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Original Article

HAART THERAPY IN GHANA: COMPARATIVE ASSESSMENT OF THE EFFECTIVENESS OF DIFFERENT HAART COMBINATIONS AT KOMFO ANOKYE TEACHING HOSPITAL

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ABSTRACT

Objective: Although all marketed antiretrovirals (ARVs) have proven efficacy, genetic differences can result in varied effectiveness. This study was conducted to determine the effectiveness of different Highly Active Antiretroviral Therapy (HAART) combinations among patients attending HIV clinic at a Major Teaching Hospital in Ghana.

Methods: The study was a retrospective study involving 500 patients at an HIV clinic in the Ashanti Region of Ghana.

Results: Twelve major antiretroviral combinations for HAART were prescribed at the study center. The most prescribed drug combinations were AZT+3TC+EFV and AZT+3TC+NVP. The study identified that HAART, irrespective of the kind of drug combination used, was effective at increasing CD4 count within the first 6 mo of therapy initiation in the study population. However, the magnitude of the increases differed from combination to combination. All HAART combinations with zidovudine as one of the drugs resulted in higher CD4 counts compared with combinations containing stavudine. HAART with nevirapine also resulted in a higher CD4 count than those with efavirenz. However, efavirenz-based combinations appeared to be more effective in critically ill patients and patients with mean $CD4^+$T helper cells count below 100 cell/mm^3. More importantly, efavirenz was common among all HAART combinations that resulted in treatment failure.

Conclusion: There was significant variation in response to different HAART combination among Ghanaian HIV patients**.** However, there was no statistically significant difference in mean CD4 count between the two most predominately used HAART i. e AZT+3TC+EFV and AZT+3TC+NVP**.**

Keywords: Haart, AIDS, HIV, Antiretrovirals, Effectiveness, Sub-Sahara Africa

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INTRODUCTION

The advent of Highly Active Antiretroviral Therapy has tremendously reduced HIV morbidity and mortality [1, 2]. Antiretroviral (ARV) are medications for the treatment of infection by retroviruses, primarily HIV. When such medicines, typically three or four, are acquired in combination, the approach is known as Highly Active Antiretroviral Therapy (HAART) [3]. Compared with Antiretroviral (ARV) monotherapy, HAART has significantly reduced treatment failures, suppressed viral transmission and mortality [4]. Although all marketed ARVs have proven efficacy, patient variability as a result of genetic differences in response to drug action can result in varied effectiveness [5]. These variations have been identified as a major problem which can lead to either sub-therapeutic or supratherapeutic treatment outcomes [6]. Pharmacokinetics of a drug can be affected by genetic polymorphism and can therefore lead to reduce plasma and tissue concentration, thereby altering the effectiveness and safety of a prescribed drug [7]. For example, it has been shown that there are variations in pharmacokinetics, efficacy and toxicity of ARVs among people of diverse ethnicity even at standard or recommended doses [8, 9].

There has not been any pharmacogenomics studies in Ghanaian population to help tailor antiretroviral drug selection for maximum health benefit of HIV patients. As such, the effectiveness or otherwise of Highly Active Antiretroviral Therapy is yet to be studied comprehensively in Ghana. It is very possible that due to genetic variation as well as some sociocultural practices, Ghanaian HIV patients may not be obtaining the expected benefits associated with HAART. CD4+T helper lymphocyte cell count has been used previously as a predictive measure of development and prognosis of AIDS especially in resource constraint settings where viral load studies may be difficult. We had earlier reported variation in HAART associated adverse effects in Ghanaian population [10]. Therefore, this study was conducted to determine the effectiveness of different HAART combinations among patients attending HIV clinic at Komfo Anokye Teaching Hospital.

MATERIALS AND METHODS

Study design

The study was a cross-sectional, descriptive and retrospective in approach. The study was carried out at an HIV clinic at the Komfo Anokye Teaching Hospital in the Ashanti Region of Ghana. Variables were extracted from the patients' folders using a data collection tool, and these included age, gender, level of education, occupation, marital status, type of combination therapy, comorbidities, as well as baseline CD4 counts before and 6 mo after initiation of HAART treatment.

Inclusion criteria

Patients with complete demographic information and documented usage of antiretroviral drugs for at least once at the study site. Patients with CD4 recorded at the start of therapy and at least 6 mo into therapy.

Exclusion criteria

Patients with incomplete medical history and records, and those with incomplete pre-adherence counselling therapy, referred patients, patients with kidney and liver co-morbidities. Patients without information on CD4 cells were also excluded.

Sample size determination

The minimum sample size was determined based on the formula modified by *Naing et al.* (2006).

$$n=Z2\ P\ (1-P)/d2.\ [10].$$

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 of Ghana [11].

Sampling technique

Systematic random sampling was used to select patients' folders for the study, covering the periods from 2011 to 2015. A total of one hundred patients were selected from each year of the study, by using a constant number (k^{th}) to select a folder, making a total of 500 folders for the entire five years. The folders were thoroughly examined using the inclusion and exclusion criteria.

Analysis of data

The data captured was entered into Statistical Package for Social Sciences (SPSS) Version 20.0, examined, cleaned and analyzed. Mean and standard deviation was used to describe continuous variables with normal distribution whiles median and interquartile rage were used to describe continuous variables with skewed distribution. Categorical variables were analyzed using chi-square test. A p-value less than 0.05 was used to assess the level of significance.

Ethical consideration

Ethical clearance (CHRPE/AP/156/16) 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.

Limitations of the study

One of the main limitations was the retrospective nature of the study. It was not possible to ensure that all patients complied with their treatment. This could confound the efficacy of the HAART in this study. The use of CD4 as a measure of efficacy instead of viral load was also a major limiting factor due to resource constraints.

RESULTS

Socio-demographic characteristics

The mean age of the patients was 39.94 y. Most of the respondents were females constituting 70.8 % (n=354,) as against (n=146, 29.2 %) of males. Over 70 % of participants had been educated up to the Junior High School or have had no formal education at all. Seventy-three percent described themselves as self-employed (see reference 9 for more details).

Drug combination types used by respondents

Out of the 500 respondents in the study, only 12 of many possible combinations of ARVs were prescribed. Among the 12 combinations, AZT+3TC with either EFV OR NVP accounted for more than 50%. However, 3TC+TDF+EFV combination was also commonly used a as second line option (see reference 9 for further details).

HAART combinations and CD4

There was a significant difference between the mean CD4 count before initiation of therapy (159.7±118.7) and that after 6 mo of initiation of therapy (344.2±173.4 ($p<0.001$)). This suggested HAART, irrespective of the kind of drug combination used, was able to increase CD4 count within the first 6 mo of therapy initiation within the study population (table 1). However, the magnitude of the increases in CD4 cells differed significantly from combination to combination (table 1).

Table 1: Mean CD4 count compared with the drug combination

Variable	Mean CD4 count (cells/mm^3)±SD	P value
Initial CD4	159.7±118.7	0.001***
CD4 after 6 mo	344.2±173.4	
ART combinations		
AZT,3TC,EFV	205.39±125.7	0.001***
AZT,3TC,NVP	220.64±138.6	
3TC,TDF,EFV	132.49±105.2	
D4T,3TC,EFV	128.68±129.8	
TDF,EFV,FTC	141.24±98.9	
D4T,3TC,NVP	190.75±118.1	
3TC,NVP,TDF	176.00±156.6	
OTHERS	112.33±75.1	

Data expressed as mean±SD. N=459. Paired samples T-test was used to compare initial CD4 to CD4 after 6months and One-way ANOVA followed by scheffe's post hoc test was used to compare CD4 amongst the different ARV combination. *** means P ≤ 0.0001

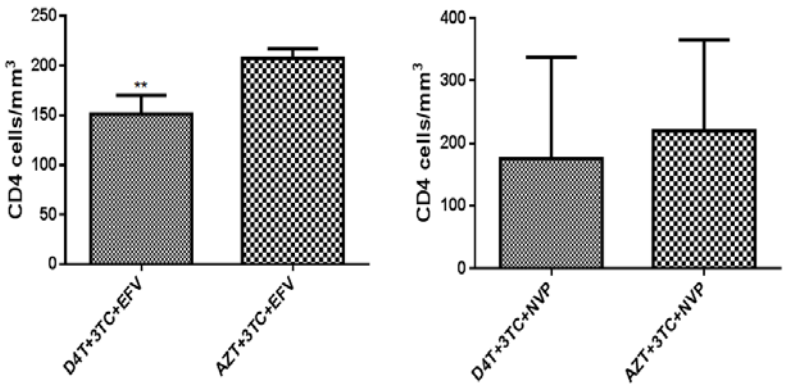

Fig. 1: (a) Comparing AZT+3TC+EFV and D4T+3TC+EFV on CD4 count, **P ≤ 0.001 using unpaired test, 1(b) Comparing AZT+3TC+NVP and D4T+3TC+NVP on CD4 count

Comparing mean CD4 of various HAART combinations

There was no statistically significant difference in CD4 count between the two most predominately used ARV combinations for HAART i. e AZT, 3TC, EFV and AZT, 3TC, NVP**.** Interestingly**,** these two major combinations increased the mean CD4 count significantly when compared to 3TC/TDF/EFV which was also highly preferred by prescribers as a second-line treatment option (table 2).

Table 2: Comparing the mean CD4 of various HAART combination

Combination type	Combination type	Mean difference
AZT,3TC,EFV	AZT,3TC,NVP	-15.25404
	3TC,TDF,EFV	72.89443*
	D4T,3TC,EFV	76.70674*
	TDF,EFV,FTC	64.15145
	D4T,3TC,NVP	14.63674
	3TC,NVP,TDF	29.38674
	OTHERS	93.05341
AZT,3TC,NVP	3TC,TDF,EFV	88.14847*
	D4T,3TC,EFV	91.96078*
	TDF,EFV,FTC	79.40548
	D4T,3TC,NVP	29.89078
	3TC,NVP,TDF	44.64078
	OTHERS	108.30744
3TC,TDF,EFV	D4T,3TC,EFV	3.81231
	TDF,EFV,FTC	-8.74299
	D4T,3TC,NVP	-58.25769
	3TC,NVP,TDF	-43.50769
	OTHERS	20.15897
D4T,3TC,EFV	TDF,EFV,FTC	-12.55529
	D4T,3TC,NVP	-62.07000
	3TC,NVP,TDF	-47.32000
	OTHERS	16.34667

All data are expressed as mean±SD (n=459), *p<0.05, using (one-way ANOVA followed by Scheffe's post hoc test).

Comparing zidovudine (AZT) based combinations to stavudine (D4T) base combination

For all HAART combinations which differed only in either AZT or D4T; AZT combinations consistently resulted in higher mean CD4 counts compared with D4T combinations (fig. 1a and b). This observation was statistically significant when AZT+3TC+EFV was compared to D4T+3TC+EFV but not when nevirapine (NVP) replaced efavirenz (EFV). It appears that AZT synergizes with EFV or a combination of 3TC+EFV in Ghanaian HIV patients.

Comparing Efevirenz (EFV) based combinations to nevirapine (NVP) combinations

Generally, the study showed that NVP improved patient baseline CD4 count across all combinations better than EFV although not statistically significant (fig. 2a), however in patients with CD4 count lower than 100 cell/mm^3, it was evident that EFV was more effective in raising CD4 count better than NVP (fig. 2b). EFV was found in all HAART regimen associated with treatment failure.

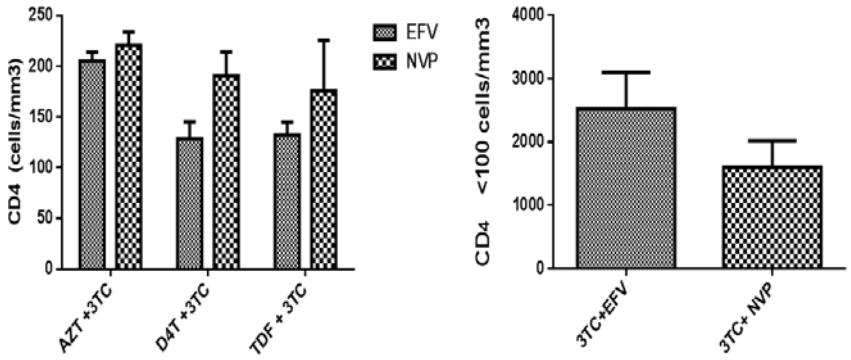

Fig. 2: a. Comparing HAART regimen that differed only in either efevirenz or Nevirapine for 6 mo on CD4 cell count, b. Comparing CD4 cell change of patients with low CD4 count (100 cell/mm^3) treated with either efevirenz or Nevirapine combinations for 6 consecutive months

DISCUSSION

This study highlighted the major HAART combinations and their effectiveness in Ghanaian population. The most prescribed combinations were AZT+3TC+EFV and AZT+3TC+NVP. This combination is similar to what has been reported elsewhere [12,13]. A study conducted in KATH also confirmed AZT+3TC+EFV was the most commonly prescribed HAART followed by AZT+3TC+NVP [13]. These combinations were in line with the recommendations of the National guidelines for the use of ARV in Ghana as well as WHO guidelines [14].

There was a significant rise in mean CD4 count after 6 mo of initiation of therapy. Kr *et al.,* (2014) also reported improvement in CD4 cell count within 6 mo of therapy in HIV patients as well as in those with HIV comorbidity [15]. It is prudent for HIV/AIDS patients to receive HAART regardless of adverse effects. It has been documented that the degree of immune restoration is dependent on

the degree of immunodeficiency at the initiation of HAART treatment [16]. This may affect both morbidity and mortality rates in HIV patients.

The mean CD4 count before initiation of therapy in this study was 159.7 cells/mm^3. This shows that most of the diagnoses occurred after patients reported clinical symptoms. Several studies have reported that initiating HAART therapy early when CD4 count is high results in higher mean CD4 levels and better treatment outcomes [17, 18]. The most essential prognosis indicator of clinical advancement and survival after HAART initiation is based on CD4 count and medication adherence [19]. Patients with lower baseline CD4 count remain at risk for opportunistic infections for a substantially longer period than patients starting HAART at higher CD4 counts hence affecting risk for serious morbidity and death [20-23].

A study conducted in high-income countries suggests that EFV is superior to NVP in achieving an undetectable viral load [24]. In this study, however, NVP proved to be more effective in improving CD4 counts than EFV although not statistically significant. Again, in all combinations that differed only in AZT and D4T, AZT patients experienced significant improvement in CD4 and less adverse effects. Subsequently, there were low CD4 count increase and high adverse effects with D4T and NVP combinations. Interestingly, when CD4 was very low and in critically ill patients, EFV proved better than NVP at increasing CD4 counts. However, EFV HAART combination was associated with treatment failures or immunologic failure during HIV management. This result conflicts with earlier reports by Van Oosterhout *et al.* [25].

AZT efficacy was remarkably consistent in all the HAART combination. It appeared that AZT synergies with EFV but its use was always associated with severe anemia, which led to a change in the drug combination in certain instances. A prospective cohort study conducted by Shet *et al.*, 2014, indicated that patients on zidovudine had 22 times higher risk of developing anemia compared to those on other regimens [26]. However, adverse drug reactions (ADRs) associated with the use of zidovudine is expected to increase because of its proven efficacy in Ghanaian HIV patients and its use in mother to child transmission [27].

Contrary to the perception of drug stock out as the more important reason for drug change, this study found that drug toxicity was rather the most important reason for medication change. This is in line with other reports [26, 28]. It emerged from the study that TDF+3TC+EFV was becoming a popular treatment option and second line drug when drug toxicity was of major concern. However, a careful analysis showed that it was less efficacious at improving CD4 when compared to traditional options of AZT+3TC with either EFV or NVP within the first 6 mo of initiation of therapy.

CONCLUSION

There were 12 major antiretroviral combinations that were employed in HAART for the treatment of HIV patients in the study. All HAART therapy resulted in statistically significant increases in mean CD4 counts within 6 mo of initiation of therapy. However, the magnitude of the increases differed from combination to combination.

ABBREVIATION

Antiretrovirals (ARVs), Human Immunodeficiency Virus (HIV), CD4+T helper cells (CD4 cells), Stavudine (D4T); Lamivudine (3TC); zidovudine (AZT); Efavirenz (EFV); Tenofovir (TDF); Lopinavir/ritonavir (LPV/r); Abacavir (ABC); Emtricitabine (FTC), Zidovudine (AZT).

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Nil

AUTHOR CONTRIBUTIONS

PKT and KBM developed concept. PKT and MA did data collection and analysis. SMA wrote the first manuscript draft.

CONFLICT OF INTERESTS

Authors have no competing interests to declare.

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