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VIRAL LOAD TESTING CASCADE FOR HIV INFECTED CHILDREN ON NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR-BASED FIRST LINE REGIMEN AT SELECTED HEALTH FACILITIES IN WESTERN KENYA

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ABSTRACT

Background: **Viral load (VL) testing is critical in monitoring response to HIV treatment for children.**

Objectives: **To describe access to VL testing and testing outcomes for children on Nevirapine or Efavirenz based first line antiretroviral treatment (ART).**

Design: **Retrospective cohort study**

Setting: **HIV clinics. Participants: Children aged 6 weeks to 14 years.**

Main outcome measures: **VL test results, viral suppression,**

Methods: **We reviewed records of children initiated on ART between 2010 and 2014. Clinic attendance within 90 days was considered active. Virological failure was defined as VL>1000copies/ml while repeat VL>1000c/ml qualified for regimen switch. Analysis used Stata Version 13.1 and Cox proportional hazard ratio was used to explore the association between outcome measures and sociodemographic at p≤0.05 level of significance**

Results: **Of 3,432 eligible children, 69.1% had VL results and 69.5% achieved viral suppression. Of 3,118 active on ART, 73.1% had VL results and 70.1% achieved viral suppression compared to 314 attritions from care with 29.5% and 55.4% respectively (P<0.001). Fewer children on ART < 24 months had VL results compared to those on**

ART for longer, 52.1% vs 76.1% (p<0.001). Probability of virological failure was higher for males and duration on ART of > 24 months but lower for age 2 – 10 years and CD4 >500 cells/mm^3 compared to age < 2 years and CD4 <350 cells/mm^3 respectively. Of 809 (30%) children with virological failure, 81.1% had repeat VL results of whom 72.0% had VL >1000 copies/ml and 58.9% had regimen switch. Of the 809, 308 (38.1%) switched regimen without repeat VL results and 79.9% had follow up VL >1000 copies/ml.

Conclusion: **Although most children achieved viral suppression, gaps in access to timely VL testing remain a challenge. Children aged >24 months and those switched without repeat VL results need additional support to achieve viral suppression.**

INTRODUCTION

Viral load testing for patients receiving antiretroviral therapy is the best predictor of treatment outcome and World Health Organization (WHO) recommends routine VL testing as part of routine care (1). Although it is desirable that all patents on effective antiretroviral treatment achieve and maintain viral suppression, studies have confirmed that children and adolescents are less likely to achieve viral suppression compared to adults (2). Those on NNRTI based ART regimens (including Nevirapine or Efavirenz) are particularly at high risk of treatment failure due to their low genetic barrier, extensive use in prevention of mother to child transmission of HIV (PMTCT) programs and high potential for development of ARV resistant mutations (3). Additional factors associated with treatment failure in children include use of nevirapine containing regimens, advanced HIV disease and poor adherence to medication (4-6). Furthermore, infants and children are dependent on others for medication administration. Barriers faced by adult caregivers that can contribute to non-adherence in children include forgetting doses, changes in routine, and child refusal among others (7, 8). Children on ART for longer periods are also less likely to achieve viral suppression (9).

WHO recommends individualized patient assessment that includes enhanced adherence support for three months for all patients with suspected treatment failure. Repeat VL test results are then used to determine the need for a regimen switch (1). Kenya HIV estimates (2015) indicated that 98,000 children were living with HIV and 81,019 (82.7%) of these were on ART of whom 63% were on NNRTI based regimens (10). In June 2014, Kenya adopted the 2013 WHO recommendation of routine VL testing as a preferred approach for diagnosis and confirmation of treatment failure. Analysis of VL test results showed that the proportion of children who achieved viral suppression in 2017 was lower compared to that of adults, 67% vs 86% (11). There is however limited information on proportion of children who achieve viral suppression by regimen. This study provides regimen specific information that will contribute towards timely interventions for children on first line ART regimen including those diagnosed with treatment failure.

MATERIALS AND METHODS

We abstracted data from electronic medical records of 46 facilities using a data abstraction guide. Patient management at the sites followed national guidelines. Variables of interest included referral source, baseline WHO clinical stage, baseline CD4 count, date of ART initiation, ART regimen at initiation, current ART regimen and date of initiation, first VL result and date results were received at the facility. Others were VL results done within the last 12 months and status (Active, transfer out, lost to follow up or death). Patients who had transferred services to another

health facility were categorized as transfer out. Those who attended clinic within 90 days from date of clinic appointment were categorized as active on ART while those who had missed clinic for more than 90 days were categorized as lost to follow up. At the time of data abstraction in June 2016, all children who were active on ART after June 2014 were expected to have at least one documented VL result.

Viral suppression was defined as VL < 1000 copies/ml. National guidelines recommend repeat VL testing for all patients with virological failure (VL ≥ 1000 copies/ml) after enhanced adherence support and those with persistent VL ≥ 1000 copies/ml are considered to have failed treatment hence eligible for an ART regimen switch. We analyzed most current VL results done within the last 12 months for 2,828 children who were active on ART to determine proportion of children with virological failure with documented repeat VL ≥ 1000 copies/ml who had been switched to second line ART.

We analyzed data using Stata Version 13.1, 1985 – 2013 Stata Corp LP, USA. Chi square test of independence was used for categorical variables to test for associations while students t – test for continuous variables was used to test for significant differences between different variables. Cox proportional hazard ratio was used to explore the association between outcome measures and sociodemographics at $p \leq 0.05$ level of significance.

Human subjects: This study received ethical approval from the University of Nairobi - Kenyatta National Hospital (UON – KNH) ethics review committee.

RESULTS

Baseline characteristics: The study included 4,250 children of whom 2,182 (51.3%) were females and 1,422 (61.3%) were aged 2 – 10 years. Approximately half (49.8%) of the children were receiving care in hospitals while the rest came from primary health facilities. More than 30% of the HIV infected children were identified through voluntary HIV testing and counseling and referred for treatment. Majority, 75.9% (3,224) had WHO clinical stage 1 or 2 and more than half, 60.2% had been on ART for more than 24 months. The median; age at enrolment was 5.0 years (IQR 2.2 – 8.3), age at ART initiation was 5.7 years (IQR 2.7 – 9.2) and duration on ART was 30.6 months (IQR 18.0 – 54). Table 1 below shows baseline characteristics of children included in the analysis.

Table 1

Baseline characteristics of children initiated on NNRTI based first line ART regimen between 2010 and 2014.

Variable	Total (n=4250)	Percent (%)
Facility type		
Hospital	2,116	49.8
Health centers	1,528	36.0
Dispensaries	606	14.2
Gender		
Female	2,068	48.7
Male	2,182	51.3
Age at enrolment		
< 2 years	953	22.4
2 – 10 years	2,605	61.3
>10 years	692	16.3
Duration on ART		
Less than 24 months	1,691	39.8
More than 24 months	2,559	60.2
Referral source		
Voluntary counseling and testing (VCT)	1,422	33.5
Transfer in	709	16.7
PMTCT	437	10.3
Others	379	8.9
Provider initiated testing and counseling (PITC)	285	6.7
Outpatient department	249	5.9
In patient department	61	1.4
Missing documentation	708	16.7
WHO Staging		
Stage 1 and 2	3,224	75.9
Stage 3 and 4	694	16.3
Missing data	332	7.8
Baseline CD4 count		
< 350 cells/mm^3	940	22.1
350 – 500 cells/mm^3	459	10.8
> 500 Cells/mm^3	1,294	30.4
Missing data	1,557	36.6

Out of the 4,250 children 3,118 (73.4%) were active on ART, 656 (15.4%) had transferred out, 315 (7.4%) were dead and 161 (3.8%) were lost to follow up (LTFU). The median time from enrolment to ART initiation was 2.1 months (IQR 0.6 – 9.3). The median time from enrolment to death was 9.8 months (IQR 4.4 – 21.7) while ART initiation to death was 6.0 months (IQR 1.8 – 18.5). The median time from enrolment to LTFU was 14.0 months (IQR 8.0 – 30.0) while ART initiation to LTFU was 10.6 months (IQR 5.6 – 20.9). The median time from enrolment to Transfer out was 18.2 months (IQR 8.0 – 30.0) while ART initiation to transfer out was 13.8 months (IQR 5.2 – 25.3).

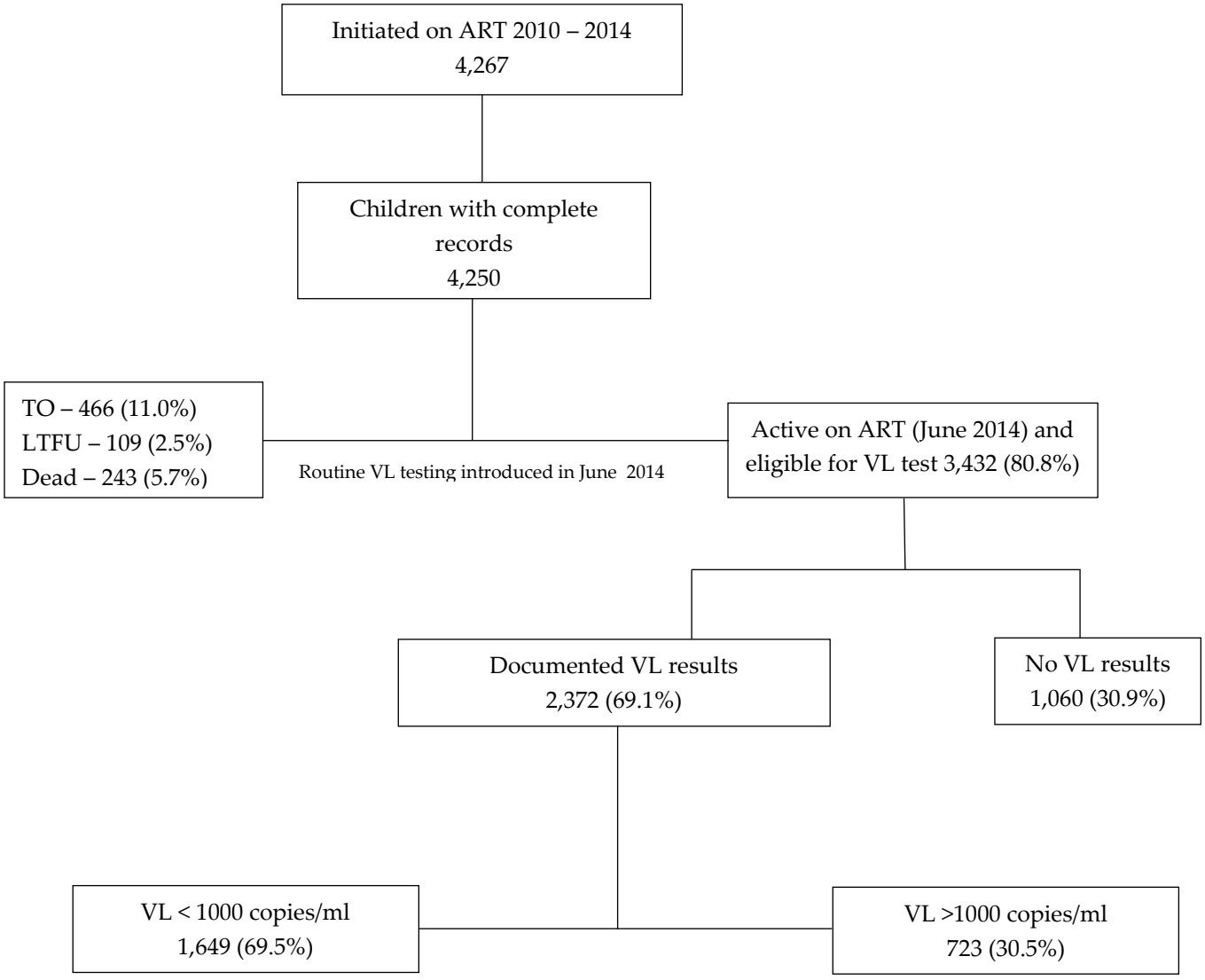

Figure 1. Flow chart on proportion of records included and excluded at each stage of analysis

Viral load testing outcomes: All children who were active on ART after June 2014 were expected to have at least one documented VL result following revision of national ART guidelines that recommended routine VL testing for all patients. In total 3,432 [72/314 of those reported as dead, 52/161 of those reported as LTFU, 190/656 of those reported as transfer out and 3,118 who were

active on ART] were expected to have at least one documented VL result. Of these, 2,372 (69.1%) had VL results and 1,649 (69.5%) achieved viral suppression. Assuming however that all those who died prior to introduction of routine VL testing did not achieve viral suppression, the adjusted proportion that achieved viral suppression would be lower at 63.1% (1,649/2,615).

Of those active on ART, 2,280 (73.1%) had at least one documented VL result and 1,598 (70.1%) achieved viral suppression while among the 314 children eligible for VL testing at the time of exit, only 92 (29.2%) had documented VL results [transfer out – 62/190 (32.6%), dead – 21/72 (29.2%), LTFU – 9/52 (17.3%)]. Of the 92 children, only 51 (55.4%) had achieved viral suppression [transfer out – 42/62 (67.7%), dead – 3/21 (14.3%), LTFU – 6/9 (66.7%)]. The difference in proportion of children active on ART with documented VL results and those who achieved viral suppression compared to those who had exited from care was statistically significant ($p<0.001$).

VL availability among children on ART for $\leq$ 24 months was 52.1% (519/997) compared to 76.1% (1,853/2,435) for those on ART for longer ($p < 0.001$). In total, 406/519 (78.2%) children on ART for $\leq$ 24 months achieved viral suppression compared to 1,243/1,853 (67.1%) of those who had been on ART for longer. Table 2 shows proportion of children with documented VL results by indicator.

Table 2

Proportion of children initiated on NNRTI based first line ART regimen between 2010 and 2014 with documented VL results

	Total (n = 3,432)	**VL Results (n=2,372)**	**Percent (%)**
Gender			
Female	1,780	1,222	68.7
Male	1,652	1,150	69.6
Age at ART initiation			
<2yrs	540	373	69.1
2 - 10yrs	2,181	1,493	68.5
>10yrs	711	506	71.2
Duration on ART			
≤ 24 months	997	519	52.1
> 24 months	2,435	1,853	76.1
WHO clinical stage			
1 and 2	2,613	1,793	68.6
3 and 4	535	383	71.6
Missing	284	196	69.0
Baseline CD4			
< 350 Cells/mm³	722	532	73.7
350 – 500 cells/mm³	391	288	73.7
> 500 cells/mm³	1,070	764	71.4
Missing	1,249	788	63.1
Referral source			
OPD	222	160	72.1
IPD	50	35	70.0
PITC	265	181	68.3
PMTCT	323	221	68.4
TI	585	371	63.4

VCT	1,072	815	74.6
Others	299	225	75.3
Missing	596	364	61.1

Although the proportion of children accessing care in hospitals with VL test results was higher compared to primary health facilities (60.4% vs 53.0%) the difference in proportion of those who achieved viral suppression was not statistically significant (OR 0.91, IQR 0.77 – 1.08, $p = 1.05$). In total, 1,191 (67.0%) children compared to 458 (77.1%) who started ART before and after 2014 achieved viral suppression and the difference was statistically significant ($p < 0.001$). Males were 1.4 times more likely to have virological failure compared to females (aOR 1.35, 95% CI 1.08 – 1.70). Likewise, children on ART for more than 24 months were 2.1 times more likely to have virological failure (aOR 2.12, 95% CI 1.52 - 2.96) compared to those on ART for less than 24 months. Children aged 2 – 10 years were less likely to have virological failure compared to age 2 years (0.56, 95% CI 0.39 – 0.81) as were those with baseline CD4 > 500 cells/mm^3 (aOR 0.70, 95% CI 0.53 - 0.91) compared to CD4 < 350 cells/mm^3. Table 3 shows summary analysis of virological failure for children included in the analysis.

Table 3

Analysis of risk factors for virological failure for children initiated on NNRTI based first line ART from 2010 to 2014

	Total (n)	**No with VL>=1000 (%)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Gender				
Female	1,222	341 (27.9)	1	1
Male	1,150	382 (33.2)	1.29 (1.08 - 1.53) *	1.35 (1.08 - 1.70) *
Age at ART initiation				
<2 years	373	146 (39.1)	1	1
2 – 10 years	1,493	396 (26.5)	0.56 (0.44 - 0.71) *	0.56 (0.39 - 0.81) *
>10 years	506	181 (35.8)	0.87 (0.66 - 1.14)	0.85 (0.56 - 1.29)
Baseline WHO clinical stage				
1 and 2	1,793	529 (29.5)	1	1
3 and 4	383	118 (30.8)	1.06 (0.84 - 1.35)	0.95 (0.71 - 1.26)
Baseline CD4 Count (cells/mm^3)				
<350 cells/mm^3	532	191 (35.9)	1	1
350 – 500 cells/mm^3	288	77 (26.7)	0.65 (0.48 - 0.89) *	0.71 (0.51 – 0.98)
>500 cells/mm^3	764	198 (25.9)	0.62 (0.49 - 0.79) *	0.70 (0.53 - 0.91) *
Duration on ART initiation (months)				
Less than or equal 24	519	113 (21.8)	1	1
Greater than 24	1,853	610 (32.9)	1.76 (1.40 - 2.22) *	2.12 (1.52 – 2.96) *

**Significant at 5% level*

Analysis of children with VL>1000 copies/ml.: Out of 2,828 children who were active on ART by December 2016, 2,712 (95.9%) had a documented VL result done within the previous 12 months. Of these, 809 (29.8%) had VL >1000 copies/ml of whom 656 (81.1%) had repeat VL results. In total 472 (72.0%) children had a repeat VL results of >1000 copies/ml of whom 278 (58.9%) had been switched to second line ART. The median duration from date of first VL result to ARV regimen switch was 12.4 months (IQR 8.5 – 18.8). There was no association between re suppression and gender (p = 0.19), age (p=0.95), or WHO clinical stage (p = 0.93). Of the 809 children with VL > 1000 copies/ml, 308 (38.1%) children had been switched to second line ART without repeat VL test result and of these, 240 (77.9%) still had a follow up VL > 1000 copies/ml.

DISCUSSION

Overall, 69% of children eligible for VL testing had a documented VL result. Fewer children with documented date of exit after introduction of routine VL testing had VL results (Dead – 29%, LTFU – 17%, and transfer out – 32%) compared to those who were active on ART at 73%. Data on access to routine VL testing for HIV infected children on ART remains scarce. In Uganda, evaluation of incidence and risk factors for first line antiretroviral treatment failure among Ugandan children attending an urban HIV clinic excluded 34% of records due to missing VL results among others (4).

Although our study found that 70% of children on NNRTI based first line ART regimens achieved viral suppression, this may be an overestimate and reduces to 63% assuming that those who died including deaths prior to introduction of routine VL testing had virological failure. This is consistent with other studies that have reported suboptimal viral suppression among children on ART. In Uganda, only 66% of children attending an urban clinic achieved viral suppression while in Zimbabwe, 69% of children and adolescents accessing ART in public health facilities achieved viral suppression (4,9). A meta-analysis of 72 studies reporting on 51,347 children initiated on first line ART after 2010 reported 12-month viral suppression rates of 73% (12). Data from the three studies above however included children who were on NNRTI and non-NNTRI based first line ART. We found the proportion of children who had achieved viral suppression prior time of exit from care to be lower compared to those who were active on ART (55% vs 73%). Data on proportion of children who achieve viral suppression prior to time of exit from care remains scarce. Our finding reinforces WHO recommendation of timely viral load testing for all patients especially for children.

Suboptimal adherence to treatment has been associated with treatment failure especially in children on NNRTI based regimens (13). In Thailand, children on NNRTI based regimen were more likely to switch to second line ART due to treatment failure (14). This study also noted that children who had been on ART for longer than 24 months were more likely to have virological failure. Our findings are consistent with other studies that have reported an increase in proportion of children who switch from first line to second line ART due to treatment failure based on duration on ART (1,4,10).

Children with a baseline CD4 > 500 cells/mm^3 were less likely to have virological failure compared to those with CD4 < 350 cells/mm^3. Other studies have also observed advanced HIV disease to be a predictor of virological failure among children on ART. In Ethiopia, the risk of virological failure was 4.3 times higher for those with baseline CD4 < 50 cells/mm^3 and 2.5 times higher for those with advanced HIV disease (15). Other studies have however failed to demonstrate a correlation between virological failure and immunological failure (16).

Our study found viral suppression rates of 65% for those initiated on ART at age less than 2 years, 73% for age 2 – 10 years and 63% for those above 10 years. Those aged 2 – 10 years were less likely

to have virological failure compared to age less than 2 years. Other studies have also demonstrated viral suppression to be lower among the youngest and the oldest children (17).

WHO recommends repeat VL testing after enhanced adherence for all patients with virological failure prior to ART regimen switch. Our study found that 81% of children with virological failure had documented repeat VL results. This was higher than findings from other studies that have documented suboptimal access to repeat VL testing for children diagnosed with virological failure (2). In contrast with other studies, we found that only 28% of those with virological failure achieved viral suppression after enhanced adherence. In South Africa, 41% of patients with viremia resuppressed after enhanced adherence while in Swaziland, although 54% of patients re suppressed, children, adolescents and those with baseline CD4 < 350 were less likely to re suppress (2,18). Similarly, we did not find any association between re suppression and gender or WHO clinical stage.

Cumulatively, 59% of children with confirmed treatment failure had an ART regimen switch. This is in contrast to other studies that have found overall proportion of children who switch to second line ART to be higher (19). We found that 78% of patients who had a regimen switch to second line ART without repeat VL results failed to re suppress on their new regimens. This reinforces WHO 2016 guidelines that recommend repeat VL testing for all patients on ART with virological failure prior to a regimen switch. A meta-analysis conducted to analyze research on VL monitoring as a tool to reinforce adherence found a pooled estimate of 71% re suppression after enhanced adherence (14). Our finding raises a possibility of adherence challenges that may have contributed to failure to re suppress prior to change of regimen.

The strength of this study is the inclusion of a well-defined study population that focuses on HIV infected children on antiretroviral treatment. The study however did not have a comparison group and focused on faith-affiliated facilities only posing challenges in generalization to other health facilities or study settings.

CONCLUSION

Most of children on NNRTI based first line regimen achieved viral suppression. Health care workers should however be more vigilant in ensuring timely VL testing for all eligible children. Children especially those aged >24 months, those at high risk of attrition from care and those switched without repeat VL results may need additional support to achieve viral suppression.

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