PRESCRIPTION PATTERN OF FIRST LINE HAART REGIMEN AMONG TREATMENT-NAÏVE HIV-INFECTED ADULTS AND ADOLESCENTS AT A TERTIARY HOSPITAL IN NORTH EASTERN NIGERIA

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ABSTRACT

BACKGROUND: Rational prescription of Highly Active Antiretroviral Therapy (HAART) have dramatically altered the natural progression of Human Immunodeficiency Virus (HIV) infection, and significantly improved the quality of life for many patients infected with the virus. **OBJECTIVE**: This study is aimed at analysing the HAART prescribing patterns in newly recruited adult HAART-naïve patients at a tertiary hospital. **METHODS**: This is a non-experimental, quantitative retrospective review of 638 initial prescriptions of first line HAART for newly recruited adults and adolescents (>15years) between January, 2011 and December, 2012 at University of Maiduguri Teaching Hospital (UMTH) in northeast of Nigeria. Prescription decisions were analysed using Chi-square test and p value < 0.05 was considered significant. **RESULTS**: A total of 392 (61.40%) of the studied sample were females while 246 (38.6%) were males. The mean age and baseline CD4 count were 36.21±9.27 and 193.82±151.13 cells/µl respectively. The most commonly prescribed HAART regimen were Emtricitabine/Tenoforvir/Efavirenz, (FTC/TDF/EFV) [220 (34.5%)] and Lamivudine/Zidovudine/Nevarapine (3TC/AZT/NVP) [202 (31.7 %)]. Most of the Patients (90.9 %) with Tb at initial HAART were prescribed EFV-based regimen while most of the patients (82.1%) with HBV were prescribed with 3TC/TDF – based HAART. However, 6 (20%) of the patients with Hb ≤ 7 had AZT-based regimen. **CONCLUSION:** Generally, Prescriptions of HAART were consistent with the recommended preferences by National guidelines for treatment of non-pregnant HAART-naïve adult and adolescent patients; however prescriptions of Zidovudine oriented regiment were non-adherent to recommendation in patients with baseline severe anaemia (Hb ≤ 7) Continuous education on treatment guideline recommendations should be emplaced.

Keywords: HIV, Maternal Outcome, Fetal Outcome, Maiduguri

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retroviral disease which causes progressive immune degeneration and result in chronic persistent infection with gradual onset of clinical symptoms[1]. HIV attack CD4+ T lymphocyte cells, resulting in gradual depletion of this subset of T cells with subsequent dysfunction of the immune system and progression to Acquired Immunodeficiency syndrome (AIDS) which is

the late and most serious stage of HIV infection [2].

More than 34 million people have died from HIV/AIDS and 36.9 [34.3–41.4] million people living with HIV at the end of 2014 with 2.0 [1.9–2.2] million people becoming newly infected with HIV in 2014 globally.[3]

Sub-Saharan Africa is the most affected region, with 25.8 [24.0–28.7] million people living with HIV in 2014. Also sub-Saharan Africa accounts for almost 70% of the global total of new HIV infections.[3]

Potent combinations of antiretroviral drugs (also called highly active antiretroviral therapy [HAART]) have dramatically altered the natural progression of human immunodeficiency virus (HIV) infection, and significantly improved the quality of life for many patients infected with HIV[4].

Guideline on the use of ART in the management of HIV infection has evolved over the last decade and the treatment guideline during the period of this study for resource limited nation like Nigeria is the 2010 WHO treatment guidelines as adopted in 2010 Treatment guideline by the Nigerian Federal ministry of health (FMoH)[5,6].

The following work studied HAART prescribing pattern among newly recruited adult HAART-naïve patients that were attending the ART clinic of the University of Maiduguri Teaching Hospital, north eastern Nigeria. This study analyses the prescription pattern of initial first-line HAART in HIV-infected adults and adolescents and assess its adherence to recommended guideline for HAART prescription in this set of patients.

METHODS

This non-experimental quantitative descriptive study was carried out in University of Maiduguri Teaching Hospital (UMTH), Maiduguri, in Northeast of Nigeria. UMTH is a tertiary hospital established to provide referral services, teaching and research for the region. It is one of the largest comprehensive HIV service center in the country and the largest in the region with currently over 5,000 adults and adolescents on HAART and about 1000 patients on care.

This study targets the population of non-pregnant adults and adolescents (> 15 years) who commenced HAART within the period of January, 2011 through December, 2012 in UMTH. Patient who presented for Prevention of mother to child transmission (PMTCT), HAART-experienced patients and patients who were ≤ 15 years were excluded from the study. When the entire databased was combed with inclusion and exclusion criteria only 1549 patients out of the 6000 patiens in the database were eligible for the study. A total of 981 (63.33 %) of the eligible patients were commenced on HAART in 2011 while 568 (36.67%) was recruited in 2012.

Sample size: The minimum sample size desired was calculated with reference to the formula: $nf = \frac{Nn}{N+n}$ where $n = \frac{Z^2p(1-p)}{d^2}$ and N is estimated size of study population (1549) as described by Araoye.[7] the z, p and d, are the standard normal deviate (1.96 considered at 95% confidence interval), proportion of the population with certain characteristics (50% was considered for maximum variability) and degree of accuracy (0.05) respectively. The minimum desired sample size was estimated to be 322 patients and this was however, increased to 644 with consideration for the each year contributing proportion for reliability and validity purpose.

A total of 644 patients, with aid of Patient unique hospital number, were randomly selected from 1549 eligible patients who met our inclusion criteria. These 1549 Eligible patients were abstracted from the pharmacy database (Filemaker pro version 12.0) arranged in ascending order of their hospital number and

assigned a serial number from 1 through 1549. A total of 644 patients' hospital number was then randomly selected from this sorted data with the aid of random number generator of Statistical package for social Sciences (SPSS) version 16.0.

Data Collection:
Data of 644 patients was abstracted from the electronic patients' treatment response folder of the FileMaker pro pharmacy database. Primary data includes demographic (Age, and sex) and baseline value of data like weight, CD4 cell count, haemoglobin (Hb) value (PCV), Serum creatinine, initial Tuberculosis status Hepatitis B virus (HBV) status and HAART regimen. Secondary data which include creatinine clearance (CrCl) was estimated using other variables such as age, gender and weight as described by Cockcroft-Gault-equation.[8]

Data analysis
Patients with Creatinine clearance of < 60/mins were considered Renal insufficient while the renal function of those with CrCl >60ml/mins was considered Normal (renal sufficient). Heamoglobin (Hb) value of ≤ 7gm/dl mm (PCV ≤ 21 %) was considered Anaemic while Hb > 7gm/dl (PCV > 21%) was considered Not Anaemic.[9] Descriptive statistics were done using simple frequency, percentages, means and standard deviation. Simple frequency and percentages were applied on categorical data (sex, class of ART) while mean and standard deviation were employed in quantitative data (age, Baseline CD4 count). In inferential analysis Chi-Square and student t- test were employed to assess association between categorical data and determine difference between mean of two quantitative variables respectively. P value of <0.05 was considered statistically significant.

RESULTS

This study reviewed the initial prescription of 644 non-pregnant adults and adolescents who commenced treatment between January 2011 and December 2012. Table 1 shows that there were more female patients (61.40%) that commenced therapy within the study period. The mean age ± SD of the study population was 36.21 ± 9.27 while that of male and female populations were 40.48 ± 9.09 and 33.54 ± 8.3 respectively. Male population was older than the female patients (p <0.01). The mean CD4 count of the population was 193.82±151.13; Male patient commenced therapy with much lower CD4 count (167.55±109.16) than the females (210.24±170.34) (p<0.01).

Most commonly prescribed HAART was FTC/TDF/EFV (34.5%) followed by 3TC/AZT/NVP (31.7%) as shown by table 2. The least commonly encountered prescription was 3TC + ABC +EFV (0.6%).

The most commonly prescribed drug among female patients was 3TC/AZT/NVP (42.3%) and 3TC/TDF+NVP (38.3%) while the least was 3TC+ABC+EFV (0.5%). Among the male patients the most commonly prescribed was FTC/TDF/EFV (63.4%) and the least prescribed was 3TC+ABC+EFV (0.8%). There was no significant difference in the prescription pattern between gender (p=0.137). The mean age for patients prescribed with each regimen differs (p=0.000) as older patient were likely to be prescribed with 3TC//AZT + EFV and FTC/TDF/EFV. The baseline CD4 count was however, different among patient with different category of HAART (P= 0.043).

Table 3 shows that NVP-based regimen was prescribed for more patients than the EFV-based regimen; while Female patients were prescribed more with NVP based regimen the male patient were prescribed with EFV based regimen.

NVP-based regimen was prescribed more than EFV-based regimen across three category of baseline CD4 count. NVP based combination drug was most prescribed (59.2%) to patient that commenced therapy without Tb infection

and EFV-based combination was prescribed for most (90.9%) patients that commenced ARV with TB infection. NVP based regimen was prescribed more in 2011(60.8%) and 2012(53.4%). Table 4 shows that Patients with impaired renal function (77.8%) were more likely to be prescribed with tenofovir than those with normal renal function [61.7 (p = 0.027)].

There was a significant difference in the prescription pattern (distribution) of HAART base on Hepatitis B status at the initial ART (P= 0.002) as shown in table 5. The most commonly prescribed HAART in patients who had hepatitis B Virus at baseline was FTC/TDF/EFV (46.4%) followed by 3TC/TDF + NVP (35.7%) while the least prescribed was 3TC/AZT + EFV (7.1%). When disaggregated by year of entry (recruitment) the prescription pattern was still associated with the hepatitis B status of patient. Most commonly prescribed HAART in patient co-infected with HBV was FTC/TDF/EFV (56.2%) and 3TC/TDF + NVP (41.7%) in 2011 and 2012 respectively.

Table 6 shows that there was no difference between the prescription pattern of HAART in patients with anaemia and those without anaemia at baseline (P= 0.177). The most commonly prescribed ART in patients who at initiation were anaemic was FTC/TDF/EFV (53.3%) followed by 3TC/TDF + NVP (26.7%) while the least prescribed was 3TC/AZT + EFV (6.7%). When disaggregated by year of entry (recruitment) there was significant difference in the prescription pattern between the anaemic and non-anaemic patients in 2011. In 2011 the most commonly prescribed ART in anaemic patient was FTC/TDF/EFV (50.0%) followed by 3TC/TDF + NVP (40.0%) (P=0.026) and in 2012 it was FTC/TDF/EFV (60.0%) followed by 3TC/TDF + NVP (20.0%) and 3TC/AZT/NVP (20.0%) (P=0.440).

Table 1: Background Characteristics of Study Population

	Female (Mean± SD)	Male (Mean± SD)	Total (Mean ± SD)	p-value
N (%)	392 (61.40)	246 (38.60)	638 (100.00)	
AGE	33.54±8.34	40.48±9.09	36.21±9.27	<0.01
BASELINE CD4+ COUNT	210.24±170.34	167.55±109.16	193.82±151.13	<0.01

SD: Standard deviation

Table 2: Comparison of patients' Characteristics among different HAART regimens

		INITIAL ART					
		3TC/AZT/N	3TC/AZT+EFV	FTC/TDF/EFV	3TC/TDF+NVP	3TC+ABC+EFV	p-value
Total n (%)		202(31.7)	46(7.2)	220(34.5)	166(26.0)	4(0.6)	
SEX	FEMALE		10(2.6)	64(16.3)	150(38.3)	2(0.5)	0.137
	MALE	36(14.6)	36(14.6)	156(63.4)	16(6.5)	2(0.8)	
Mean Age (SD)		33.9(8.5)	40.4(7.4)	39.2(9.7)	34.2(8.7)	31.5(4.0)	0.000
Mean CD4 Count (SD)		220.5 (192.6)	170.4 (125.0)	182.9 (136.3)	179.4 (102.)	239.5 (253)	0.043

3TC: Lamivudine, AZT: Zidovudine, ABC: Abacavir, TDF: Tenofovir, NVP: Nevirapine, EFV: Efavirenz, SD: Standard Deviation

Table 3: Comparison of Patient Characteristics among between NNRTI groups

	NVP GROUP	EFV GROUP	P-VALUE
N (%)	368(57.7%)	270(42.3%)	
SEX Male	52(21.1%)	194(78.9%)	<0.001
Female	316(80.6%)	76(19.4%)	
Baseline Line CD4 Group	194(55.7%)	154(44.3%)	
<200	194(55.7%)	154(44.3%)	
200-<350	118(59.0%)	82(41.0%)	0.112
>350	34(68.0%)	16(32.0%)	
TB at initial HAART f (%)			
No	362 (59.1)	250 (40.8)	<0.001
Yes	2 (9.1)	20 (90.9)	
Year of initial HAART			
2011	226 (60.8)	146 (39.2)	0.074
2012	142 (53.4)	124 (46.6)	

Table 4: Pattern of Prescription of Tenofovir by Renal Status

NON TDF GROUP	TDF GROUP	Total	P-Value		
Renal Status	Renal insufficiency	12(22.2%)	42(77.8%)	54(100.0%)	0.027
	Normal Renal	82(38.3%)	132(61.7%)	214(100.0%)	
Total		94(35.1%)	174(64.9%)	268(100.0%)	

TDF: Tenofovir

Mishemi FM et al ORIGINAL ARTICLE

Table 5: Pattern of initial ART (All Regimen)

Year of initial ART			Initial ART: FCD 3TC/AZT/NVP	FDC 3TC/AZT+EFV	FDC FTC/TDF/EFV	FDC 3TC/TDF+NVP	3TC +ABC +EFV	p-value
2011-2012	Hepatitis B at Initial ART	No	196(34.3%)	38(6.6%)	194(33.9%)	140(24.5%)	4(0.7%)	0.002
		Yes	6(10.7%)	4(7.1%)	26(46.4%)	20(35.7%)	0(0.0%)	
2011	Hepatitis B at initial ART	NO	118(35.1%)	16(4.8%)	112(33.3%)	90(26.8%)		0.041
		YES	4(12.5%)	0(0%)	18(56.2%)	10(31.2%)		
2012		NO	78(33.1%)	22(9.3%)	82(34.7%)	50(21.2%)	4(1.7%)	0.024
		YES	2(8.3%)	4(16.7%)	8(33.3%)	10(41.7%)	0(0%)	

3TC: Lamivudine, AZT: Zidovudine, ABC: Abacavir, TDF: Tenofovir, NVP: Nevirapine, EFV: Efavirenz, FDC: Fixed Dose Combination

Table 6: Pattern of Prescription of Initial ART in anaemia by Year of Initiation

			Initial ART: FCD 3TC/AZT/NVP	FDC 3TC/AZT+EFV	FDC FTC/TDF/EFV	FDC 3TC/TDF+NVP	3TC +ABC +EFV	p-values
	Severe anaemia	No	194(34.0%)	38(6.7%)	186(32.6)	148(26.0%)	4(0.7%)	0.177
		Yes	4(13.3%)	2(6.7%)	16(53.3%)	8(26.7%)	0(.0%)	
2011	Severe anaemia	No	118(34.9%)	12(3.6%)	118(34.9)	90(26.6%)		0.026
		Yes	2(10.0%)	0 (.0%)	10(50.0%)	8(40.0%)		
2012	Severe anaemia	No	76(32.8%)	26(11.2%)	68(29.3%)	58(25.0%)	4(1.7%)	0.440
		Yes	2(20.0%)	2(20.0%)	6(60.0%)	0(.0%)	0(.0%)	

DISCUSSION

The most commonly prescribed ART in treatment-naïve patient within the study period was FTC/TDF/EFV followed by 3TC/AZT/NVP. This finding is comparable with those reported at a tertiary hospital in South India.[10] The least commonly encountered prescription was 3TC + ABC +EFV.

The prescription pattern was comparable between male and female but differed between baseline CD4 cell count and age. However when the prescription was defined by the NNRTI component (NVP-based or EFV-based), the prescription pattern differed by gender and was comparable by the CD4 group. The mean baseline CD4 Count in this study population was relatively low compared to the finding of Prakash et al. at a tertiary hospital in South India.[8] This low baseline CD4 implied that therapy were relatively commenced late in this setting than the finding from the south India and most patient in this setting have no contraindication to NVP based regimen which is recommended for patients with CD4 count of < 250 cells/ml and < 400 cells/ml in male and female respectively.

The efavirenz-containing regimens were mostly prescribed for older patients and the mean age of this sub-set of patients revealed that male subjects were relatively older than their female counterparts ($p < 0.01$). This is comparable with that reported by Prakash et al at a tertiary hospital in South India.[10]

Nevirapine-based combination regimen was prescribed mostly to patient that had no TB-HIV co-infection at the commencement of therapy. Majority (90.9%) of patients who presented with TB-HIV co-infection were commenced on EFV based therapy and this is in line with the treatment guidelines and only 9.1% were commenced on NVP group after TB therapy. Rifampicin is a potent anti-TB drug which when co-administered with nevirapine is known to decrease the plasma concentration of NVP to suboptimal level because it induces the cytochrome P450 enzyme in the liver; and thus the potency of nevirapine. The reduction in Efavirenz plasma concentration by rifampicin do not significantly impact on clinical efficacy of efavirenz and thus in the treatment of HIV-associated TB efavirenz is preferred over nevirapine to avoid drug-drug interaction.[9,7,11,12] This however, makes efavirenz a preferred NNRTI in the management of HIV-TB co-infection. Efavirenz is less hepatotoxic than NVP, and there are several studies showing better ART outcomes with efavirenz than NVP.[7,11,12]

There was an association between the tenofovir prescription pattern and the renal status of patients. This implies that tenofovir prescriptions were influenced by the patients' renal status and there is difference in the proportion of tenofovir prescription between group with renal impairment and those without renal impairment. Interestingly, tenofovir is more likely to be prescribed for patient with renal impairment than the group with normal renal function. This observation may be explained by the emerging evidence that tenofovir is no longer absolutely contraindicated in patient with renal impairment but may need dosage adjustment depending on the severity of the renal impairment: though there is reported increased risk of tubular renal dysfunction in patient with underlying renal problem, older age and BMI <18.5. [11] Nucleoside reverse transcriptase inhibitors (NRTIs) form the backbone of the majority of ARV regimens, but the degree to which renal elimination contributes to total body clearance differs among NRTIs. Since renal excretion is the primary route of tenofovir elimination through a combination of glomerular filtration and active tubular secretion, there is need for tenofovir dosage adjustment in renal impaired situation.

Hepatitis B (HBV) status of patient was significantly associated with the choice of initial HAART. Patient with HBV co-infection were more likely to be prescribed with combination of TDF/3TC as the NRTI backbone of HAART than patients without HBV co-infection; a potent combination for treatment of HBV. When these prescriptions were disaggregated by year of entry or recruitment the prescription pattern was still associated with the hepatitis B status of patient. This finding is consistent with WHO guideline in 2010) and 2015 which recommend the inclusion of at least two ARV drugs active against HBV (such as TDF +3TC or FTC). This ART combination is effective against both viruses i.e. HIV and HBV, and may also prevent development of significant liver disease by directly suppressing HBV replication.[12,13]

The prescription pattern of AZT-based regimen reveals that 20 % of patients with severe baseline anaemia (Hb ≤ 7) had AZT in their regimen which is non-adherent to 2010 Federal Ministry of Health recommendation that contraindicate AZT in patient with severe anaemia.[7] AZT causes bone marrow toxicity and can lead to drug induced anaemia and thus AZT based regimen is not recommended in patients with low baseline HB because several studies have reported increased risk in patient with severe baseline anaemia.[15,16,17] The previous guideline and current Integrated National Guideline for HIV prevention, treatment and care by Federal Ministry of Health of Nigeria (FMoH) recommends 3TC/TDF/EFV as the preferred first line HAART for most patients including patient with severe baseline anaemia (Hb <7gm/dl).[7,11]

CONCLUSION

Most commonly prescribed HAART regimen was TDF/3TC/EFV and AZT/3TC/NVP. Prescription pattern was generally consistent with National treatment guidelines. Baseline CD4 count, Tb status, age, and HBV status were considered in choice of HAART but some patients with baseline severe anaemia were prescribed AZT-based regimen contrary to treatment guideline recommendation. The guidelines on prescription of HAART will continue to change and thus informing the need for a continuous education of prescribers on adherent to treatment guideline.

REFERENCES

1. Charles F. Antiretroviral Agents and Treatment of HIV Infection in Goodman Gilman's; The Pharmacological Basis of Therapeutic 2011; 50(1):1451-1458.
2. Levy R A, James D, Johnson M K, Hogg SR, Harrigan, PR. et al. The Direct Cost of HIV/AIDS Care. The Lancet, 2006; 6:171-177
3. Joint United Nations Programe On HIV/Aids /World Health Organization. Aids Epidemic Update,December 2015, Geneva, Switzerland.
4. Stone VE, Mansourati FF, Poses RM, and Mayer KH. Relation of physician speciality and HIV/AIDS experience to choice of guideline- recommended antiretroviral therapy.Journal of general internal medicine 2001; 16: 360-368.
5. World Health Organisation. (2010) WHO: Antiretroviral therapy for HIV infection in adults and adolescents, Recommendations for a public health approach.[Online] Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf accessed on 12 October, 2014.
6. Federal Ministry of Health Nigeria. (2010) FMOH: National guidelines for HIV and AIDS treatment and care in adolescents and adults. [Online] Available at: http://www.who.int/hiv/pub/guidelines/nigeria_art.pdf [Accessed on 29th September 2014.

7. Araoye MO. Research Methodology with Statistics for Health and Social Sciences. 2003; 118-119, ISBN 978-36450-8-0, Ilorin, Nigeria.
8. Schwartz CR and Garrison MW. Interpretation of clinical laboratory tests in applied therapeutics; the clinical use of drugs 2008; (2); 2.
9. World Health Organization:WHO. Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for Public Health Approach. Geneva, Switzerland: 2006.
10. Prakash Raju GJK, Chowta MN, Rather ZA and Mubeen F. Anti-retroviral drug regimens in HIV patients.Journal of Clinical And Diagnostic Research,2012;6(7):1178-1180.
11. Federal Ministry of Health Nigeria. FMOH: Integrated National guidelines for HIV Prevention, Treatment and Care. 2014.
12. World Health Organisation:WHO. Consolidated Guideline for HIV Prevention, Treatment and Care. 2015.
13. Matthews GV, Avihingsanon A, Lewin SR, et al. in Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents march, 2012;6.
14. Ssali F, Stöhr W, Munderi P, Reid A, Walker AS, et al. DART Trial Team. Prevalence, incidence and predictors of severe anaemia with zidovudine-containing regimens in African adults with HIV infection within the DART trial. Antivir Ther 2006; 11: 741-9.
15. Curkendall SM, Richardson JT, Emons MF, Fisher AE and Everhard F. Incidence of anaemia among HIV-infected patients treated with highly active antiretroviral therapy. HIV Med 2007; 8 : 483-90.
16. Agarwal D, Chakravarty J, Chaube L, Rai M, Agrawal NR. et al. High incidence of zidovudine induced anaemia in HIV infected patients in eastern India. Indian J Med Res 2010; 132, pp 386-389.