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HIV Viral Suppression in Children in a Subnational Antiretroviral Treatment Programme in Nigeria

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Abstract

Background: Despite years of Paediatric Antiretroviral therapy in Nigeria, the National implementation plan for the scale up of viral load testing was only recently launched. Viral load determination is the most important indicator of ART response. **Material & methods:** First viral load samples were collected from 663 children living with HIV between December 2017-December 2019 aged 0 - 18 years on highly active antiretroviral therapy from 4 states within Nigeria. Samples were analyzed at a Polymerase Chain Reaction laboratory of the Federal Teaching Hospital, Gombe. **Results:** Males were 311 (46.9%) and 352 (53.1%) female. Children aged 0 - 9 years constituted 44.9% (298); 55.1% (365) were aged 10 - 18 years. This first viral load was primarily routine in 94.2% (625); 2.9% (19) of children respectively had suspected clinical or immunological failure. ART combination was AZT/3TC/NVP in 78.1% (518/663) of CLHIV; TDF/3TC/EFV in 21.2% (141); AZT/3TC/LPV/rtv in 4 (0.6%). Prior to initiation of routine viral load testing, 55.2% (366/663) CLHIV had received HAART for 1 - 5 years; 7.8% (52/663) for 6 months but < 1 year; 32.8% (218/663) 6 - 10 years and 4.1% (27) for >10 years. The most recent CD4 count before viral load request was ≥1000/μL in 24.7% (164) of CLHIV; 500 - 999/μL in 42.9% (285); 350 - 499 μL in 11% (73) and <350 μL in 21.3% (141) of children. Viral load was ≥1000 c/ml in 51.3% (340/663) of children. Viral load was >1000 c/ml in 59.9% (174/311) males and 47.2% (166/352) females. Viral load was significantly lower among females (P-value 0.02). Of children aged 0 - 9 years, 50.3% (150/298) had viral load > 1000 c/ml and 10 - 18 years, 52.1% (190/365) (P value 0.660). Viral load was >1000 c/ml in 38.5% (20/52)

of children on HAART for 6 months - 1 year and 52.2% (191/366) after receiving HAART for 1 - 5 years. 52.3% (114/218) and 55.6% (15/27) CLHIV had viral load > 1000 c/ml after receiving HAART for 6 - 10 and >10 years respectively (P value 0.29). **Conclusion:** About half of children on HAART have viral load > 1000 c/ml after more than 1 - 5 years on HAART. Longer duration of ART and use of AZT/3TC/NVP are associated with viral load > 1000 c/ml. Key considerations are poor adherence and/or viral drug resistance. Optimizing ART adherence and resistance monitoring remain key strategies for ART programmes.

Keywords

Children, ART, Viral Load > 1000 c/ml, Nigeria

1. Introduction

World Health Organization recommended viral load testing as the preferred monitoring tool for diagnosing and confirming antiretroviral therapy failure [1]. Plasma HIV 1RNA levels provide a direct measure of the efficacy of antiretroviral therapy (ART), predicting immunological and clinical outcomes and the risk of transmission [1].

The WHO's immunologic and clinical failure criteria performed poorly in predicting virological treatment failure leading to unnecessary switch to second-line ART during periods of viral load suppression, or delayed switch because of the misclassification of treatment failure [2] [3] [4].

More recently, WHO identified HIV-infected infants and children as a priority group for preferential routine viral load monitoring [5]. The third prong of UNAIDS target, realizable by 2020, aimed to achieve viral suppression in 90% of the 90% on ART including children. Sustained viral suppression, which is the key goal of cART, facilitates restoration of the immune function and significantly reduces the risk of onward HIV transmission [6]. Viral suppression rates among children on ART in LMICs were low and considerably poorer than those previously found in adults in LMICs and children in high-income countries [7] [8].

Viral suppression in children on ART is challenging for various reasons, including variability in children's weight, variability in antiretroviral pharmacokinetics [9]; pretreatment HIV drug resistance (PDR) due to prior exposure to drugs as part of prevention of mother-to-child transmission (PMTCT) interventions [10] [11]; and adherence problems due to poor palatability of drugs or dependence on caregivers who are frequently ill themselves [7] [9].

According to WHO, children represent a very vulnerable population: one out of two children newly diagnosed with HIV is infected with virus harboring resistance to Efavirenz (EFV) and Nevirapine (NVP), thus at high risk of suboptimal treatment [12].

Recent reports from Nigeria [13], Ethiopia [14] and Brazil [15], demonstrated pretreatment HIV drug resistance to NNRTI and NRTIs in newly diagnosed children with HIV and treatment naïve. The PDR prevalence in African children is high and rapidly increasing. Even in PMTCT-unexposed children, the most recent reports indicate that PDR is present in up to a third of children starting first-line therapy [16]. PDR increases the risk of failure of first line ARV and accumulation of resistant mutations [17] [18]. Determination of virological suppression status of children and adults enrolled 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 [19]. WHO guidelines recommend cross-sectional studies to monitor virological efficacy and resistance to ART [20], or the use of cohort studies to assess one of eight early warning indicators of HIV drug resistance: viral load suppression 12 months after ART initiation [21].

Nigeria has the second highest burden of HIV with 26.7% of the paediatric HIV and AIDS globally. It is estimated that 35% of children living with HIV in Nigeria are receiving cART with viral load monitoring as standard of care [22] [23]. The national viral load implementation strategy and plan was launched in 2016 [24], and the reported national viral load suppression rate in adult and children as 44.5% and 34% respectively. Among adults the prevalence of VLS was 46.2% among females and 40.9% among males [25].

The National Guideline on HIV prevention and treatment [26] recommends viral load determination 6 months after initiating cART and then annually if viral suppression was 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. Treatment failure is defined by two viral load measurements > 1000 c/ml, 3 months apart after the initial viral load determination and such individuals are switched to second-line ART [26].

After many years of ART among Nigeria children living with HIV and the lack of routine viral load testing until 3 years ago, these children were at risk of non-viral suppression and HIV drug resistance. Therefore, the aim of this study was to report viral load suppression among children living with HIV in a sub national ART programme in Northern Nigeria.

2. Methods

2.1. Study Design

The study is descriptive cross sectional.

2.2. Study Setting

Blood samples for HIV viral load estimation were collected from 663 CLHIV aged 0 - 18 years on HAART from several health facilities including primary, sec-

ondary and tertiary health institutions in 4 states in the North of Nigeria between 2017 and 2019.

The following information; age, sex, date of HIV diagnosis, date of ART start, current ART regimen; first or second line, date of sample collection, viral Load result were retrieved from the RNA PCR register from the laboratory. The sample size was the number of children in the ART programme in the reporting ART sites who had their samples sent to the PCR laboratory.

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. The lower limit of detection of the assay is <40 copies/mL of HIV-1 RNA.

The laboratory, situated in the Federal Teaching Hospital Gombe, has been certified by the Federal Ministry of Health and the 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. Gombe state has the enviable record of starting the DBS for EID PMTCT of HIV DBS programme in the country.

2.4. Inclusion Criteria

Children with the following information age, sex, date of HIV diagnosis, date of ART start, current ART regimen; first or second line, date of sample collection, together with a VL result were included. Children on treatment with cART for less than 6 months were excluded. Age groups were defined as follows: children (0 - 9 years), adolescents (10 - 18 years). 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 [26]. Children with incomplete data entry were excluded from this analysis.

2.5. Ethical Clearance

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 viral suppression and characteristics of 663 children and adolescents enrolled in the study. All of them have been receiving cART for at least 12

Table 1. Children living with HIV and viral suppression.

Variable	Frequency	<1000 cp/ml	>1000 cp/ml	P
Ages				
0 - 9 yrs	298 (44.9)	148 (49.7)	150 (50.3)	0.660
11 - 18 yrs	365 (55.1)	175 (47.9)	190 (52.1)	
Sex				
Males	311 (46.9)	137 (44.1)	174 (55.9)	0.024
Females	352 (53.1)	186 (52.8)	166 (47.2)	
ART Regimen				
AZT + 3TC + NVP	518 (78.1)	240 (46.3)	278 (53.7)	0.015
TDF + 3TC + EFV	141 (21.3)	79 (56.0)	62 (44.0)	
AZT + 3TC + LPV/r	4 (0.7)	4 (100.0)	0 (0)	
ART Type				
1st line	651 (98.2)	316 (48.5)	335 (51.5)	0.501
2nd line	12 (1.8)	7 (58.3)	5 (41.7)	
Duration on ART				
1 yr	52 (7.8)	32 (61.5)	20 (38.5)	0.299
1 - 5 yrs	366 (55.2)	175 (47.8)	191 (52.2)	
6 - 10 yrs	218 (32.8)	104 (47.7)	114 (52.3)	
>10 yrs	27 (4.1)	12 (44.4)	15 (55.6)	
CD4 count				
<350	141 (21.3)	54 (38.3)	87 (61.7)	<0.001
350 - 499	73 (11.0)	31 (42.5)	42 (57.5)	
500 - 999	285 (42.9)	137 (48.1)	148 (51.9)	
>1000	164 (24.7)	101 (61.6)	63 (38.4)	
Reason for request of viral load				
Routine	625 (94.2)	302 (48.3)	323 (51.7)	0.671
Suspected clinical failure	19 (2.9)	10 (52.6)	9 (47.4)	
Suspected immunological failure	19 (2.9)	11 (57.9)	8 (42.1)	
ART start year				
2000-2004	5 (0.8)	3 (60.0)	2 (40.0)	0.690
2005-2009	107 (16.1)	53 (50.5)	54 (49.5)	
2010-2014	349 (52.6)	163 (46.7)	186 (53.3)	
2015-2018	202 (30.5)	104 (51.5)	98 (48.5)	

months before viral load determination. Adolescents 10 - 18 years, constituted 55.1% (365) of children who had viral load estimation. Of 298 children 0-9 years, 66% (168) had viral suppression of <1000 cp/ml when compared with adolescents 10 - 18 year of age (47.9%) but was not statistically significant. Overall 48.7%

of children 0 - 18 years had viral load of <1000 cp/ml (Figure 1). Non-viral suppression occurred more in adolescents (52.1) than in younger children (47.9), P < 0.66.

Females constituted 53.1% of 663 children with viral load quantification; 52.8% (186) of females had viral load < 1000 cp/ml; 44.1% of males had viral load suppression with a P < 0.02. Overall 48.8% of both sex had viral suppression. Males (55.9%) were more likely to be virally non-suppressed than females (44.1%) but the distribution was not significant (Table 1).

Among children and adolescents on ART, 98.2% were on first line and 1.8% were on second line. Of those on first line, 48.5% had viral suppression with HIV RNA < 1000 cp/ml; 58.3% of children and adolescents on second line had achieved viral suppression (P < 0.50). Only 48.7% of children living with HIV on both first and second line ART were virally suppressed with VL < 1000 cp/ml. Viral non-suppression occurred in 55.1% of children and adolescents on first line.

Of the cART, 78.1% of CLHIV were receiving AZT + 3TC + NVP and 21.2% were on TDF + 3TC + EFV. Only 4 (0.7%) children were receiving lopinar/ritonavir based regimen. 46.3% of children on NVP based triple regimen had viral suppression and in TDF + 3TC + EFV cART 56% had HIV RNA copies of <1000 cp/ml (P < 0.01). All children on LPV/r had achieved viral suppression. Viral load was >1000 c/ml in 53.7% (278) and 44% (62) of CLHIV receiving AZT/3TC/NVP and TDF/3TC/EFV respectively.

In relation to the duration on ART, 55.2% of children living with HIV had received ART for between 1 - 5 years; 32.8% for 6-10 years. Only 7.8% (52) had received ART for 12 months and 4% for >10 years.

Figure 2 showed that viral suppression was achieved in 61.5% of children who had ART for 12 months; 47.8% viral suppression in those on ART for 1 - 5 years; 47.7% viral suppression in 6 - 10 years on ART and 44.7% in those on ART for >10 years. Viral suppression decreased with increasing duration of ART use and the distribution was statistically significant (P < 0.01).

Viral suppression increased from 38% in children with lowest CD4 of <350 count to 64.5% in those with CD4 > 1000 (Figure 3).

Out of the 663 children and adolescents on ART, 94.2% (625) had viral load determined because of routine request by health worker; suspected clinical and immunological failure was the reason for viral load determination in 19% of each of the children respectively. Viral suppression was achieved in 48.3% of children whose reason for VL determination was routine. Of those with suspected immunologic and clinical failure, 42.1% and 47.4% had viral non-suppression respectively.

Majority of the children started ART between 2010 and 2014 and 46.7 were virally suppressed; 53.3% were not virally suppressed. More than half of those who started ART between 2000-2004, 2005-2009 and between 2015 and 2018 had viral suppression.

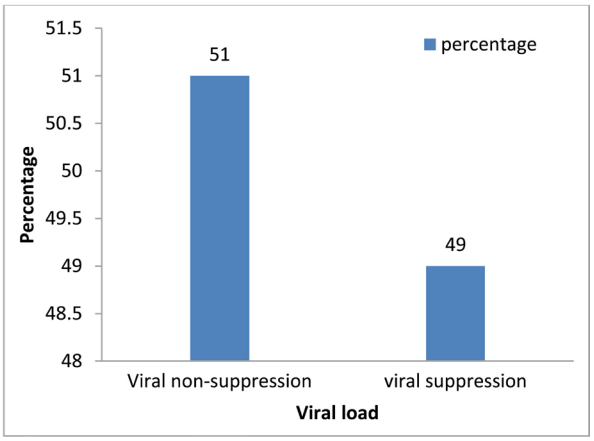

Figure 1. Viral load suppression status in children 0 - 18 years.

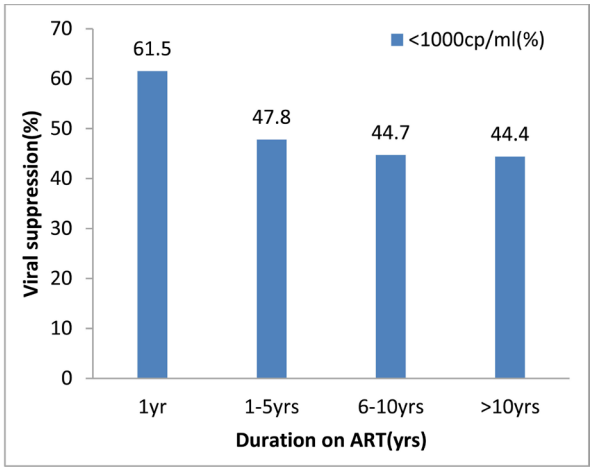

Figure 2. Viral suppression rate and duration of ART in years in children 0 - 18 years.

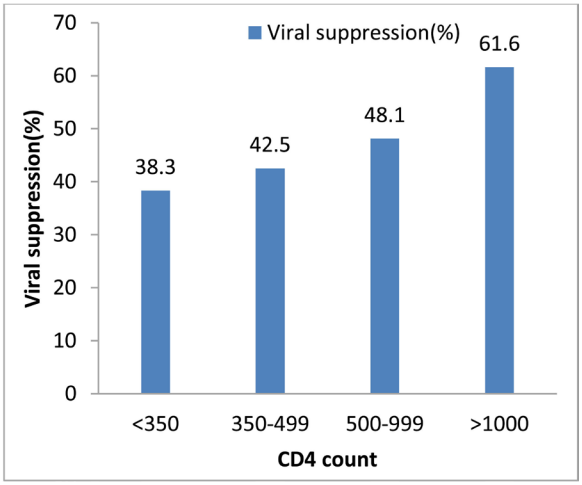

Figure 3. Viral suppression rate and CD4 count in children 0 - 18 years.

4. Discussion

In this study we determined viral suppression in large number of children and adolescents enrolled in the national ART programme in 4 states in Northern

Nigeria. A significant proportion of these children were receiving NNRTI based regime for many years before routine viral load testing started recently. Routine regularly scheduled VL monitoring has the potential to preserve treatment options through early identification of those with non-suppression who might benefit from timely intensified adherence support to prevent treatment failure and the need for regimen changes [12] [27].

The overall viral suppression rate of 48.7% in this study is higher than the reported national viral suppression of 34% in children in Nigeria [22].

Also our findings in children 0 - 9 years and adolescents 10 - 18 years of viral suppression of 66% and 47% respectively are higher than the national viral load suppression report in children. Sub-national data are not representative especially in Nigeria where there is wide variation in regional and state HIV data [26]. Nationally representative viral suppression rates in children in Kenya [28], Uganda [29] and Cameroun [30] were also low.

None nationally representative viral suppression rates below the WHO 90% threshold have been reported in children in South Africa [31], Kenya [32], Eswatini [33], Cameroon [34], and Uganda [35].

A meta-analysis in 2016 showed sub optimal viral suppression in HIV infected children in low and medium income countries with little progress made in improving on viral suppression rates over the years [7].

The differences in VS rates are generally related to, study design, population characteristics, ART type and duration of treatment and suggest substantial differences in programme performances within and across countries [27] [36].

Adolescents had lower rates of viral suppression than children 0 - 9 years in our study. This is similar to findings in Cameroon [34] and data combined from east and southern African countries that showed only 45% of adolescent girls living with HIV were virologically suppressed [37] [38].

Africa bears disproportionately 85% of HIV infected adolescents globally and have the highest.

Rates of attrition from HIV treatment and care of any age group, resulting in higher rates of treatment failure, morbidity, and mortality compared with children and adults [39] [40].

Non-Disclosure, suboptimal adherence levels and lack of psychosocial support are major causes of loss of follow up and virogical failure in adolescents [8] [35] [41].

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 [42] [43].

ART adherence and dose calibration influenced by weight changes, emesis, regurgitation, and spillage are contributory to poor virologic outcomes in children [9] [10].

Viral suppression in children and adolescents on first line cART was less than

half of WHO threshold value. Largely consisting of NVP and EFV based regimen as first line ART, Children on both NNRTI and NRTI ARVs are at high risk of suboptimal treatment from pretreatment drug resistance to NNRTI [19] [20], while infant exposure through PMTCT has greater risk for pretreatment drug resistance and drug resistant mutations [44] [45]. PMTCT naïve infants have also demonstrated this drug resistance harboring mutations [13] [46] and therefore suboptimal viral suppression.

In children and adolescents on cART detection of viral non suppression in the presence of supportive adherence may indicate virologic failure and at risk of acquired drug resistance. Children on NNRTI based regimen were shown to harbor both nucleoside reverse-transcriptase inhibitor (NRTI) and NNRTI resistance mutations including multiclass resistance in many of them [47] [48].

In Nigeria [26] and many more countries in sub-Saharan Africa [20], nationally representative HIV drug resistance surveillance and monitoring has yet to become routine only recently with thousands on ART for many years without the benefit of resistance testing.

HIVDR is associated with poor virological outcomes, increased mortality and reduced durability and effectiveness of regimens. Compared to those without NNRTI resistance, people with NNRTI PDR who receive NNRTI-containing regimens are 30% less likely to achieve viral suppression, 23 times more likely to experience virological failure or death, and nine times more likely to discontinue treatment [17] [49] [50] [51].

In our study the proportion of children on second line ART was low. Non nationally representative data from Kenya [32], Eswatini [33], Uganda [34], and Ethiopia [52], reported equally small numbers of children on Second line ART. In Africa, a three year incidence of switching to second line was about 2%, compared to 12% in Europe and about 30% in the United States [53].

Viral suppression was higher in those with higher CD4 count and the suppression rate increased with increasing CD4 count. This is similar to reports from Zimbabwe [8], Ethopia [52], Cambodia [54] and Vietnam [55]. 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 [6] [52] [56].

Viral suppression of 61% after 12 -24 months of ART in our study is lower than 69.2% from Togo [57], 75% from Cote d'Ivoire [58], 86.4% from Congo [59] and 75% from Cameroun [34] and similar to 62% from Kenya [32] but higher than 32% from Uganda [35]. Unlike our study there is paucity of reports on viral suppression after 10 years of ART in children in our sub region. A study from Cambodia [54] demonstrated decreasing viral suppression after 10 years of ART. Limited access to viral load and HIVDR testing especially to NNRTI made failing and ineffective regimes being administered for many years.

With the recent commencement of routine VL monitoring in Nigeria, a large proportion of children on cART hitherto monitored by clinical and immuno-

logic means, are now undergoing HIV RNA quantification as recommended in the National guideline [26].

Males in our study were more likely to be virally none suppressed compared to female children. This is similar to several reports in adults [60] [61] [62] [63] and as a consequence they have poor HIV immuno virologic and clinical outcomes compared to females. Some studies [64] [65] [66] on the other hand, did not find an association between gender and virologic success or failure.

5. Conclusion

HIV viral suppression in children and adolescents on ART in our study is low. The viral suppression is higher than the reported rate in the country but far below the threshold recommended by World health organisation. Transition to more efficacious ART regimen and implementation of nationwide HIVDR surveillance and monitoring, including quality adherence support will improve viral suppression rate in the country.

6. Limitations

We were unable to disaggregate data into those with prior or NNRTI exposure through PMTCT. This is the first viral load results in these children and therefore could not establish treatment or virologic failure especially as we did not determine level of adherence and a second viral load.

Author's Contribution

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

Ajani Ayomikun: Conducted quantitative data analysis and reviewed all drafts of the manuscript.

Jalo Iliya: Oversaw the study design and critically reviewed and commented on the final manuscript.

Oyeniyi Christianah: Conducted quantitative analysis

Danlami Mohammed Hassan: Reviewed and commented on data

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Conflicts of Interest

Authors have no conflict of interest to declare.

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