CYP3A may minimize the influence of *CYP2B6* variants [30], accounting for the difference in individuals who expressed the variant allele but showed no clinical manifestation. NVP induces CYP2B6 and CYP3A4 expression over several weeks, increasing its own clearance [31] which could also account for the lack of association.

This study did not find any significant association between hepatotoxicity development and hepatitis B virus (HBV) co-infection as reported in other population [32]. Contrary to reports of correlation between HBV and elevation of AST and ALT serum concentration, none of the subjects' co-infected with HBV developed the observed hepatotoxicity.

No significant association was observed between NVP hypersensitivity reaction (hepatotoxicity) and the baseline AST and ALT serum concentrations in this study. Patients starting therapy on low serum concentration of ALT and AST at baseline could account for the lack of association. This study found no significant association between the baseline $CD4^+$ T-cells count and the development of hypersensitivity reaction. This support the cohort study with similar findings of no association of $CD4^+$ T-cells count >250 cells/$mm^3$ to the development of severe adverse effects including severe hepatotoxicity and/or cutaneous rash [33].

There was no significant association between baseline BMI and NVP induced hypersensitivity, which may be due to the low number of recruited patients who had their BMI within the overweight and obesity group. HIV/AIDS disease progression in most cases results in loss of weight accounting for the low and normal BMI values. Female gender was not statistically significant even though 99% of the cases were females.

Our study had some limitations. The sample size was relatively small and related to only patients at the Korle-Bu Teaching Hospital, one out of the over 37 HIV treatment centers across the country. The analysis could not cover NVP trough concentration as well HLA SNPs implicated in NVP hypersensitivity in other populations. Further work is required to evaluate in more detail the effects of risk and competing HLA alleles.

## Limitations

The authors were unable to recruit more patients from other health centers providing antiretroviral therapy due to insufficient resources. The ratio of men to women was relatively small; the authors were not able to confirm the female gender as a risk factor for nevirapine hypersensitivity development. This study was also undertaken in a single medical center, Korle-Bu Teaching Hospital, which may not be a general representation of Ghana. Although the patients came from variety of ethnic groups and socioeconomic backgrounds.

## Conclusion

This is the first study to determine risk factors to NVP hypersensitivity among HIV-1 Ghanaian patients. The findings are of clinical significance even though none of the factors considered was statistically significant to the NVP HSR. The 15.7% NVP hypersensitivity reaction recorded in this study shows that HIV-1 infected Ghanaian patients on NVP regimen also experienced this reported reaction as in other populations

This calls for investigation of other SNPs as well as other parameters linked to this reaction towards tailored NVP prescription and better management of these reactions by clinicians.

In the light of the above, exhaustive pharmacogenetic tests combined with therapeutic drug monitoring (TDM) of parent drugs and/or metabolites are recommended towards the achievement of personalized medicine. For medical conditions like HIV infection for which current management is lifelong drug administration, it is essential to ensure that the most effective drug/s is given (based on pharmacogenetic profile for a population, if not individual prescription), in order to minimize long-term side effects.

### Authors' Contributions

The study was conceived and designed by WK. He also assisted in drafting the manuscript. ETA collected the clinical data and performed all the experimental analysis. DB and DGA supervised the experimental analysis and assisted in the interpretation of the results. ETN assisted with the data analysis and drafting of the manuscript. All authors read and approved the final draft of the manuscript.

### Acknowledgement

The authors are grateful to Mr. Rudolf Mba Adaboro of the Applied Radiation Biology Centre of the Radiological and Medical Sciences Research Institute (RAMSRI), Ghana Atomic Energy Commission (GAEC) for his support during the laboratory analysis of this research work. We also extend special thanks to Ms. Esenam Buatsi of Department of Biochemistry, Legon, for assisting with samples collection.

### Funding

This work was supported by grant funding from Office of research and Development (ORID), University of Ghana.

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**Citation:** Kudzi W, Aboagye ET, Dzudzor B, Nartey ET, Achel DG (2017) Risk Factors of Nevirapine Hypersensitivity Reaction among Human Immunodeficiency Virus-1 Infected Treatment Naïve Patients at Korle-Bu Teaching Hospital. J AIDS Clin Res 8: 654. doi: 10.4172/2155-6113.1000654