

# HAART Therapy in Ghana: Assessment of Adverse Drug Reaction Reports of Patients at an HIV Clinic and a Teaching Hospital

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## ABSTRACT

**Background:** Highly Active Antiretroviral Therapy has changed the therapeutic approach to HIV/AIDS treatment. Due to genetic variation, there may be variability in response to HAART in different populations. Inappropriate HAART impacts directly on treatment outcomes as well as have financial implications fragile economy of a developing country. This study was a retrospective study on the adverse effect profile of different HAART combinations in patients attending an HIV clinic at Komfo Anokye Teaching Hospital in Ghana. **Methods:** Systematic random sampling was used to select 500 patient records covering a period of 5 years from 2010 to 2014. The variables captured and reviewed included patients' demographic information, HAART medication, CD4 counts and adverse drug reports. **Results:** Among the 12 common combinations, AZT+3TC with either EFV OR NVP accounted for more than 50%. In general, a lower CD4 count was associated with a lower adverse drug effect. After adjusting for the presence of other Anti-retrovirals in a HAART, Efavirenz was associated with higher incidence of adverse drug reactions reports than Nevirapine. However patients on nevirapine reported multiple adverse drug reactions than patients on efavirenz. Zidovudine's adverse effect on the hematopoietic was enhanced when it was combined with Efavirenz than with nevirapine. The worst

HAART in terms of adverse drug reactions was one having both stavudine and nevirapine. Tenofovir usually used as second line was rarely associated with any peculiar adverse drug event. **Conclusion:** Patients attending HIV clinic in Ghana responded differently to HAART combinations commonly prescribed in Ghana.

**Key words:** Adverse drug reactions, ARVs, HAART, AZT-3TC-EFV, AZT-3TC-NVP

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## BACKGROUND

There is an estimated 36.9 million (34.3 million-41.4 million) people living with HIV Globally as in 2014.<sup>[1]</sup> The HIV and AIDS epidemic remains a menace to the economies of many nations, particularly in sub-Saharan Africa.<sup>[2]</sup> HIV prevalence in Ghana was 1.3% in 2013 with an estimated 189,931 adults and 34,557 children living with HIV.<sup>[3]</sup> Due to its pathophysiology with high tendency of resistance development, the role of evidence based treatments guidelines is necessary to control the spread.<sup>[4]</sup> Highly Active Antiretroviral Therapy (HAART), a regimen consisting typically of three or four antiretrovirals has radically changed the therapeutic approach towards HIV infection.<sup>[5,6]</sup> But in spite of the numerous advantages and benefits associated with its introduction, the issues of drug-induced toxicities remains a great challenge;<sup>[7-10]</sup> a major cause of non-compliance and discontinuation of the HAART.<sup>[7]</sup>

Several studies demonstrate that genetic variation between individuals has been identified as a reason why HIV-infected patient on HAART experience adverse drug reaction and virologic failure with some antiretroviral drugs.<sup>[11]</sup> Studies have identified a correlation between these genetic variations and some antiretroviral drugs due to variations in expression of metabolic enzymes.<sup>[12]</sup> Due to ethnic and racial variability in response to some antiretroviral it's not recommendable to transpose results across different regions and populations. This study therefore, aimed at assessing the adverse drug reaction of HAART by comparing different HAART combinations among patients attending HIV clinic at Komfo Anokye Teaching Hospital.

## METHODS

### Study area

The study was conducted at the Medicine Directorate of Komfo Anokye Teaching Hospital (KATH). The hospital is the only tertiary health institution located in the middle belt of the country. The hospital is located in Kumasi, the capital of the Ashanti Region. It serves as the referral center for other hospitals in and around Kumasi and also from the middle and northern parts of the country. The Medicine Directorate

has the HIV clinic which offers voluntary counselling and testing, ART services and patients' medication counselling.

### Study design

This study was a cross-sectional descriptive retrospective study done at the HIV clinic of the Komfo Anokye Teaching Hospital (KATH), in Kumasi, Ghana. Systematic random sampling was used to select 500 patient records covering a period of 5 years from 2010 to 2014 (100 folders per year). The variables that were captured and reviewed in the study using the data collection tool included patients' demographic information such as age, gender, marital status, educational background and occupation. Base line CD4 counts before and after initiation of therapy was captured.

### Sample size

The minimum sample size was determined based on formula modified by Naing *et al.*  $n = Z^2 P (1-P) / d^2$ .<sup>[13]</sup>

Where  $n$ =sample size,  $Z$ =Z statistic for a level of confidence,  $P$ =expected prevalence (in proportion of one) and  $d$ =precision (in proportion of one). Using a Z statistic for a 95% confidence level (i.e.,  $Z=1.96$ ), precision of 5% (i.e.,  $d=0.05$ ) and a prevalence of 3.2% representing the prevalence of the disease in the Ashanti Region.

### Sampling method

Systematic random sampling technique was used to select patients for

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the study. Records of patients covering a period of 2010 to 2014 were sampled and reviewed from February to May 2015. Hundred patients' records were selected from each year. Out of the total number of patients seen during the various years under review, a constant number (kth) was determined, such that each (kth) patient record in respect of each year was selected and reviewed.

## ELIGIBILITY CRITERIA

### Inclusion criteria

Records of HIV patients with morbid conditions, or patients with a change medication treatment as well as patient with completely documented demographics information and prescribed medications in the folders were also included. Records of patient with documented usage of antiretroviral at least once and getting their services at Komfo Anokye Teaching Hospital were included

### Exclusion criteria

HIV Patients with incomplete records or those whose records indicate incomplete pre adherence counselling therapy were all excluded.

## DATA HANDLING AND ANALYSIS

The data captured was entered into Statistical Package for Social Sciences (SPSS) Version 20.0 database and examined, cleaned and analyzed. Mean and standard deviation was used to describe continuous variables with normal distribution whiles median and interquartile range were used to describe continuous variables with skewed distribution. Chi squared test was used to test the level of significance of association between any two variables compared. A p-value < 0.05 was used assess the level of significance of the assumed hypotheses.

## RESULTS

### Socio-demographic characteristics

Majority of the respondents were females constituting 70.8% (n=354,) as against (n=146, 29.2%) of males. The mean age of the patients was 39.94 years. Over 70% of participants had no education at all or a basic education. Only 12.4% had a tertiary education or a vocational training [Table 1].

**Table 1:** Socio-demographic characteristics of respondents

Bio Data	Number	Percentage
Age (years)	Mean (*SD)=39.9 (± 9.7)	
OCCUPATION		
Employed	57	14.4
Self-employed	381	73.6
Unemployed	62	12.4
Total	<b>500</b>	<b>100.0</b>
Educational qualification		
No formal education	130	20.4
Basic/JHS	223	47.6
Secondary	98	19.6
Tertiary	22	4.0
Technical/vocational	27	8.4
Total	<b>500</b>	<b>100.0</b>
Marital status		
Single	86	17.6
Married	249	49.6
Co-habitation	33	8.8
Divorced	80	17.6
Widow/widower	52	6.4
Total	<b>500</b>	<b>100.0</b>

Drug combination types used by respondents

Out of the 500 patients records reviewed in this study, it was noted only 12 combinations of ARVs were prescribed. Among the 12 common combinations, AZT+3TC with either EFV OR NVP accounted for more than 50%. However, 3TC+TDF+EFV combination was also commonly used (14.0%) [Figure 1].

Among the patients records reviewed for this study, 13.6% (n=68,) had their medications switched from one combination to the other for various reasons. Among the various reason cited for change in patient medications, drug toxicities and adverse effects was major accounting for 44.1% (n=30). Change in drug policy (17.6%), immunologic failure (14.7) and drug availability (11.8%) [Figure 2].

### CD4 count and experiencing of adverse effects

There was an association between the CD4 count of an individual at therapy initiation and the occurrence of an adverse drug reaction [Table 2]. Low CD4 (less than 250 cells/mm<sup>3</sup>) appeared to provide some protection against adverse drug reaction.

### Adverse effects experienced by respondents

There was a statistically significance association between drug combination type and incidence of adverse drug reaction [Table 3].

The prevalence of adverse effects experienced by organ systems was also captured; central nervous system recorded the highest (23.29%), followed by respiratory system (14.34%). Special senses disorder such as pain and numbness in the hands and feet's recorded the lowest [Table 4].

Comparing adverse effect profile of Efavirenze and Nevirapine combinations

Generally, in any two forms of HAART combination which differed only in either Efavirenze or Nevirapine, patients on Efavirenze were more likely to report an adverse event with treatment. Although there were fewer patients on nevirapine combinations, they reported multiple adverse events. Gastro-intestinal and hematological adverse effects were common with patients on efavirenze than patients on nevirapine while central nervous system related adverse effects were common with patients on nevirapine. Interestingly, peculiar CNS effects such as depression, anxiety and abnormal dreams were mostly associated with Efavirenze use.

Comparing adverse effect profile of Zidovudine and Stavudine combinations

**Table 2:** CD4 count and experiencing of adverse effects

CD4 count	Adverse Drug Reaction		Total	P value
	Yes	No		
Below 250	190	188	378	<b>0.036*</b>
Above 250	48	74	122	

Cross tabulation of respondents CD4 count against experiencing adverse effect; \*P ≤ 0.05 (using chi square test)

**Table 3:** Proportion of patients on HAART experiencing adverse effects

Combination type	Adverse effects experienced		P value
	Yes	No	
<b>AZT-3TC-EFV</b>	86(35.7%)	109(42.1%)	0.005**
<b>AZT-3TC-NVP</b>	51(21.2%)	60(23.2%)	
<b>3TC-TDF-EFV</b>	27(11.2%)	43(16.6%)	
<b>D4T-3TC-EFV</b>	38(15.8%)	23(8.8%)	
<b>TDF-EFV-FTC</b>	10(4.1%)	9(3.5%)	
<b>D4T-3TC-NVP</b>	5(2.1%)	2(1.7%)	
<b>3TC-NVP-TDF</b>	19(7.9%)	6(2.3%)	
<b>*OTHERS</b>	5(2.1%)	4(1.5%)	

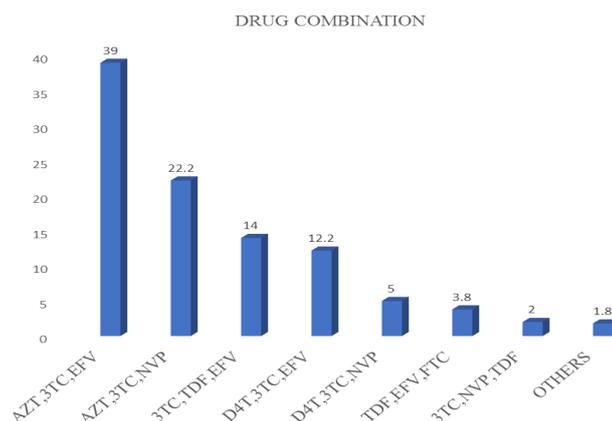


Figure 1: The figure represents the proportion of patients on different HAART combinations

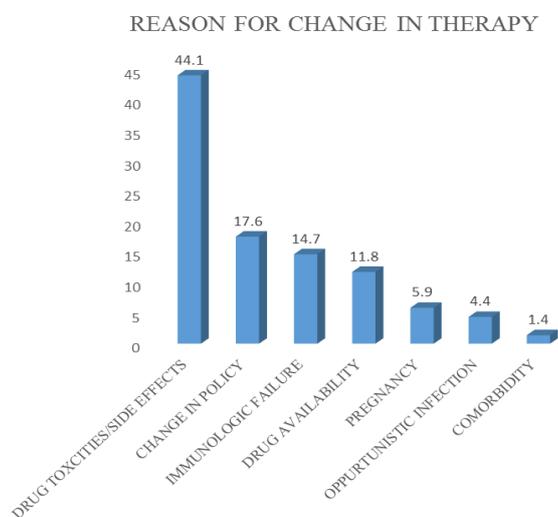


Figure 2: The figure represents reasons for change in HAART for patient during HIV management

Table 4: The prevalence of HAART side effects as against organ system

Combination type	% patients	GI	CNS	MUSCULAR SKELETAL	ANAEMIA	RESPIRATORY
AZT+3TC+EFV	195	32(16.4%)	38(19%)	13(6.0%)	20(10.3%)	18(9.2%)
AZT+3TC+NVP	111	16(14.4%)	30(27%)	8(7.2%)	8(7.2%)	11(9.9%)
3TC+TDF+EFV	70	4(5.7%)	5(7%)		5(7.0%)	1(1.4%)
D4T+3TC+EFV	61	15(24.6%)	22(36.1%)	3(4.9%)	2(3.2%)	11(18%)
TDF+EFV+FTC	19	1(5.3%)	3(15.8%)	1(5%)	1(5.3%)	2(10.5%)
D4T+3TC+NVP	25	6(24%)	20 (80%)	2(8%)	1(4%)	6(24%)
3TC+NVP+TDF	10	-	2(20%)	5(50%)	1(10%)	1(10%)
OTHERS	9	6(66.6%)	5(55.6%)	3(30%)	4 (44%)	5(5.5%)
TOTAL	500	80 (16%)	126(25.2%)	35 (7%)	42 (8.4%)	38 (7.6%)

AZT-3TLPV/r, 3TC-FTC-EFV, AZT-TDF-FTC

Generally in patients on zidovudine reported lesser Gastro-intestinal and central nervous system related adverse events than patients Stavudine. However, on the red blood cells patients on zidovudine combinations reported more adverse effects than patients on D4T. Subsequently 10.3% of patients on AZT+3TC+EFV experienced low red blood cell count; higher than any of the other combinations used for HAART. The worse combination items of adverse events were one involving Stavudine and Nevirapine. The incidences of itchy skin and skin rashes could not be attributed to any particular medicine used in HAART. However Stavudine and nevirapine combinations were associated with the most frequently reported adverse effect associated with the use of ARV in this study was skin rashes (8.87%) and were more associated with the Non-Nucleoside Reverse Transcriptase

Inhibitors, Efavirenze and Nevirapine. However, stavudine appeared to increase skin rashes and itchy skin caused by nevirapine.

Cough was the second most common adverse reaction reported in this study. Diarrhoea was a common reported adverse event in this study. It represented about 6.34% of ADRs reported in this study. Also hepatotoxicity recorded 1.08% of adverse drug reaction reported in the study.

## DISCUSSION

This study highlighted the major antiretroviral drug combinations prescribed at Komfo Anokye Teaching Hospital, a tertiary hospital in Kumasi-Ghana, and the adverse events associated with their use.

These adverse events described in this study are mostly well known and documented. The most often prescribed combinations were AZT+3TC+EFV and AZT+3TC+NVP. An earlier study conducted in KATH,<sup>[14-18]</sup> also confirms AZT+3TC+EFV was the most prescribed ARV combination followed by AZT+3TC+NVP.

This study revealed that majority of the participants were females who were in their reproductive ages of 15 to 45 years and had similar demographics characteristic to others studies in sub-Saharan Africa in terms of gender distribution, socio-economic status and educational level.<sup>[18-21]</sup> There are conflicting reports about the relation between gender and adverse effects from HAART,<sup>[21,22]</sup> but our study did not find any association between gender and incidence of adverse drug report. We realized that the incidence or an adverse episode was significantly associated with patient CD4 count at initiation therapy with patients having high CD4 (above 250 cells/mm<sup>3</sup>) experiencing more adverse effects confirming previous findings.<sup>[21]</sup>

Generally, in our study, NNRTIs were associated with skin rashes and itchy skin and was consistent with other study.<sup>[14]</sup> This was not seen with any of the NRTIs but was increased when NNRTI was combined with D4T. This reaction is known to resolve following withdrawal of the offending agent.<sup>[23]</sup>

Cough was the second most common adverse reaction reported in this study. With the exception of maraviroc, which was not prescribed in the hospital, cough is not a notable adverse events to the antiretroviral drugs prescribed in this study.<sup>[24]</sup> Patient with advance HIV infection could present cough as symptom. An evidence supporting this finding is found in other studies.<sup>[25,26]</sup> However, it was observed that 19 out of the 42 folders had tuberculosis as a comorbid condition. This could account for the cough documented as a side effect in this study. Diarrhoea has been linked with the use of protease inhibitor 21, but in this study PI were seldom use. Also hepatotoxicity recorded 1.08% of adverse drug reaction reported in the study. A study conducted in 2006,<sup>[27]</sup> reported incidence of hepatotoxicity linked with the use of lamivudine and zidovudine, however other studies have also reported hepatotoxicity among patient receiving non-nucleoside reverse transcriptase inhibitors.<sup>[28,29]</sup>

Distinguishing antiretroviral-related renal toxicity from either direct effects of HIV-1 on the kidney or from a multitude of non-HIV-related kidney diseases is often challenging.<sup>[30]</sup> Some studies have found an association between certain class of HAART and hypertension.<sup>[31,32]</sup> Persons living with HIV are known to be at risk for developing cardiovascular diseases or exacerbating a pre-existing one.<sup>[33]</sup> Hypertension is known to be a precursor to the development of other cardiovascular diseases, efforts to control this condition should be emphasized.

## CONCLUSION

The most prescribed combination of HAART at Komfo Anokye Teaching Hospital was AZT+3TC+EFV, followed by AZT+3TC+NVP. Patients attending HIV clinic in Ghana responded differently to HAART combinations commonly prescribed in Ghana.

## Abbreviations

HAART: Highly Active Antiretroviral Therapy; ADR: Adverse Drug Reaction; ART: Antiretroviral Therapy; AZT: Zidovudine; EFV: Efavirenz; NVP: Nevirapine; 3TC: Lamivudine; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; TB: Tuberculosis.

## DECLARATIONS

### Consent for publication

Not applicable in this study

### Availability of data and material

Not applicable for that section.

### Authors' contributions

Paa Kofi Tawiah Adu-Gyamfi, Kwesi Boadu Mensah, Eric Boakye-Gyasi participated in the conception and design of the manuscript. Paa Kofi Tawiah Adu-Gyamfi and Kwesi Boadu Mensah performed the statistical analysis and drafted the manuscript. All authors revised the script critically. All authors read and approved the final manuscript.

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### Competing interests

The authors declare that they have no competing interests. Availability of data and materials. Personal data from this study will not be shared publicly for ethical reasons.

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The study was funded by the authors.

### Ethics approval and consent to participate

Ethical clearance was obtained from the Committee on Human Research, Publication and Ethics of the Kwame Nkrumah University of Science and Technology, Kumasi. Permission was obtained from the head of the directorate of Medicine at Komfo Anokye Teaching Hospital before data collection was started. Names and addresses of patients were not recorded to ensure that their identities are not exposed. Case Record Forms were stored in a safe place with restricted access. The computer used for the data entry was password protected and secured and only the principal investigator had access to it. Data obtained was used exclusively for the purposes of this study.

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