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Virologic Response among Children and Adults in an Antiretroviral Therapy Programme in Northern Nigeria: A Cross-Sectional Descriptive Study

Elon Warnow Isaac[1*], Ayomikun Ajani[2], Mohammed Manga[3], Abubakar Joshua Difa[4], Oyeniyi Christianah Oluwaseun[5], Mohammed Hassan Danlami[6]

[1]Department of Paediatrics, College of Medical Sciences, Gombe State University, Gombe, Nigeria
[2]Kettering General Hospital, University Hospitals of Northamptonshire, Northamptonshire, UK
[3]Department of Medical Microbiology, College of Medical Sciences, Gombe State University, Gombe, Nigeria
[4]Department of Community Medicine, College of Medical Sciences, Gombe State University, Gombe, Nigeria
[5]Infectious Disease Training and Research Group, Gombe, Nigeria
[6]Department of Molecular Microbiology, Federal Teaching Hospital, Gombe, Nigeria
Email: *drwarnow@yahoo.com

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Abstract

Introduction: Viral load suppression is a key determinant of successful anti-retroviral therapy. The study aimed to determine virologic response to Antiretroviral therapy in the large cohort of children and adults living with Human Immune deficiency Virus. **Materials and Methods:** Viral Load results from the HIV Ribonucleic Acid Polymerase Chain Reaction register of 10,887 children and adults on cART in 4 states in Northern Nigeria between 2017 and 2019 were retrieved and analyzed in the PCR Molecular Laboratory of the Federal Teaching Hospital, Gombe. **Results:** 10,887 children and adults were analyzed. Males were 28.4% (3094) and 71.6% (7793) females. 2.9% (311); 3.5% (386); 7.3% (797); 65.2% (7098); 14.5% (1583); 5.2% (562) and 1.3% (150) were aged 0 - 9 years, 11 - 18 years; 19 - 25 years, 26 - 45 years; 46 - 55 years; 56 - 65 years and <65 years respectively. This first viral load was primarily routine in 96.3% (10,479). ART combination was Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP) in 53.8% (5855/10887), Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV) in 44.7% (4864). Prior to viral load testing, 48.5% (5275/10887) had received HAART for 1 - 5 years; 7.4% (811/10887) for 6 months but <1 year; 37.4% (4075) 6 - 10 years and 6.7% (726) for >10 years. The most recent CD4count before viral load request was ≥1000/μL in 7.4% (810/10887); 500 -999/μL in 39.0% (4240); 350 - 499 μL in 22.7% (2466) and <350 μL in 30.9% (3371) in these patients. Viral load was ≥1000 c/mL in

24.8% (2697) of PLHIV tested. Viral load was >1000 c/mL in 26.5% (821/3094) males and 24.1% (1876/7793) females. Viral load was significantly lower among females (p-value 0.007). 50.5% (157/311); 52.1% (201/386); 28.5% (227/797); 23.5% (1670/7098); 19.9% (315/1583); 17.8% (100/562) and 18.0% (27/150) aged 0 - 9 years, 11 - 18 years; 19 - 25 years, 26 - 45 years; 46 - 55 years; 56 - 65 years and <65 years had viral load >1000 c/mL respectively. Viral load was >1000 c/mL in 28.2% (229/811) for those on HAART for 6 months - 1 year and 23.6% (1243/5275) after receiving Highly Active Antiretroviral Therapy (HAART) for 1 - 5 years. 26.3% (1072/4075) and 21.1% (153/726) had viral load > 1000 c/mL after receiving HAART for 6 - 10 and >10 years respectively (p-value 0.001). **Conclusion:** HIV viral suppression was below the WHO recommended threshold.

Keywords

HIV, cART, Viral Load, Viral Suppression, Children, Adults, Nigeria

1. Introduction

Globally, the increased access to HIV treatment has saved millions of lives and reduced HIV transmissions; with an estimated 25.3 million currently on antiretroviral treatment [1]. Sub-Saharan Africa still bears disproportionately the greatest burden of this pandemic with 25.7 people living with the virus and 16.3 million accessing antiretroviral treatment in 2018. The continuing decline in AIDS-related deaths in the African Region is largely driven by the steady scale-up of antiretroviral therapy [2]. Globally 59% of people living with HIV have undetectable levels of the virus and 47% are virally suppressed. In sub-Saharan Africa, of the 25.7 million infected people, 60% are on ART and only 47% have achieved viral suppression [1].

With an estimated 1,900,000 people living with HIV in Nigeria, the country has the second-largest HIV burden worldwide after South Africa [3]. Of all adults aged 15 years and over living with HIV, 55% were on treatment, while only 35% of children aged 0 - 14 years living with HIV were on treatment in the country [1]. In 2018 in Nigeria: 67% of people living with HIV knew their status; 53% were on treatment and 42% of people living with HIV were virally suppressed [1].

Nigeria is currently trailing behind the ambitious treatment targets set by the Joint United Nations Programme on HIV/AIDS (UNAIDS), the 90-90-90 strategy by 2020. This goal stipulates that by 2020, 90% of all people living with HIV will know their HIV status; 90% of all people diagnosed with HIV infection will receive sustained antiretroviral therapy; and 90% of all people receiving antiretroviral therapy will have viral suppression; as well as the elimination of AIDS as a public health threat by 2030 [4]. Early and sustained suppression of viral replication evident by undetectable levels of HIV-1 RNA is the ideal and the ultimate

goal of ART and HIV 1RNA levels in blood provide a direct measure of the efficacy of antiretroviral therapy (ART) predicting immunological and clinical outcomes and the risk of transmission [5].

Viral load quantification is a standard of care quality and the recommended monitoring tool for diagnosing and confirming antiretroviral therapy failure [6]. Virological suppression status of children and adults on ART is important as it allows for timely detection of treatment failures, identification of patients in need of more intensive adherence counseling and support and minimizes development of drug resistance and unnecessary switch to expensive and limited ART regimen options [7].

The use of cross-sectional studies to monitor virological efficacy and resistance to ART, or cohort studies to assess one of eight early warning indicators of HIV drug resistance: viral load suppression 12 months after ART initiation are currently recommended [8]. As the availability of viral load testing grows in developing countries, the percentage of patients with virological suppression can be an important measure of overall ART clinic and program success [9].

In children on ART in Low and Medium income countries, viral suppression rates were low [10] [11] and in sub-Sahara Africa, proportions of virological success in adults were highly variable [9] [12] [13]. Children on ART present enormous challenges for viral suppression and include adherence problems due to poor palatability of drugs or dependence on caregivers who are frequently ill themselves [10] [14]; variability in children's weight and antiretroviral pharmacokinetics; pretreatment HIV drug resistance (PDR), due to prior exposure to drugs as part of prevention of mother-to-child transmission (PMTCT) interventions [15]; Children are at high risk of suboptimal treatment as one out of two children newly diagnosed with HIV is infected with virus harboring resistance to Efavirenz (EFV) and Nevirapine (NVP) [16].

Pretreatment HIV drug resistance prevalence is high and rapidly increasing [10] [17]. HIV exposed children have been known to harbour PDR virus [12]. PDR increases the risk of failure of first line ARV and accumulation of resistant mutations [18].

Nigeria harbors 26.7% of the paediatric HIV and AIDS globally with viral suppression rate of 34% in children and 44.6% in adults [19]. The national viral load implementation strategy and plan was launched in 2016 [20] and the National Guideline on HIV prevention and treatment recommends viral load determination six months after initiating cART and then annually if viral suppression is achieved. In individuals without viral suppression, adherence counseling support is intensified followed by another viral load testing so as to differentiate poor adherence from treatment failure [21]. After many years of ART, Nigeria has shown steady progress in increasing access to treatment for people living with HIV with the adoption of a test and treatment policy in 2016 [19].

However, routine viral load testing had lagged behind until recently with risk of non-viral suppression and HIV drug resistance. Therefore, the aim of this

study was to report virologic response among children and adults living with HIV receiving ART in 4 states of Northern Nigeria.

2. Methods and Materials

2.1. Study Design

Descriptive cross-sectional.

2.2. Study Setting

Blood samples for HIV Viral load estimation were collected from 10,887 children and adults on cART from both private and public health facilities cutting across tertiary, secondary and primary health centers in 4 states in Northern Nigeria between 2017 and 2019.

The following information; age, sex, date of HIV diagnosis, date of ART start, current ART regimen; first, second or third line, date of sample collection, Viral Load result were retrieved from the RNA/DNA Polymerase Chain Register from the Microbiology Molecular Laboratory. The number of children and adults in the ART programme in the reporting ART sites who had their samples sent to the PCR laboratory during the collection period constituted the sample size for this report.

2.3. Viral Load Determination

Viral load quantification of HIV-1 RNA was performed on plasma samples using COBAS 96 CAP//C TaqMan HIV-1 assay (Roche Diagnostics, Indianapolis, IN) at a limit of detection of 40 copies/mL. A protocol using 0.6 mL of plasma was used for RNA extraction with strict adherence to manufacturer's protocol. The lower limit of detection of the assay is 40 copies/mL of HIV-1 RNA and specificity of 100%.

The sample size was all consecutive blood samples received in the PCR laboratory for HIV-RNA quantification obtained from PLHIV on cART during the study period.

The laboratory, situated in the Federal Teaching Hospital Gombe was established in 2010, has been certified by the Federal Ministry of Health and the President Emergency Plan for AIDS Relief (PEPFAR) CDC in Nigeria. It's one of the earliest DNA PCR Laboratories established in the country to support the Early Infant Diagnosis for PMTCT of HIV in the country.

2.4. Inclusion criteria

Children (0 - 18 years) and adults (>19 years) with the following information age, sex, date of HIV diagnosis, date of ART start, current ART regimen; first, second and third line, date of sample collection, together with a VL result were included. Children and adults on treatment with cART for less than 6 months were excluded. Virologic response were defined/categorized as follows: undetectable, very low level viraemia < 40 RNA copies/mL; low level viraemia > 41

copies/mL-500 copies/mL. Virological suppression (VS) was defined as viral load (VL) < 1000 RNA-copies/mL of blood plasma and virological non suppression (VNS) as VL ≥ 1000 RNA-copies/mL [22] Patients with incomplete data entry were excluded from this analysis.

Ethical clearance was received from the research and ethics committee of the Federal Teaching Hospital, Gombe.

Data Analysis Data was analyzed using Epi info version 3.5.1 All data were analysed with a statistical significance level set at $p < 0.05$. Frequencies, proportions, confidence interval were computed. Data were summarized using tables and figures. Hypothesis testing was performed using Pearson Chi-square and Chi-square as appropriate.

3. Results

Table 1 shows that 24.8% of both children and adults had viral load greater than 1000 copies/mL. Slightly more than half of Children 0 - 18 years had viral load greater than 1000 copies/mL. Viral non suppression decreased with increasing age. The age distribution and viral load were statistically significant. Overall, 24.9% of children and adults had undetectable viral load; 24.8% were virally non suppressed (Figure 1).

Females constituted approximately 72% of people living with HIV in this study (Table 1). Overall, 26.5% and 24.1% of males and females respectively were virally non suppressed. The distribution of gender and viral load category was statistically significant (p-value = 0.007).

Majority of children and adults were on Nevirapine (NVP) and Efavirenz (EFV) containing regimen (Table 1). Children and adults on Nevirapine and Efavirenz based ART regimen constituted 73.2% and 77.8% of those with viral load <1000 copies/mL. Seventy-three percent and seventy-eight percent of children and adults on Nevirapine and Efavirenz-based regimen had viral load <1000 copies/mL. The distribution of regimens and viral load was statistically significant (p-value ≤ 0.001).

Approximately 98% of children and adults were on first line and 24.5%of those on first line had viral load >1000 copies/mL while 37.8% of those on third line had viral load >1000 copies/mL. This was not statistically significant (Table 1).

About 86% of children and adults were receiving cART for between 1 and 10 years duration. Viral non suppression was 28.2% and 21.1% in those on ART for 1 year and >10 years respectively. The distribution of the duration on ART and viral load category was statistically significant (p-value ≤ 0.001).

According to CD4 Count, 29.7% of children and adults with CD4 > 1500 had viral non suppression; 36.4% with CD4 < 350 had viral non suppression. The distribution of CD4 count and viral load category was statistically significant (p-value ≤ 0.001) (Table 1).

Figure 2 shows that there is a trend of increasing CD4 count with decreasing

Table 1. HIV viral load categories in children and adults.

Variable	Frequency n = 10887 (100%)	Undetectable N = 2708 (24.9%)	<40 cp/mL 3197 (29.4%)	41 - 500 cp/mL 1922 (17.6%)	501 - 1000 cp/mL 363 (3.3%)	>1000 cp/mL 2697 (24.8%)	p-value
Ages							
0 - 9 yrs	311 (2.9)	54 (17.4)	54 (17.4)	38 (12.2)	8 (2.6)	157 (50.5)	<0.001
11 - 18 yrs	386 (3.5)	73 (18.9)	54 (14.0)	42 (10.9)	16 (4.1)	201 (52.1)	
19 - 25 yrs	797 (7.3)	198 (24.8)	181 (22.7)	168 (21.1)	23 (2.9)	227 (28.5)	
26 - 45 yrs	7098 (65.2)	1810 (25.5)	2114 (29.8)	1256 (17.7)	248 (3.5)	1670 (23.5)	
46 - 55 yrs	1583 (14.5)	400 (25.3)	550 (34.7)	274 (17.3)	44 (2.8)	315 (19.9)	
56 - 65 yrs	562 (5.2)	137 (24.4)	188 (33.5)	117 (20.8)	20 (3.5)	100 (17.8)	
>65 yrs	150 (1.3)	36 (24.0)	56 (37.3)	27 (18.0)	4 (2.7)	27 (18.0)	
Sex							
Males	3094 (28.4)	702 (22.7)	912 (29.5)	560 (18.1)	99 (3.2)	821 (26.5)	0.007
Females	7793 (71.6)	2006 (25.7)	2285 (29.3)	1362 (17.5)	264 (3.4)	1876 (24.1)	
ART Regimen							
AZT + 3TC + NVP	5855 (53.8)	1473 (25.2)	1677 (28.6)	929 (15.9)	205 (3.5)	1571 (26.8)	<0.001
TDF + 3TC + EFV	4864 (44.7)	1196 (24.6)	1479 (30.4)	956 (19.7)	152 (3.1)	1081 (22.2)	
TDF + FTC + EFV	114 (1.0)	28 (24.6)	24 (21.1)	29 (25.4)	3 (2.6)	30 (26.3)	
AZT + 3TC + LPV/r	54 (0.5)	11 (20.4)	17 (31.5)	8 (14.8)	3 (5.6)	15 (27.8)	
ART Type							
1st line	10568 (97.1)	2667 (25.2)	3113 (29.4)	1848 (17.5)	348 (3.3)	2592 (24.5)	0.942
2nd line	282 (2.6)	28 (9.9)	82 (29.0)	67 (23.8)	14 (5.0)	91 (32.3)	
3rd line	37 (0.3)	13 (35.1)	2 (5.4)	7 (19.0)	1 (2.7)	14 (37.8)	
Duration on ART							
1 yr	811 (7.4)	180 (22.2)	221 (27.3)	146 (18.0)	35 (4.3)	229 (28.2)	<0.001
1 - 5 yrs	5275 (48.5)	1345 (25.5)	1484 (28.1)	1023 (19.4)	180 (3.4)	1243 (23.6)	
6 - 10 yrs	4075 (37.4)	1042 (25.6)	1185 (29.1)	644 (15.8)	132 (3.2)	1072 (26.3)	
>10 yrs	726 (6.7)	141 (19.4)	307 (42.3)	109 (15.0)	16 (2.2)	153 (21.1)	
CD4 count							
<350	3371 (31.0)	633 (18.8)	812 (24.1)	605 (17.9)	94 (2.8)	1227 (36.4)	<0.001
350 - 499	2466 (22.7)	631 (25.6)	765 (31.0)	473 (19.2)	82 (3.3)	515 (20.9)	
500 - 999	4240 (39.0)	1197 (28.2)	1366 (32.2)	722 (17.0)	158 (3.7)	797 (18.8)	
1000 - 1500	662 (6.0)	208 (31.4)	213 (32.2)	106 (16.9)	21 (3.2)	114 (17.2)	
>1500	148 (1.3)	39 (26.4)	41 (27.7)	16 (10.8)	8 (5.4)	44 (29.7)	

Continued

Reason for request of viral load							
Routine	10479 (96.3)	2604 (24.8)	3091 (29.5)	1847 (17.6)	351 (3.3)	2586 (24.7)	
Suspected clinical failure	258 (2.4)	71 (27.5)	76 (29.5)	53 (20.5)	8 (3.1)	50 (19.4)	<0.001
Suspected immunological failure	150 (1.4)	33 (22.0)	30 (20.0)	22 (14.6)	4 (2.7)	61 (40.7)	
ART START YEAR							
2000-2004	92 (0.8)	23 (25.0)	38 (41.3)	18 (19.6)	1 (1.1)	12 (13.0)	0.076
2005-2009	2945 (27.1)	750 (25.5)	945 (32.1)	433 (14.7)	82 (2.8)	735 (24.9)	
2010-2014	5172 (47.5)	1309 (25.3)	1454 (28.1)	941 (18.2)	185 (3.6)	1283 (24.8)	
2015-2018	2678 (24.6)	626 (23.4)	760 (28.4)	530 (19.7)	95 (3.5)	667 (24.9)	

Table 2. HIV Viral load categories among children and adult.

Ages	Undetectable	<40 cp/mL	41 - 500 cp/mL	501 - 1000 cp/mL	>1000 cp/mL
0 - 18 years	127 (4.7)	108 (3.4)	80 (4.2)	24 (6.6)	358 (13.3)
19 - >65 years	2581 (95.3)	3089 (96.6)	1842 (95.8)	339 (93.4)	2339 (86.7)
Total	2708	3197	1922	363	2697
p-value	**<0.001**	**<0.001**	**<0.001**	**0.868**	**<0.001**

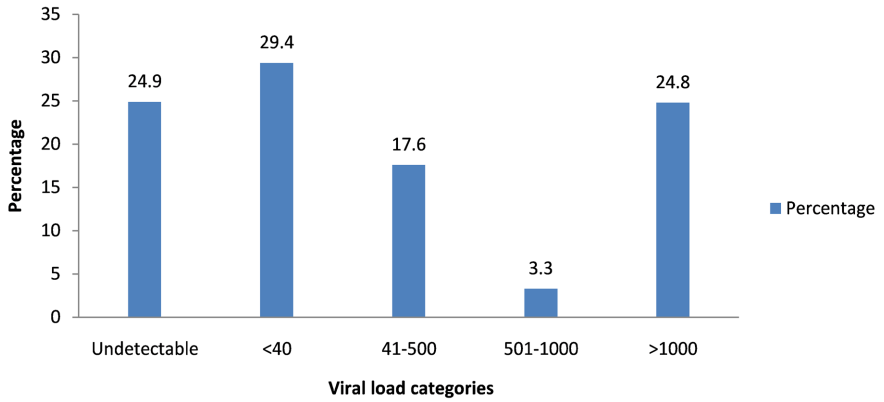

Figure 1. Percentage distribution of viral load categories in children and adults.

Viral load. At CD4 count of <350, 36% (1227/3401) of children and adults had viral load of >1000 cps/mL and 24% had Viral load of >1000cp/mL at CD4 count of >1000 (p = 0.001).

Viral load determination was requested for majority of children and adults on account of routine test for viral load. Of those suspected to have clinical and immunologic failure, 40.7% of them had viral load >1000 copies/mL. The distribution of reason for request for viral load test and viral load category was statistically significant (p-value = 0.001).

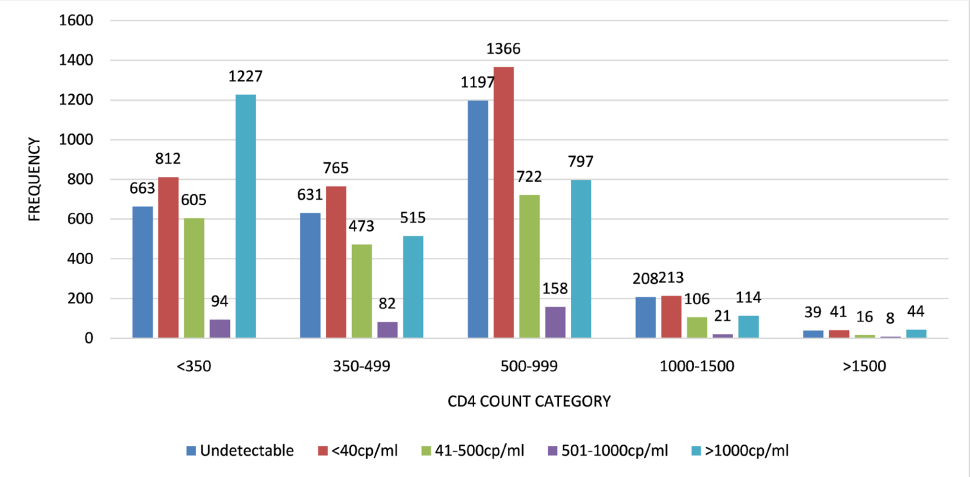

Figure 2. CD4 count and viral load categories in children and Adults.

Majority of children and adults started ART between the year 2010 and 2018. The distribution between the year of ART start and viral load category was not statistically significant (p-value = 0.07).

Table 2 shows the viral load categories between children and adults. The distribution of undetectable, <40 copies/mL, 41 - 500 copies/mL and >1000 copies/mL viral load categories between children and adults were statistically significant (p-value = 0.001, 0.001, 0.001, 0.001). In Table 2, 51% (358/697) of all children 0 - 18 years had viral of >1000 cp/mL and in adults about 30% (2339/7851) had viral non-suppression with a p = 0.001.

4. Discussion

This study established HIV viral response to ART in a fairly large population of children and adults living with the virus in Northern Nigeria. With launch of National Viral Load implementation strategy and plan in 2016, viral load determination became routine and a standard of care in the country [20].

Until 2017, Non virologic monitoring of children and adults on ART was the standard of care in Nigeria, using clinical and CD4 parameters [23].

The implication for the National ART programme was significant: substantially large numbers of children and adult PLHIV were receiving nevirapine and efavirenz based ART with risk for drug resistance and treatment failure. The implementation of Viral load monitoring as care package for PLHIV ensures preservation of treatment options through early detection of non-viral suppression and timely adherence counselling to prevent treatment failure and the need for regimen changes [24].

The overall HIV viral suppression rate in children and adults of 75.2% in this study is higher than Nigeria's average of 34% in children and 44.5% in adults respectively [3] [19].

While there is paucity of comparable studies in the country, substantial difference exits in HIV dynamics and burden within states and regions in Nigeria,

and therefore sub-national data will not be reflection of national performance [21] [24].

In several countries in sub-Saharan Africa, nationally representative Viral suppression rates in children [25] [26] and adults [27] [28] were higher than the rates in Nigeria. However, subnational HIV viral suppression rates in these countries [29] [30] [31] were generally comparable to our study result. These studies showed wide variation in viral suppression rates but fell below the UNAIDS recommended viral suppression threshold. Programme performance and attributes including study design, population characteristics, ART type, duration of treatment would have influenced the variation in viral suppression rates in sub-Saharan Africa [9] [10] [13].

Systematic reviews showed high viral suppression in children and adults in low- and middle-income countries but were below UNAIDS threshold of 90% [32] [33].

There was female preponderance in all viral load categories and females were virally suppressed than males. This virologic success in the female PLWHA on cART was also demonstrated in these studies [34] [35].

However, these other reports did not establish any association between gender and virologic success or failure [36] [37].

In all viral load categories in our study, HIV viral suppression was lower in children compared to adults. In Infants and children, HIV-1 viral loads are substantially greater, vertically infected infants are slow to suppress virus and many do not attain a discernable viral load set-point and as a consequence infants have slower viral suppression and higher incidence of virologic failure [10] [38].

ART adherence and dose calibration influenced by weight changes, emesis, regurgitation, and spillage are contributory to poor virologic outcomes in children [14].

Adolescents and young adults were less virally suppressed compared to infants and older adults. Indeed, data combined from east and southern African countries showed only 45% of adolescent girls living with HIV were virologically suppressed [39].

Studies in the USA [40] and in sub-Saharan Africa [9] [29] [41] had similar-findings. Stigma and fear of disclosure, substance abuse and alcohol consumption, lack of psychosocial support, age transition challenges contributed to low viral suppression in adolescents and young adults [11] [29] [42].

Even though the distribution between ART regimen and viralload categories was significant, viral non suppression rate was similar between NVP and EFV based regimen in children and adults. This lack of difference between ART regimen and viral suppression has been reported from large studies in Cameroon [27] and Ethiopia [43].

However studies by Desta *et al*. [29] and Kiweewa *et al*. [44] found an association between ART regimen and viral non suppression. The study design including sample size and ART programme performance could have accounted for this

finding. In particular Children on both NNRTI and NRTI ARVs are at high risk of suboptimal treatment from pretreatment drug resistance to NNRTI [45] while infant exposure through PMTCT has greater risk for pretreatment drug resistance and drug resistant mutations [46].

PMTCT naïve infants have also demonstrated this drug resistance harboring mutations [10] [46] and therefore suboptimal viral suppression. While most children and adults were on first line ART, there was no difference between HIV viral load categories and ART type; viral suppression rate was similar. The proportion of children and adults on second and third line cART was small as reported in nationally representative data from Kenya [31] in children and adults [47].

A three-year incidence of switching to second line was about 2% in Africa, compared to 12% in Europe and about 30% in the United States [48].

The determination of viral suppression status on a routine basis and HIV Drug Resistance testing and surveillance in ART programme enables early detection of treatment failure which is amenable to adherence counseling and or switching to second- or third-line ART regimen [21] [24].

The proportion of subjects with viral non suppression did not vary significantly with duration of ART. Limited access to routine viral load and HIV drug resistance testing especially to NNRTI in resource limited countries made failing and ineffective ART regimens being administered for many years [7] [8]. Decreasing viral suppression after 10 years of ART was demonstrated from a study from Cambodia [49].

Viral load decreased with increasing CD4 count in almost all the viral load categories with viral suppression higher in subjects with higher CD4 count. This relationship trend was reported from Zimbabwe [11], Ethiopia [29], Cambodia [49], and Vietman [50]. Low CD4 count might slow viral clearance. Sustained viral suppression, which is the key goal of cART, facilitates restoration of the immune function with resultant increase in CD4, the marker of this reconstitution [1] [4].

5. Conclusion

HIV viral suppression in this cohort of children and adults is below the WHO recommended threshold of viral suppression. Children living with HIV/AIDS were virally less suppressed than their adult counterparts living with the virus.

Recommendation

Strengthening ART adherence programme and Implementing HIV drug resistance surveillance and monitoring should be the top most priority for Nigeria's big ART programme.

Limitation of the Study

As the first HIV viral load test results in this fairly large number of children and

adults, we were unable to determine virologic failure in the absence of at least second viral load test.

Authors Contribution

Elon Warnow Isaac: Conceived the study and study design, developed the first manuscript draft and critically reviewed all drafts of the manuscript.

Dr. Iliya Jalo, Dr. Abubakar Joshua Difa, and Ms. Oyeniyi Christianah Oluwaseun: Conducted quantitative data analysis and reviewed all drafts of the manuscript.

Dr. Mohammed Manga and Mr. Muhammad Danlami Hassan: Reviewed and commented on the data.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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