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Virologic Outcomes Following Enhanced Adherence Counselling among Treatment Experienced HIV Positive Patients at University College Hospital, Ibadan, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author OAA conceived the idea of the study, participated in the design of the study, reviewed the protocol, statistical analysis, first draft of the manuscript and vetted the final manuscript, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author OO wrote the first protocol, supervised the collection of the data, performed the data analysis and wrote the first draft of the manuscript. Authors MM and JA performed the abstraction of the data and reviewed the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To explore the impact of enhanced adherence counseling (EAC) in achieving viral suppression among our patients unsuppressed viral load in a large Anti-retroviral therapy (ART) program in South West Nigeria.
Study Design: This study was a descriptive cross-sectional review of patients' records.

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Place and Duration of Study: The study was conducted in human immunodeficiency virus (HIV) Program located in Infectious Disease Institute, College of Medicine, University of Ibadan, Nigeria involving review of data of patients with unsuppressed viral loads between 1st March 2017 – 30th September 2018.
Methodology: We described the viral loads (VL) outcomes of patients with VLs >1 000 copies/ml after at least 6 months on ART and a comprehensive 3 monthly EAC support programme. We calculated adherence using pharmacy refill data. Patients with one VL measurement after the EAC sessions were eligible for analysis.
Results: Out of 400 patients with VL >1 000 copies/ml reviewed during the study period, only 204(51.0%) were virally suppressed at the end of the 3 EAC sessions. Those with initial VLs between 1000-5000cp/ml had the highest adherence rate (73.0%) and VL suppression rate (68%). The youngest age group (16-30 years) had the least adherence (55.2%) and the least viral suppression (44.8%) while the oldest age groups (61-80years) were the most adherent (69.0%) and the most virally suppressed (55.2%). The proportion of patients on second line regimen were significantly more virally suppressed than those on the first line regimen (P <0.002).
Conclusion: This study showed the role EAC in accomplishing VL suppression and the need to intensify adherence counseling at commencement of highly active anti-retroviral therapy (HAART) to strengthen adherence in people living with HIV (PLHIV) and consequently preventing raised VL at the next laboratory testing of viral load. We strongly advocate for better measurement of adherence to antiretroviral therapy that will be accessible and reliable as this was a limitation of this study.

Keywords: Viraemia; EAC; adherence; viral load; pharmacy refill.

1. INTRODUCTION

The World Health Organization (WHO) 2010 Guidelines for ART in resource-limited settings proposed an algorithm for using viral load as a monitoring tool for patients on ARVs and a means for differentiating patients in need of adherence support and those who require a switch to second-line therapy [1]. In 2013, routine annual viral load (VL) testing was recommended by WHO for all patients virally suppressed on Antiretroviral Therapy (ART), as the preferred monitoring tool for effective treatment response [2]. The implementation of these quality improvement measures did not take place in many resource constrained countries immediately due to the limited capacity to implement routine viral load testing.

However, the Nigeria National Guideline for HIV prevention and treatment in 2016 recommended that all clients initiating ART should have viral load determined after 6 months of ART initiation and thereafter annually for those that have achieved viral suppression [3]. An elevated VL of ≥1000 copies/ml in a patient who has been on ART for at least six months can indicate either poor adherence to treatment and /or therapeutic failure due to antiretroviral resistance [2,3]. A study conducted in six African countries aimed at investigating the consequences of using clinical and immunological criteria to determine ART failure and guide regimen switches found that there were frequent unnecessary regimen switches without viral load testing [4]. Hence the importance of ensuring that adherence to antiretroviral drugs (ARVs) is ensured prior to switch cannot be over emphasized in patients' clinical response to treatment. Adherence to Antiretrovirals is critical to viral suppression in people living with HIV (PLWHIV) because poor adherence predisposes PLHIV to treatment failure and increased co-morbidities. The acceptable ARVs adherence rate that enhances viral suppression is ≥95% [5,6]. Poor adherence to antiretrovirals causes a rise in plasma viral load which has been confirmed to be an important risk factor for the emergence of drug-resistant HIV strains leading to increased infectivity rate [7,8].

Enhanced Adherence Counseling (EAC) is a structured support using implementation tools like session guide, patient file and register to engage virally unsuppressed patients in 3 monthly sessions. These support strategies explore the barriers to adherence and identifies, together with the patients, strategies to overcome them with the aim of suppression. Following completion of EAC, the patient is scheduled for a repeat viral load testing at the fourth month. According to the WHO guidelines, patients whose VL are not suppressed at re-testing after undergoing the EAC can be classified as having

'virologic failure' due to probable drug resistance and should be switched to second- or third-line therapy [2]. While routine VL testing levels and coverage among PLWHIV in Africa are high, there remain major gaps in enrolling PLHIV with high VLs into EAC and achieving VL suppression [9]. This and many other issues make full potential of EAC on achieving viral load suppression still sub-optimal in this setting calling for the need to assess the reasons for these gaps in further to inform suitable changes in policies/practices. Many of the identified gaps include lag time in patients' identifications and enrolment into counseling session, delayed completion of counseling session and repeat viral load testing after completing the session [10,11].

The measurement of adherence to antiretrovirals is quite difficult both in clinical care and research settings because most available methods of measurements are patient related thereby impeding objectivity [12]. As much as there is no gold standard with which to measure adherence, there are several strategies available but with respective strengths and weaknesses [13]. Medication Event Monitoring System (MEMS) are special bottle caps microchip that fit on standard medication containers, storing the date and time the medication container is opened and closed. Data are retrieved by downloading the information from the cap device to a computer to view individual adherence [13,14]. The setback here is that actual ingestion of medications is uncertain. Pharmacy refill data measures the duration of time the patient had the medications available, relative to the total number of days between refills for Antiretrovirals [15]. In the pill counts method, the health care provider views the actual pill container and calculate how many pills should be left, given the date of the inspection, dosing and last refill [15]. The disadvantage of this is that the patients get habituated to pill count exercise and brings the exact number of pills for inspection. Self -report method involve patients' voluntarily reports to the health care provider the doses of antiretrovirals missed over a period. The limitation of this method is that patients tend to overestimate actual adherence [13,16]. Clinician assessments utilises low cost, simple, and real-time feedback methods. These methods can involve administration of structured interviews, online assessments, written questionnaires, or voice response system. Due to their practicality and flexibility, these questionnaires can identify individual patient concerns to allow appropriate interventions [17,18]. However, there are scarce HIV-related studies that have assessed the accuracy of clinician assessments of actual or potential adherence of their patients and preliminary data suggest that physicians overestimate patients' adherence to HIV medication [15]. Biological assays involve the assessment for the presence of the medication or its metabolites in some of the body media like the blood, urine or hair. Given the half-life of most medications, the assays have the capacity to only measure adherence for the most recent doses taken in media like urine and blood while medication compliance over longer periods can be assessed using the hair. Data on the use of biological assays to measure levels of antiretroviral medications are not readily available and use of biological materials can be limited by decline to provide the materials by the patients due to socio-cultural believes, consequently further limiting these as viable strategies to monitor adherence [15,16]. Coupled with this is failure of many programs and facilities to have processes in place to measure treatment adherence or defaulting at either the patient or program level [19]. For the few facilities that conduct measurements, definitions used and data collection practices varied widely [20].

Many studies have consistently shown the benefits of VL monitoring [21,22]. Likewise, there are numerous studies that identified the factors influencing the adherence of patients to medications [23-25]. However, there are limited studies especially in Nigeria to show the various virologic outcomes with respect to specific HAART regimen following enhanced adherence counseling for intervention.

In achieving the last "95" of the UNAIDS "95-95-95" target by 2030, this study sets out to explore the impact of Enhanced Adherence Counseling in achieving viral suppression and various characteristics in relation to virologic suppression following EAC to the end of inclusion of routine best practices among HIV population at the HIV Clinic, Infectious Disease Institute, College of Medicine, University of Ibadan.

2. MATERIALS AND METHODS

2.1 Study Design

This study was a descriptive cross-sectional review of patients' records conducted at the HIV clinic domiciled within the Infectious Disease Institute, College of Medicine, University of Ibadan. The data abstraction was done between April and June 2019.

The study participants included HIV positive patients aged 16years and above accessing care who had been on ART for at least 6 months and were not virally suppressed (VL ≥1000cp/ml) during the reviewed period of March 2017 - September 2018. Pregnant women who accessed the Prevention of Mother to Child Transmission of HIV (PMTCT) services within the study period were excluded. The HIV clinic, which is opened during weekdays (Monday through Friday) currently manages over 6000 adults, HIV positive patients and offers several services including HIV testing services, ARV provision and other treatments as well as laboratory investigations. The clinic maintains a comprehensive electronic database, alongside regular paper-based files where patients clinical information are recorded on every clinic visits.

2.2 Adherence Measurement

We calculated adherence to HAART using the pharmacy refill data and defined adherence as the duration of time the patient had the medications available, relative to the total number of days between the first and the last refills for all Antiretrovirals. An average of the adherence during the EAC was calculated. The minimum needed adherence was defined as ≥95% [26].

This was calculated for each person as follows:

> Number of days supplied with drug in a month/ Total number of days between the first and last refill X 100

2.3 Data Collection

A total sampling of medical records of all consenting patients enrolled in the HIV treatment programme in our centre and received care between March 2017 - September 2018 and the report of this review included records of those with VL ≥1000cp/ml. These patients had three months counselling sessions aimed at identifying the problems influencing their adherence and finding appropriate solutions. At the fourth month, they had a repeat VL test done which was evaluated at the next clinic visit. The relevant individual patient demographic and clinic data were abstracted from the electronic medical record system. The demographic data collected included sex, age, marital status, level of education and co-morbidities. Clinical data included Initial antiretroviral regimen and line of regimen and the duration on HAART, adherence from Pharmacy refill data and laboratory data which included the VL results pre- and post- EAC which was grouped into virally suppressed and not virally unsuppressed. All duplicate entries were removed; patients with missing ART information, erroneous VL data, or had conflicting information were also removed.

2.4 Statistical Analysis

The data was analyzed using Statistical Package for Social Science statistical software, version 23.0 (SPSS Inc., Chicago, Illinois). Continuous variable such as age, duration on HAART were summarized using means and standard deviation. Variables such as gender and virologic outcome were expressed as proportions and percentages. Relationship between two quantitative variables was assessed using student's t-test and the level of correlation was determined using spearman's correlation statistics. The statistically significant differences for qualitative data were evaluated by chi squared statistics with significant association ($p<0.05$).

3. RESULTS

The results on social demographic characteristics are shown in Table 1. A total of 400 patients participated in the study. The majority of the participants were females (69.0%). Their mean age was 44.6 ± 10.3 years ranging from 16 to 80 years. Almost two-thirds (63.3%) of the study participants were married, and 14.5% were single. The bulk of the patients (42.5%) had secondary school as their highest level of education followed by 24.0% of patients for both Tertiary and Primary education.

The median duration on HAART was 7.5 ± 3.4 years ranging from 0.5 to 14 years. Majority of the patients (78.0%) were on 1st line HAART regimen, while the most common ARV regimen was TDF/3TC/EFV (38.5%) followed closely by Zidovudine / Lamivudine / Nevirapine (ZDV/3TC/NVP) (37.0%). The most used 2nd line HAART regimen was TDF/3TC/ATVr (18.5%). Patients with initial VL >50,000cp/ml constituted the bulk of the patients while most of the patients (84.5%) had no Opportunistic infection and the commonest of the OIs was Oral Candidiasis (10.5%).

In Table 3, overall, of the 400 patients with initial high viral load, only 204(51.0%) were virally suppressed and the virally suppressed females (51.4%) was no different among males (50.0%).

Table 1. Social demographic characteristics of the study participants

Characteristics	Variables	Total N (%) N=400
Gender		
	Male	124 (31.0%)
	Female	276 (69.0%)
Age group		
	16-30years	29(7.3%)
	31-45years	195(48.8%)
	46-60years	147(36.8%)
	61-80years	29(7.3%)
Marital status		
	Married	253(63.3%)
	Single	58(14.5%)
	Widowed	41(10.3%)
	Separated	32(8.0%)
	Divorced	7(1.8%)
	Not stated	9 (2.3%)
Level of education		
None	None	30(7.5%)
Primary	Primary	96(24.0%)
Secondary	Secondary	170(42.5%)
Tertiary	Tertiary	96(24.0%)
Not stated	Not stated	8 (2.0%)

Table 2. Clinical characteristics

Characteristics	Variables	Total N (%) N=400
Duration on HAART		
	0.5-3years	57(14.3%)
	4-9years	217(54.3%)
	10-14years	126(31.5%)
HAART regimen		
	1st line	312(78.0%)
	2nd line	88 (22.0%)
Specific HAART regimen		
	TDF/3TC/EFV	154(38.5%)
	AZT/3TC/NVP	148(37.0%)
	ABC/3TC/EFV	10(2.5%)
	TDF/3TC/ATVr	74(18.5%)
	TDF/3TC/LPVr	7(1.8%)
	AZT/3TC/ATVr	2(0.5%)
	ABC/3TC/ATVr	1(0.3%)
	ABC/3TC/LPVr	4(1.0%)
First viral load		
	1000-5000	74(18.5%)
	5001-50 000	146(36.5%)
	>50 000	180 (45.5%)
Presence of opportunistic		
infections	None	338(84.5%)
	Oral Candidiasis	42(10.5%)
	Tuberculosis	3(0.8%)
	Herpes Zooster	8(2.0%)
	Multiple	9(2.3%)

Table 3. Patients characteristics in relation to good adherence and viral load suppression

Characteristics	Total N (%)	Good adherence >95%	Suppressed viral load <1000 copies/ml
	400	266 (66.5%)	204(51%)
Gender			
Male	124 (31.0%)	83 (66.9%)	62(50.0%)
Female	276 (69.0%)	183 (66.3%)	142 (51.4%)
Age group			
16-30years	29(7.3%)	16(55.2%)	13(44.8%)
31-45years	195(48.8%)	129(66.2%)	96(49.2%)
46-60years	147(36.8%)	101(68.7%)	79(53.7%)
61-80years	29(7.3%)	20(69.0%)	16(55.2%)
Marital status			
Married	253(63.3%)	166(65.6%)	125(49.4%)
Single	58(14.5%)	38(65.5%)	32(55.2%)
Widowed	41(10.3%)	26(63.4%)	21(51.2%)
Separated	32(8.0%)	24(75.0%)	19(59.4%)
Divorced	7(1.8%)	5(71.4%)	2(28.6%)
Level of education			
None	30(7.5%)	26(86.7%)	15(50.0%)
Primary	96(24.0%)	60(62.5%)	47(49.0%)
Secondary	170(42.5%)	106(62.4%)	91(53.5%)
Tertiary	96(24.0%)	68(70.8%)	46(47.9%)
Duration on HAART			
0.5-3years	57(14.3%)	41(71.9%)	29(50.9%)
4-9years	217(54.3%)	150(69.1%)	117(53.9%)
10-14years	126(31.5%)	75(59.5%)	58(46.0%)
HAART regimen			
First line	312(78.0%)	216(69.2%)	146(46.8%)
Second line	88 (22.0%)	50(56.8%)	58(65.9%)
Specific HAART regimen			
TDF/3TC/EFV	154(38.5%)	107(69.5%)	84(54.5%)
AZT/3TC/NVP	148(37.0%)	105(70.9%)	55(37.2%)
ABC/3TC/EFV	10(2.5%)	4(40%)	6(60%)
TDF/3TC/ATVr	74(18.5%)	43(58.1%)	51(68.9%)

Characteristics	Total N (%)	Good adherence >95%	Suppressed viral load <1000 copies/ml
TDF/3TC/LPVr	7(1.8%)	3(42.9%)	4(57.1%)
AZT/3TC/ATVr	2(0.5%)	1(50.0%)	1(50.0%)
ABC/3TC/ATVr	1(0.3%)	1(100.0%)	1(100.0%)
ABC/3TC/LPVr	4(1.0%)	2(50.0%)	2(50.0%)
First viral load			
1000-5000	74(18.5%)	54 (73.0%)	51(68.9%)
5001-50 000	146(36.5%)	85 (58.2%)	55(37.7%)
>50 000	180 (45.5%)	127(70.6)	98(54.4%)
Presence of opportunistic infections			
None	338(84.5%)	219(64.8%)	183(54.1%)
Oral candidiasis	42(10.5%)	33(78.6%)	12(28.6%)
Pulmonary tuberculosis	3(0.8%)	2(66.7%)	0(0%)
Herpes zooster	8(2.0%)	3(37.5%)	3(37.5%)
Multiple	9(2.3%)	9(100.0%)	6(66.7%)
Adherence measurement during EAC			
Good adherence	266(66.5%)		135(50.8%)
Poor adherence	134(33.5%)		69(51.5%)
Viral load outcome after EAC			
Virally suppressed	204(51.0%)	135(66.2%)	
Virally unsuppressed	196(49.0%)	131(66.8%	

The two extremes of age group exhibited a distinct feature; 55.2% of the 16-30 years age group had the least adherence and the least viral suppression (44.8%) while 69.0% of 61-80years age group adhered most and eventually the most virally suppressed (55.2%).

There was no significant difference in the marital status though the separated had the highest suppressed viral load (59.4%). The level of education did not significantly affect the adherence and the viral suppression, though those with no education had the highest adherence (86.7%) but with a 50% suppression while those with secondary school education had the highest suppression (53.5%) and they had the lowest adherence (62.4%).

More than two-thirds (71.9%) of patients that have been on HAART for 6 months -3 years adhered to their medications during the EAC but only about half were virally suppressed, while less than half of those on HAART for more than 10 years were virally suppressed. The proportion of patients on second line regimen were significantly virally suppressed than those on the first line regimen (P <0.002). The specific HAART regimen was significant in viral suppression; a second line regimen ABC/3TC/ATVr a 100% viral load suppression which is closely followed by another second line regimen TDF/3TC/ATVr (67.6%); P <0.003. About 73% of patients with initial viral load between 1000-5000 cp/ml had a good adherence and 68% were virally suppressed, closely followed by 70.6% those with an initial VL >50000 having good adherence but about 54% became virally suppressed.

This figure shows the viral load outcomes relative to the specific HAART regimen following EAC. 62.8% of patients on AZT/3TC/NVP were not virally suppressed compared to its most used 1st line regimen in this study TDF/3TC/EFV; 45.5%.TDF/3TC/ATV/r; a second line regimen had the least 31.1% proportion of failure while ABC/3TC/LPV/r and AZT/3TC/ATV/r had an equal proportion (50.0%) of viral suppression. ABC/3TC/ATV/r had a 100% suppression.

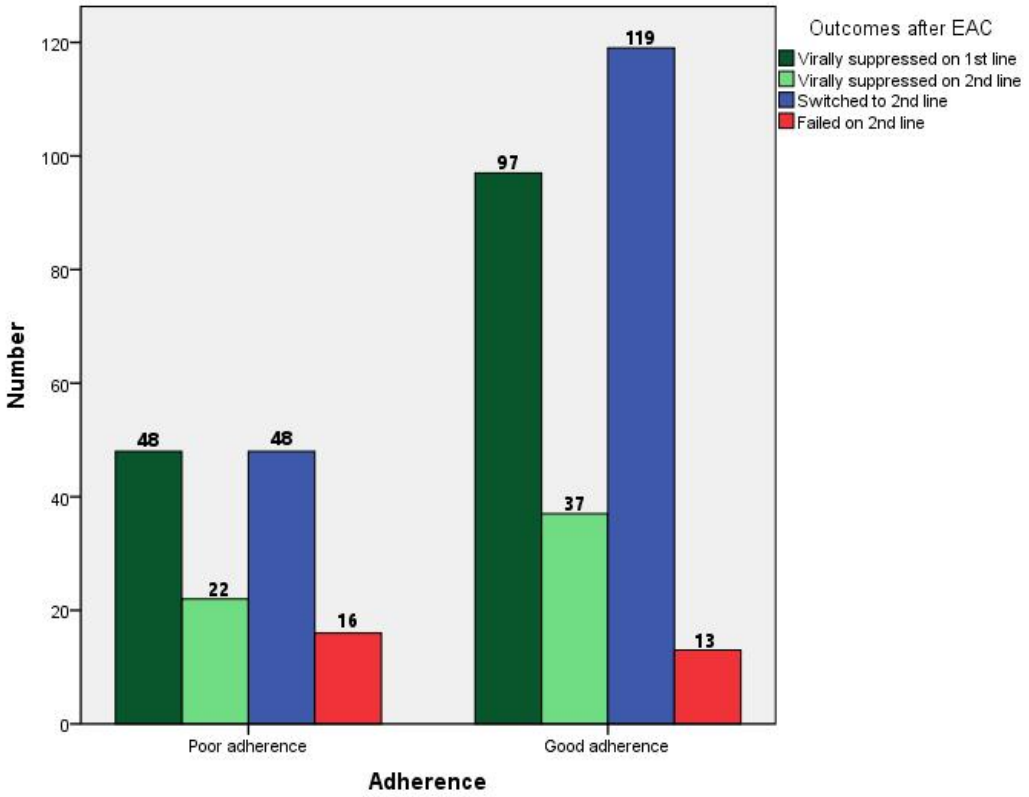

Fig. 1. Virologic outcomes relative to adherence measurement following enhanced adherence counseling

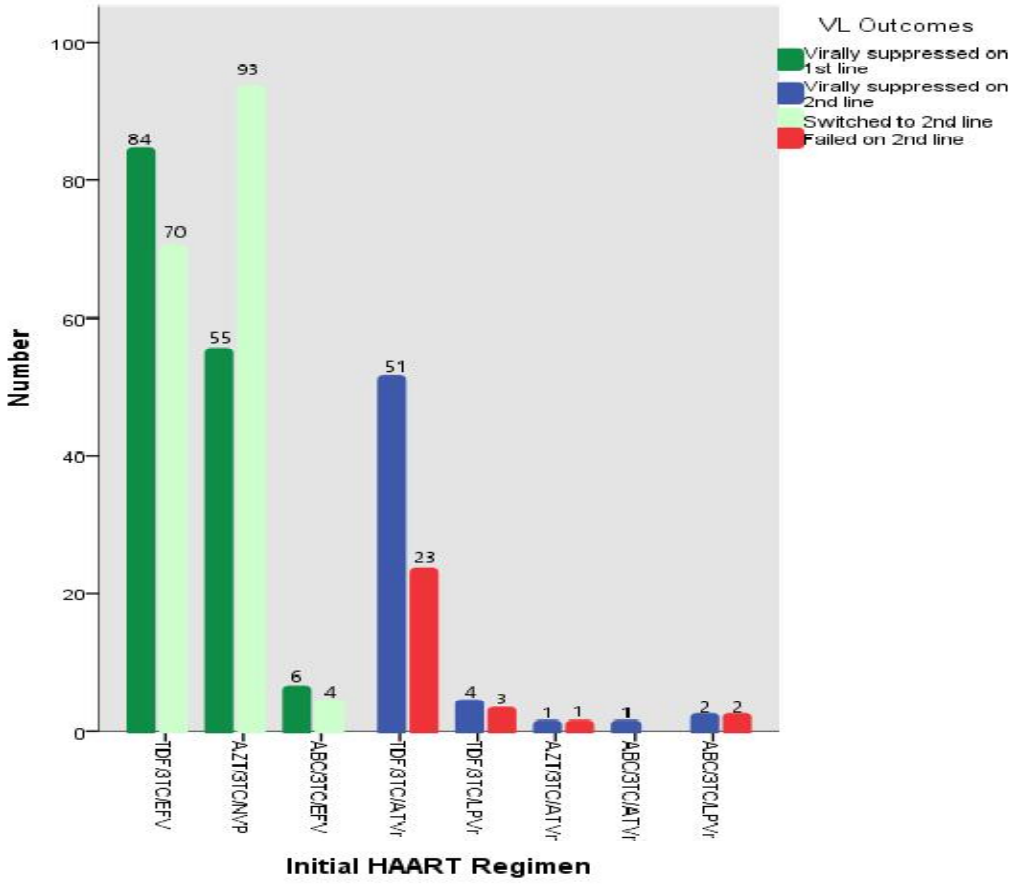

Fig. 2. The viral load outcomes relative to the specific initial HAART regimen after enhanced adherence counseling.

4. DISCUSSION

This is one of the few studies from Nigeria that has assessed the viral load outcomes following EAC. About 51% of the patients who underwent EAC were virally suppressed afterwards, this is higher compared to a study to explore the Virologic outcome among patients receiving antiretroviral therapy at five hospitals in Haiti where 25% of those with an initial HIV-1 RNA 1000 copies/mL, achieved virologic suppression after intensive adherence counseling [27] and almost at par with two studies; one done at Swaziland where of those with detectable VLs, (54%) resuppressed following planned adherence counseling [28]; the second at Zimbabwe where 47.1% of virally unsuppressed patients' became suppressed following EAC [29].

None of the socio-demographic characteristics such as age, sex, marital status, highest level of educational attainment significantly affects adherence levels and virologic outcomes amongst our study population. This supports the findings of some other authors [30,31]. Our study was consistent with previous reports, in that the adolescents and young adults have greater risk of virologic failure, because this age group faces multiple social, psychological and adherence challenges increasing their susceptibility to failure to suppress [27,32]. About two thirds of the patient on second line regimen achieved viral suppression after EAC which is almost as the case in South Africa, where more than two thirds of patients failing second-line ART achieved virological re-suppression without changing regimen and following an enhanced patient-support intervention [33]. Out of the 148 patients on AZT/3TC/NVP regimen, 70.9% of them had good adherence during EAC and just 37.2% of them were virally suppressed, thereby supporting previous studies that have shown reduced potency of AZT/3TC/NVP [34]. Those on 2nd line regimen were significantly more virally

suppressed than those on first line regimen which is similar to a study reported in Zimbabwe; this could be associated with the lower resistance to second line drugs [29] and also an initial defective adherence which was addressed during EAC as reported [29,33]. Also, the patients on 2nd line regimen might have perceived the therapy as their "last chance" hence went an extra mile to adhere exceptionally to the medications and because lower resistance to second line has been reported the efforts in adherence translated to viral suppression. Patients with initial VL between 1000 -5000 were significantly adherent and virally suppressed ($p<0.005$) than those with VL between 5001-50 000, which supports a similar study previously done in Zimbabwe [29]. However, it was observed that 70.6% of patients with an initial VL>50,000 had good adherence translating to 54.4% of them virally suppressed, this could be thought that the high VL kind of motivated them to adhere to their meds during EAC however, viral suppression seems not to be dependent on adherence in our setting due to a probable drug resistance. In as much as EAC led to a degree of viral suppression, we however observed that EAC did not significantly improve viral suppression of an initially high VL, which is in line with findings in a previous study done in Zimbabwe and Swaziland [29,35]. Lastly our study showed that 50.8% of patients with good adherence and 51.5% of those with poor adherence during EAC were virally suppressed suggesting the need for use of better assessment methods of adherence to drugs rather than the Pharmacy refill methods. Concerning the Viral Load outcomes following EAC, out of 88 patients on second line 29 (32.95%) of them failed on second line regimen while 13 (44.8%) of those failed had good adherence, this still further drives home the point that there are more factors affecting viral suppression rather than adherence only. Those 29 patients that have failed on second line would have benefited from resistance testing for maximal treatment however this is not readily available.

5. CONCLUSION

In conclusion, this study has shown the limitation of EAC in accomplishing viral load suppression and the need to intensify adherence counseling at commencement of HAART to strengthen adherence in PLHIV and consequently preventing raised VL at the next laboratory testing of viral load. We strongly advocate for better measurement of adherence to antiretroviral therapy that will be accessible and reliable as this was a limitation of this study. This is a clarion call to further intensify genetic studies in HIV research especially in Nigeria to know if there are Genetic barriers to some HAART effectiveness and proffer solutions to them. Finally, there is a need for inclusion of resistance testing especially for those that have failed on second line regimen will help in separating patients that are eligible for Third line regimen from those that would be benefit from more adherence counseling.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

This study is covered under program quality improvement activities under the original program implementation ethical approval.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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