VIRAL LOAD TESTING OUTCOMES FOR CHILDREN ON NEVIRAPINE/EFAVIRENZ BASED ANTIRETROVIRAL TREATMENT REGIMENS AT SELECTED HEALTH FACILITIES IN WESTERN KENYA

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Viral Load Testing Outcomes for Children on Nevirapine/Efavirenz Based First Line Antiretroviral Treatment at Selected Health Facilities in Western Kenya

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University.

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This thesis has been submitted for examination with our approval as the University Supervisors

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DEDICATION

This work is dedicated to my late mother Milkah Kemunto Obinchu, for her encouragement that has kept me going in pursuit of knowledge.

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LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral treatment
ARV	Antiretroviral drugs
CLHIV	Children Living with HIV
DHHS	Department of Human and Health Services
DNA	Deoxyribonucleic Acid
HIV	Human Immunodeficiency Virus
HIV DR	HIV Drug Resistance
HTC	HIV Testing and Counseling
JKUAT	Jomo Kenyatta University of Agriculture and Technology
KEMRI	Kenya Medical Research Institute
KENPHIA	Kenya Population-based HIV Impact Assessment
KNH	Kenyatta National Hospital
MOH	Ministry of Health
NASCOP	National AIDS and STI Control Program
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PEPFAR	President's Emergency Plan for AIDS Relief
PITC	Provider Initiated Testing and Counseling
PLHIV	People Living with HIV

PMTCT	Prevention of Mother to Child Transmission of HIV OR Odds Ratio
aOR	Adjusted Odds Ratio
PI	Protease Inhibitor
RNA	Ribonucleic Acid
VL	Viral Load
VCT	Voluntary Counseling and Testing
UNAIDS	United Nations Program on HIV/AIDS
UNICEF	United Nations International Children's Emergency Fund
USA	United States of America
WHO	World Health Organization

OPERATIONAL DEFINITION OF TERMS

NNRTI Drugs	These are antiretroviral drugs that include nevirapine and Efavirenz that terminate HIV replication cycle by binding the enzyme reverse transcriptase leading to blockage of polymerization of viral DNA. Mutation in the HIV virus reduces the affinity of the inhibitors for the enzyme and generally leads to high level resistance. Drugs in this class include nevirapine, efavirenz, etravirine and Delavirdine.
Treatment failure	Loss of antiretroviral drug efficacy that triggers a consideration in switching a patient's treatment regimen.
Treatment naïve	A patient who does not have history of having received HIV treatment
UNAIDS 95-95-95	Global targets for achievement of HIV epidemic control: 95% testing, treatment and viral suppression targets. As well as 95% access to combination prevention services; 95% access to sexual reproductive health services; and 95% coverage of prevention of mother to child transmission of HIV
Viral suppression	Refers to plasma HIV viral load of less than 1000 copies/ml at last viral load test as defined by the World Health Organization (WHO)
Virologic failure	Inability to achieve expected maximal viral suppression after 6 months of effective antiretroviral treatment (ART). It may also refer to sustained increase in viral load after achieving suppression on treatment.

ABSTRACT

Access to Antiretroviral treatment (ART) has rapidly expanded in resource limited settings. Gaps however remains for children in maintaining long-term adherence to ART, and thus sustain virological suppression and prevent treatment failure. The general objective of this study was to determine viral load (VL) testing outcomes and reasons for missed opportunities for children on non-nucleoside reverse transcriptase inhibitor (NNRTI) – based first line ART regimen at selected health facilities in western Kenya.The specific objectives included to determine the proportion of HIV infected children initiated on Nevirapine or Efavirenz based first line treatment between 1st January 2010 and 31st December 2014 at selected health facilities in western Kenya who achieved viral suppression; to explore reasons for missing documentation of repeat VL tests for children with virological failure and to document proportion of children with confirmed treatment failure who had regimen switch to second line ART. The study was carried out in 46 health facilities in Western Kenya. Data was abstracted from central electronic medical records using a data abstraction guide, transferred to Microsoft excel and analyzed using Stata Version 13.1, 1985 – 2013 Stata Corp LP, USA. Individual chart reviews for those with missing repeat VL test results was done using a chart abstraction guide and data entered in excel 2013 and analyzed using descriptive statistics. Overall, out of 4,250 children, 3,118 (73.4%) had visited clinic within 90 days (active), 656 (15.4%) transferred out, 315 (7.4%) were deceased and 161 (3.8%) were lost to follow up. There was approximately 3-month and 4-month delay in ART initiation for those reported to have lost to follow up (LTFU) and deceased respectively. Of 3,432 children eligible for VL testing, based on time of implementation of routine VL testing (June 2014), 2,372 (69.1%) had VL results and 1,649 (69.5%) achieved viral suppression. This would however reduce to 63.1% if it is assumed that all those who died had not achieved viral suppression. Lower proportion of children who had exited from care had documented VL results compared with those who were active on care (29.3% versus 73.1%).The Odds of having documented VL results was higher for those who had been on ART for more than 24 months compared to those who had been on ART for less than 24 months (Adjusted odds ration [aOR] 1.7, 95% confidence interval [CI] 1.2 – 2.5) and for those initiated on ART before implementation of routine VL testing compare with those initiated after (aOR 1,6, 95% CI 1.2 – 2.1). Lower proportions of the very young (<2 yrs) and older children (>10 years) achieved viral suppression compared to age 2 – 5 and 5 – 10 years [64.6% and 63.7% versus 75.6% vs 71.9%). Likewise, lower higher proportion of children who had been on ART for less than 24 months achieved viral suppression (79.4%) compared to those on ART 24 – 60 months (67.5%) and more than 60 months (67.7%) although the difference was also not statically significant. The odds of achieving viral suppression was 1.4 times higher for children with baseline CD4 >500cells/mm^3 compared to those with baseline CD <350 cells/mm^3. (aOR 1.39, 95% CI 1.03 – 1.89). A higher proportion of children who started ART after implementation of routing VL testing achieved viral suppression compared to those who started ART before (82.8% versus 67.8). Of the 2,828 children who were active in care by December 2016, 2,712 (95.9%) had documented VL results out of whom 809 (29.8%) had VL >1000 copies/ml and of these, 673 (83.2%) had documented repeat VL results. In total 491 (73.0%) had repeat VL results of >1000 copies/ml out

of whom 272 (55.4%) had been switched to second line ART. The median duration from date of first VL test result to switch to second line ART was 13.3 months (IQR 9.8 – 19.2). Of the 809 children with VL > 1000 copies/ml, 38.1% had been switched to second line ART without repeat VL test result and of these, 77.9% still had a follow up VL > 1000 copies/ml. Out of 112 records of children with missing repeat VL results, VL samples had been taken for 54 (48.2%) of the children and of these, 32 (59.3%) results were available at facility level but not documented in client records. In total, 49 (43.8%) had delayed sample collection and 9 (8.0%) had exited from care. Although most children achieved viral suppression, gaps in access to timely VL testing remain a challenge. Younger and older children, those on ART >24 months and those switched without repeat VL results may need additional support to achieve viral suppression.

CHAPTER ONE

INTRODUCTION

1.1 Background Information

The expansion of Prevention of Mother to Child Transmission (PMTCT) of HIV programs and use of more effective antiretroviral regimens have continued to prevent more children from becoming infected with the Human Immunodeficiency Virus (HIV) virus. Despite this, globally, children under the age of 15 years' account for 5% of all people living with HIV (PLHIV), 10% of new HIV infections and 15% of acquired immunodeficiency syndrome (AIDS) related deaths. Of the 1.5 million people newly infected with HIV, children accounted for 10.7 percent most of whom were in sub-Saharan Africa (UNAIDS, 2021) Kenya Population-based HIV Impact Assessment (KENPHIA) 2018 estimated prevalence of HIV among children to be 0.7% translating to a total of 139,000 children living with HIV (KENPHIA, 2018).

It is recommended that Children Living with HIV (CLHIV) be initiated on treatment as soon as possible after diagnosis and monitored to ensure they achieve viral suppression as mortality has been shown to be significant for those who start treatment late and those diagnosed with treatment failure (Violari et al., 2008). Treatment coverage among CLHIV has remained suboptimal compared with adult in most sub-Saharan Africa countries. Across all countries, pediatric treatment coverage rose from 18% in 2010 to 52% by 2021 (UNAIDS, 2022) World Health Organization (WHO) recommendations for paediatric HIV treatment were however reviewed in 2013 and recommended earlier initiation on treatment for all CLHIV which may have contributed to the slow increase in treatment coverage (WHO, 2013).

UNAIDS estimates that of the 1.3 million adults living with HIV in Kenya, 139,000 are children of whom 64% are on treatment. Treatment coverage however varies by county and ranges between 17% in Angola to 96% in Namibia (UNAIDS, 2021). Coverage may vary from year to years based on actual CLHIV estimates that takes into count new pediatric HIV infections following failed PMTCT interventions.

Drugs used to treat HIV are classified based on their mode of action. They include nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and HIV integrase inhibitors. Commonly used NNRTI drugs include nevirapine and efavirenz. Reverse transcriptase inhibitors suppress HIV replication by competitive inhibition of viral reverse transcriptase enzyme while PIs prevent the late stages of viral replication by interfering with the formation of structural proteins of the virion core proteins. NNRTIs have a long plasma half-life compared to other antiretroviral drugs and their use in the background of undiagnosed HIV infection leads to development of drug resistant mutations. Use of these drugs also in the context of suboptimal adherence or abrupt stopping of treatment leads to the same phenomenon. It has been observed that a single viral mutation to NNRTI drugs confers viral resistance to the drugs hence are considered to have a low genetic barrier. Children with an Antiretroviral (ARV) drug resistant virus have an increased risk of suboptimal viral suppression that leads to decline in CD4 counts and increased risk of HIV related morbidity and mortality.

It has been observed that if HIV infected children are not initiated on treatment, 35% die before their first birthday and 53% die before their second birthday (Newell et al., 2004) Treating HIV infected children with antiretroviral drugs within their first 12 weeks of life reduces mortality by 76 percent and the risk of HIV disease progression by 75 percent (Violari et al., 2008) and those who start Antiretroviral treatment (ART) early, before reaching severe immunosuppression stage, recover their CD4 levels more quickly. Research has however demonstrated that only triple combination ART appears to significantly reduce the relative hazard ratio of death compared with no treatment. Drug combinations for treatment include a backbone of two NRTIs plus either an NNTRI or a PI drug. WHO recommended that all HIV infected children aged less than three years be initiated on a PI based antiretroviral treatment regimen as the preferred option (WHO, 2016). This has however evolved, and the current WHO guidelines recommend use of dolutegravir based regimen as preferred first line treatment (WHO, 2021). Kenya national guidelines (2011) recommended use of NNRTI drugs only for children who did not have previous history of exposure to nevirapine (MOH, 2011), but subsequent guidelines

recommended use NNRTI based regimens for all children aged more than three years irrespective of history of previous exposure to nevirapine (MOH, 2014a). Although these guidelines recommended use boosted lopinavir based regimen as preferred first line treatment for children aged less than 3 years old, majority may have opted for NNRTI based regimens as the syrup formulation of boosted lopinavir is unpalatable. Current Kenya guidelines on HIV prevention and treatment recommend use of dolutegravir based regimen as preferred first line treatment for all HIV infected children aged more than 4 weeks old. Efavirenz based regimen may however only be used as alternative first line treatment in case of intolerance to dolutegravir (MOH, 2022a) The main goal of antiretroviral treatment is to lower plasma Viral Load (VL) to undetectable levels and allow immune recovery. Adherence support, clinical and VL monitoring however continue to remain core to the success of anti-retroviral treatment based on WHO recommendations. Kenya adopted this in 2014 and recommended VL testing for all HIV infected children on treatment at 6 months and 12 months' post ART initiation, and thereafter yearly (MOH, 2014a). VL testing in Kenya is centralized and samples are transported to testing laboratories though laboratory networks. Since adoption of routine VL monitoring, the number of VL testing laboratories has increased from 3 in 2012 to 10 in 2022 while the number of blood samples collected for VL testing from children has increased from 18,630 in 2014 to 75,398 in 2022 (MOH, 2014b). Data on proportion of HIV positive children on treatment who get a timely VL test is not readily available. A systematic review done to assess feasibility of treatment monitoring for people living with HIV who were on ART in low and middle-income countries found variations in proportion of those with timely VL test. The proportions of patients on first-line ART who received a first VL monitoring test within 6–12 months of ART initiation ranged from 12% to 94%. Annual uptake of VL monitoring varied across countries, from 25% in Zimbabwe to 94% in Kenya. Coverage for follow-up VL monitoring after an initial elevated VL was however lower than that of initial VL monitoring and ranged from 25% to 88%. The proportions of patients with two consecutives elevated VL measurements (confirmed treatment failure) varied from 26% to 83%. The reported proportion of patients switching to second-line ART after confirmation of treatment failure also varied, ranging from 18% to 85% (Pham et al., 2022).

Despite improved access to VL testing, some children may not achieve viral suppression and are considered to have virological failure. This is defined as VL above 1000 copies/mL based on two consecutive VL measurements three months apart, with adherence support following the first VL test. Failure to suppress may be due to adherence failure or drug potency failure. Potency failure may be due to either weak regimen, suboptimal dose, prior drug resistance or drug interactions. Approximately one third of HIV positive children are prescribed incorrect doses of ART with approximately 21% being underdosed and 16% overdosed (Dakshina et al., 2019). Adherence to treatment for children continue to remain a concern as they depend on caregivers. Despite the cited 95% adherence to antiretroviral therapy for successful virological outcomes in HIV treatment, a systematic review that included 43 studies from 26 countries found the mean rate of patients reporting optimal adherence at 63.4%. The odds of virological failure were 66% lower for those with optimal adherence compared to those with suboptimal adherence (Bezabhe et al., 2016).

High rates of baseline resistance and virological failure among ART naïve HIV infected children has been reported. WHO guidelines recommend initiation of nevirapine prophylaxis for all HIV exposed infants. Kenya HIV care and treatment guidelines recommend extended infant nevirapine prophylaxis till one after complete cessation of breastfeeding (MOH, 2022a). In the SWEN study, HIV exposed infants on daily nevirapine prophylaxis but diagnosed to be HIV infected by six weeks of age were found to have a significantly higher prevalence of NVP-resistance than those who received single dose nevirapine (Puthanakit et al., 2005). In Mali, 32.5% of children, initiated on ART failed to suppress at 6 months. Baseline NNRTI resistance was common in children without reported NNRTI exposure at 23% and was associated with increased risk of treatment failure. The odds of virological failure or death were 6 times higher for those with poor adherence compared to those with optimal adherence. In this study, the odds of virological failure were 23 times higher for those with baseline NNRTI resistance and initiated on NNRTI based regimen (Crowell et al., 2017). In Kenya, KENPHIA 2018 estimated that of the 78.9% children living with HIV who had known HIV status, 98.3% were on treatment of whom only 67.1% were virally suppressed (KENPHIA, 2018). Data on

proportion of children who achieve viral suppression by individual regimen is not readily available.

1.2 Statement of the problem

Use of nevirapine for PMTCT has been associated with nevirapine resistance in women and their infants. Equally, women on triple ARV prophylaxis with suboptimal adherence have an increased risk of ARV resistance in addition to transmitting an ARV resistant virus to their infants. In Kenya, whereas administration of daily nevirapine to HIV exposed infants to prevent transmission is started immediately after delivery, the first HIV diagnostic test is done at 6 weeks. Administration of nevirapine to infants with undiagnosed HIV infection has been associated with development of ARV resistant mutations.

Kenya HIV treatment guidelines recommended use of nevirapine or efavirenz based regimen for treatment of HIV infected children (MOH, 2011) and more than 90% of children were on either nevirapine or Efavirenz based regimen as of June 2014. Of the 105,213 CLHIV, 82,325 were on ART. Eight counties (Busia, Kakamega, Bungoma, Siaya, Kisii, Migori, Kisumu and Homabay) contributed 46.5% of all CLHIV in Kenya and 49.1% of CLHIV on ART (MOH, 2018). Majority of these children may however have had prior exposure to nevirapine. Children with history of nevirapine exposure who are initiated on an NNRTI based regimens are at increased risk having a pretreatment nevirapine resistant virus and hence may not respond to treatment (Boender et al., 2016; WHO, 2019). Children depend on adults for drug administration. Adherence challenges in children and low genetic barrier for NNRTI drugs increases the risk of virological failure and potentially treatment failure. Of the 55,867 CLHIV on ART by December 2022, 11% were on second line ART (MOH, 2022b). Delayed diagnosis of treatment failure may lead to disease progression and death.

WHO recommends repeat VL testing after 3 months of enhanced adherence counseling for all children with virological failure prior to treatment regimen modification (WHO, 2013). Data on proportion of children who access a timely VL test and proportion of children who achieve viral suppression by regimen is not

readily available. Similarly, data on repeat VL coverage for children with virological failure including appropriate management of those with treatment failure also remains scarce.

1.3 Justification of the study

Children on NNRTI based regimen have an increased risk of virological failure based on maternal or infant previous exposure to nevirapine, low genetic barrier of the drugs and adherence challenges in children. Kenya adopted WHO guidelines on routine VL testing for all individuals on ART and access to VL testing has been scaled up from three to ten regional testing laboratories. Despite this, logistics of sample collection from children, transport to the testing laboratories as well as return of results to facilities has not been without challenges. Data on proportion of children on ART who have documented VL test results is not readily available.

Routine laboratory data (2020) from Kenya HIV care and treatment program show suboptimal pediatric viral suppression rate defined as VL <1000 copies/ml, at 68%, 85% and 88% for age < 2 years, 2 – 9 years and 10 – 14 years respectively compared to that of adults (25 years+) at 95% (MOH, 2014b). Data of proportion of children who achieve viral suppression by regimen remain scares. Results from this study would contribute towards recommendations for transition from first line HIV treatment regimens for children from NNRTI based regimens to more durable regimens.

National guidelines recommend repeat VL testing for all children diagnosed to have virological failure and regimen modification for those with persistent high VL despite enhance adherence support. Data on proportion of children with documented repeat VL and proportion that get a regimen switch following persistent high VL is also not readily available.

Data from central electronic medical records was abstracted using a data abstraction guide to determine the proportion of eligible children with documented VL test result and proportion that achieved viral suppression. A review was also done to check proportion of those persistent high VL who had regimen modification as per national

guidelines. The study also sought to document reason for missing repeat VL testing for this with persistent viraemia. Results from this study would contribute towards improved repeat VL coverage for children diagnosed with virological failure as well as ensure the repeat VL results are available at user points in a timely manner to inform decision making processes.

1.4 Study literatives

1.4.1 Broad objective

To determine VL testing outcomes and reasons for missed opportunities for children on NNRTI-based first line ART regimen at selected health facilities in western Kenya

1.4.2 Specific objectives

1. To determine the proportion of HIV infected children initiated on Nevirapine or Efavirenz based first line ART between 1st January 2010 and 31st December 2014 at selected health facilities in western Kenya who had documented VL results.
2. To determine the proportion of HIV infected children initiated on Nevirapine or Efavirenz based first line ART between 1st January 2010 and 31st December 2014 at selected health facilities in western Kenya who achieved viral suppression.
3. To explore reasons for missing documentation of repeat VL tests for children with virological failure
4. To document proportion of children with confirmed treatment failure who had regimen switch to second line ART.

1.5 Research questions

1. What proportion of HIV infected children initiated on NNRTI based first line ART regimen between 1st January 2010 and 31st December 2014, on treatment for a minimum of 12 months and with documented VL results achieved viral suppression?

2. What were the reasons for missed documentation of repeat VL test results for children with virological failure?
3. What proportion of children with confirmed treatment failure had a regimen switch to second line ART?

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Of the estimated 1.7 million children under 15 years of age living with HIV, 88 per cent live in sub-Saharan Africa. Commendable progress has been made to increase pediatric HIV treatment coverage. In 2021, 878,000 (52%) children living with HIV were on antiretroviral treatment up from 410,000 in 2010. Coverage is however not uniform and varies by region (UNAIDS, 2021). According to Kenya national AIDS control council, the number of children living with HIV on antiretroviral treatment increased from 36,096 in 2010 to 86,325 by 2018 (MOH, 2018). VL monitoring remains the gold standard of measurement of treatment response. In 2013, WHO recommended VL testing as the preferred test to monitor patients on ART (WHO, 2013). In 2016, WHO further identified children and infants as a priority group for preferential routine VL monitoring (WHO, 2016). This was informed by several factors. The number of antiretroviral drugs for treating HIV positive children were limited and most of the available formulations were not palatable posing a challenge with regimen switches. Additionally, children depend on caregivers for administration of drugs and keeping clinic appointments. Indeed, caregiver changes have been noted to be a common cause of disruptions in drug adherence leading to virological failure (Cruz et al., 2014). Dose-adjustment is required as the child grows and failure to do so may result in under-dosing of one or more antiretroviral agents in a regimen. In addition, emotional and developmental issues particular to children can make daily medication administration difficult and pose a challenge to adherence and achievement of sustained viral suppression (Arpadi et al., 2017). VL monitoring is particularly important for those on NNRTI based regimens given their long plasma half-life and the fact that one-point mutation confers cross resistance to multiple drugs in this class of ARVs.

The objective of this study was to determine VL testing coverage and testing outcomes for children on NNRTI based first line treatment regimen as well as assess

the proportion that had a timely regimen switch following confirmation of treatment failure.

2.2 Theoretical Framework

Early antiretroviral therapy (ART) initiation in infants results in long-term viral suppression, maintenance of high CD4 T cells, and a slower progression to AIDS and mortality (Violari et al., 2008). Thus, the World Health Organization (WHO) guidelines recommend ART for all infants younger than 5 years of age regardless of clinical, immunologic, or virologic criteria. Previous exposure to nevirapine was a critical consideration in this guideline (WHO, 2010). Subsequent WHO guidelines however recommended protease inhibitor (PI)-based ART for children less than 3 years of age, regardless of prior non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure and Efavirenz based regimen for children older than 3 years (WHO, 2013). However, in many settings nevirapine (NVP) continues to be used in NVP-unexposed infants because of its lower cost and drug availability at clinic sites.

In adults without prior NVP exposure, NVP and PI regimens in initial ART result in comparable virologic suppression. A multisite randomized clinical trial (RCT) among adult women without prior NVP exposure in seven African countries (OCTANE) demonstrated equivalent virologic efficacy in those treated with NVP-based ART versus PI-based ART. However, women in the NVP – based ART arm had higher rates of treatment discontinuation and drug resistance (Lockman et al., 2012). There are conflicting data regarding NVP- based vs. PI – based ART among NVP-unexposed children. In a multisite pediatric RCT (P1060) comparing NVP- versus PI-based ART in NVP-unexposed children, there were more primary events (virologic failure or treatment discontinuation by 24 weeks) in the NVP- based ART than PI – based ART arm (40.8% versus 19.3%) In this study, among a subset of 32 children who received NVP- based ART, 66% had NVP resistance at the time of virologic failure and none of the children who failed PI-based ART developed resistance to PIs (Violari et al., 2012). In contrast, the PENPACT-1 trial noted no difference in virologic outcomes in NVP-unexposed children treated with NNRTI- or PI- based ART regimens (Team et al., 2011).

Infants have higher pre-ART HIV RNA VL levels than adults and may experience suboptimal drug levels, which could account for the higher rate of virologic failure, mortality, and drug resistance seen in infants compared with adults. Furthermore, younger infants may have slower viral decay rates than older children, and this could explain differences between the P1060 RCT and the PENPACT-1 trial, the latter of which had a broader age range and higher median age. These previous studies have examined NVP resistance at the time of virologic failure.

2.3 Conceptual framework

The conceptual framework was guided by literature review. Determinants of viral suppression included sociodemographic characteristics, facilitators, and barriers of viral suppression.

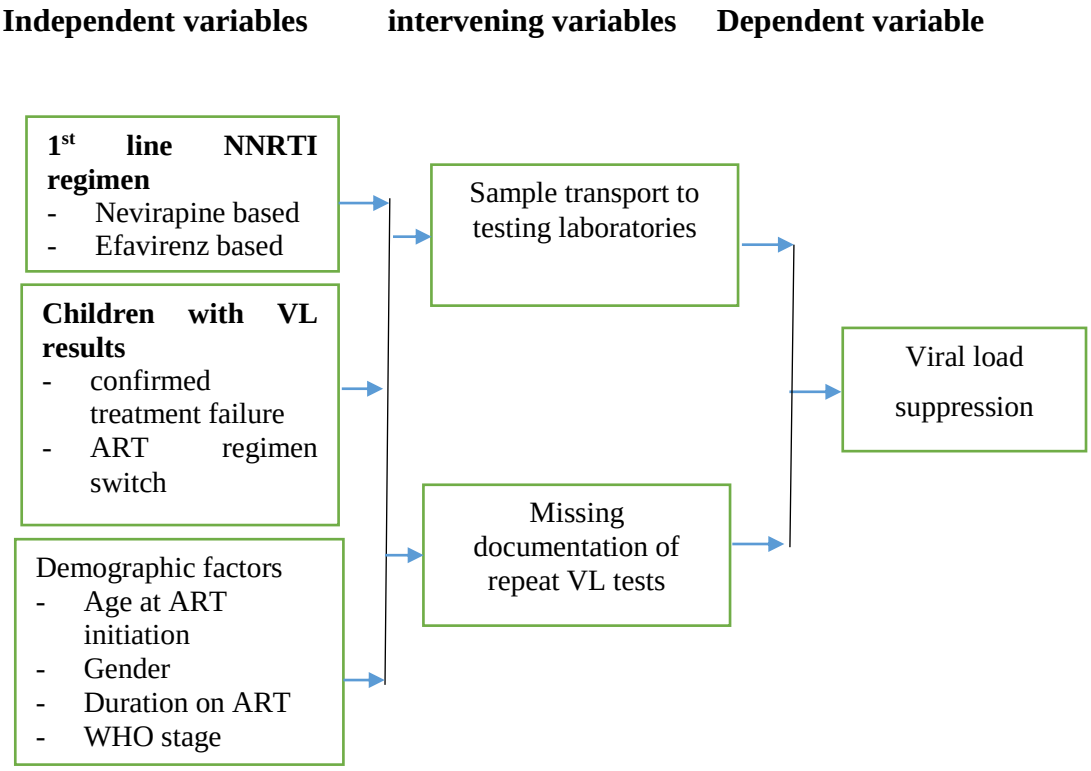

Figure 2.1: Conceptual framework

2.4. Empirical review

2.4.1 Access to VL testing.

VL monitoring is critical for the measurement of response to treatment and is a crucial contributor towards the third 95 of UNAIDS 95-95-95 targets, defined as 95% of people living with HIV know their status, 95% of all diagnosed PLHIV on anti-retroviral treatment, and 95% of those on treatment virally suppressed. VL testing serves as an important tool to implement patient-centered differentiated care so that patients who are virally suppressed may be seen less often by the health care providers, while those not suppressed are targeted for enhanced adherence counselling and potential regimen switch. Where VL testing is not routinely available, WHO recommends use of CD4 cell count and clinical monitoring with targeted VL testing to confirm treatment failure (WHO, 2013). Although routine VL monitoring has been shown to improve earlier detection of treatment failure, timely regimen switches, better adherence to treatment and survival, data on VL testing coverage for children remains scarce. A review of scale-up of HIV VL testing during 2013–2018 in eight sub-Saharan African countries documented successful efforts to increase access to VL monitoring for patients receiving ART. During this period, the proportion of ART patients who had at least one VL test result increased from 3.8% to 74.1% in Côte d'Ivoire, 8.4% to 85.8% in Kenya, 4.9% to 51.9% in Lesotho, 6% to 51.3% in Malawi, 4.9% to 89% in Uganda and 60.6% to 99.9% in Namibia (Lecher et al., 2021). A systematic review that included 34 studies from low- and middle-income countries found marked variations in initial VL monitoring coverage across countries/study settings. VL testing coverage for children was however found to be slightly higher than that of adults at 72% vs 67% (Pham et al., 2022). Elsewhere in Malawi, the proportion of clients with documented VL results increased from 27% to 71% following implementation of quality improvement initiative. In this study children had the lowest VL coverage throughout the study (Kamwendo et al., 2022). In Uganda, 33% of clients who had been on treatment for at least 6 months did not have a documented VL result. Short duration on ART and receipt of treatment in a health center among others were associated with non-uptake of VL testing (Nakalega et al., 2020).

In Kenya, routine VL monitoring was rolled out in 2014 following adoption of WHO guidelines. VL testing intervals is currently at 6 months, 12 months, and every 12 months thereafter if an individual is suppressed. Although the total number of tests done has increased over time, data on VL testing coverage by regimen for children remains scares. One objective of this study was to determine the VL testing coverage for HIV infected children initiated on either nevirapine or efavirenz based regimen who had been on treatment for at least 12 months.

2.4.2 Viral suppression in children

Use of antiretroviral drugs has been shown to reduce HIV associated morbidity and mortality through suppression of viral replication, restoration, and preservation of immunological function. UNAIDS estimated that 1.7 million children under age 15 were living with HIV in 2021 and whereas the number of children receiving antiretroviral treatment increased from 441,000 in 2010 to 878,000 in 2021, treatment coverage for children remains suboptimal at 52% (UNAIDS, 2021). In November 2018, UNAIDS released the 95 – 95 – 95 ambitious targets to end the HIV epidemic globally by 2030. In Kenya, of the estimated 83,000 children living with HIV in 2021, 58.9% were on treatment (UNAIDS, 2021). Among those on treatment, 89% were virally suppressed an improvement from 62% in 2014 (MOH, 2014b). Although achievement of viral suppression is a key determinant of survival of HIV infected children on treatment, the proportion of children who achieve viral suppression remains suboptimal compared to adults. Lower rates of viral suppression may be related to the fact that children have other multiple factors such as dependence on caregivers, under dosing of medications, lack of disclosure, stigma, frequent change of caregivers, and forgetfulness among others (Nyogea et al., 2015). In Zimbabwe, the proportion of children suppressed at baseline in longitudinal follow up of children and adolescents on ART in eight community outreach sites was reported at 68% (Mapangisana et al., 2021). In south Africa, the proportion of children reported as virally suppressed in the international epidemiology Databases to Evaluate AIDS (IeDEA) collaboration study was found to be suboptimal at 72.4% compared to adults at 85.7% (Pillay et al., 2020).

In Kenya, a study to determine factors affecting adherence to antiretroviral therapy among children and adolescents living with HIV in Homabay- Kenya found overall viral suppression at 74.2%. Predictors of viral suppression included 3- month clinic appointment return rates and enhanced adherence counseling (Tanyi et al., 2021). Another study whose objective was to understand viral suppression in children with HIV in eastern and southern Africa reviewed laboratory information management systems records of 66,158, 71,941 and 121,370 of children from Malawi, Uganda and Zimbabwe for the period 2016, 2017 and 2018. It was noted that viral suppression remained low across the three years ranging from 69% in 2016, 64% in 2017 and 63% in 2018. Lower viral suppression rates were noted for children with history of PMTCT exposure (57%), those on nevirapine based regimen (64%), history of poor adherence (59%) and age 1 – 4 years (53%) (UNICEF, 2021). Similarly, in Kenya, children on alternative regimens were 10 times more likely to achieve viral suppression compared to those on NNRTI based regimen (Kadima et al., 2019).

Pretreatment drug resistance following use of NNRTI drugs for PMTCT poses yet another challenge among HIV infected children initiated on NNRTI based first line ART. Although NNRTI drugs are well tolerated, they have a low genetic barrier and single mutation in the NNRTI binding pocket of the enzyme confers high level resistance to one or more of these drugs. In 21 of 30 surveys reported to WHO, pretreatment HIV drug resistance to nevirapine or efavirenz in populations initiating first-line ART reached levels above 10%. The surveys found that Pretreatment HIV drug resistance to the NNRTI class of drugs was up to 3 times more common in people with previous exposure to antiretroviral drugs. Nearly half of infants born to mothers infected with HIV had HIV drug resistance to one or more NNRTIs (WHO, 2019). In Uganda, pretreatment NNRTI drug resistance mutations were observed in 7.5% of HIV infected children and HIV drug resistance (HIVDR) occurred post ART initiation in 35.7% of children who had received PMTCT related interventions (Kityo et al., 2016). In Zambia, studies on relationships in antiretroviral (ARV) resistance between HIV-1 infected mother-infant found the prevalence of NNRTI drug resistant mutations to be disproportionately higher in infants compared to their mothers at 67% vs 23% (Bennett et al., 2020). In Kenya, the Kisumu Breastfeeding

study found that of the 287 mothers initiated on triple ARV regimen from 34 weeks' gestation till 6 months post-delivery where all mothers were allowed to breastfeed, 14 (4.9%) infants were confirmed HIV infected by 6 months and of these 6 (43%) were found to have mutations that conferred resistance to nevirapine. The study concluded that there was evidence of infant drug resistance following exposure to maternal ART through breast milk (Thomas et al., 2011). Likewise, in Kenya, among NVP unexposed infants initiated on NVP based regimen, cumulative probability of developing NVP resistance at 3 months was 5.9% and at 6 months was 43.5%. Among these infants, development of NVP resistance was frequent and was associated with virological failure during the first year of ART (Chohan et al., 2015). WHO has continued to raise concern about high levels of pretreatment drug resistance to NNRTI drugs and recommend the need to fast-track transition to optimal regimens specifically dolutegravir-based first-line regimens.

In Kenya, routine laboratory data from HIV care and treatment program show that whereas the proportion of adults who achieved viral suppression increased from 75% to 88% between 2015 and 2019, that of children was suboptimal from 63% to 77% during the same period (MOH, 2014b). Guidelines for antiretroviral treatment in Kenya recommended use of nevirapine based regimen for all HIV positive children aged 3 years or less than 10 kg and efavirenz based regimens for all children aged more than 3 years (MOH, 2011). Ministry of health further revised the guidelines based on revised WHO guidelines in 2014 that recommended switch to lopinavir based regime for children aged less than 3 years (MOH, 2014a). Based on national guidelines recommendations, majority of children were initiated on NNRTI based regimens. Regimen specific data on proportion of children who achieve viral suppression remains scarce. This study sought to document proportion of children on nevirapine of Efavirenz based regimen who achieved viral suppression.

2.4.3 Repeat viral load testing for suspected treatment failure.

WHO defines treatment failure as persistently detectable VL exceeding 1000 copies/mL, that is two consecutive VL measurements within a 3-month interval with

adherence support between measurements after at least 6 months on ART (MOH, 2016)

The guideline recommends regimen modification for all persons living with HIV diagnosed with treatment failure. Data on proportion of individuals including children who access repeat VL testing and proportion that achieve viral suppression after enhanced adherence remains scanty. In Uganda, 77% of 449 children with VL above 1000 copies/ml completed the recommended three enhanced adherence sessions but only 69% had repeat VL test results. Of those with repeat VL results, only 25% achieved viral re suppression contrary to WHO projection of more than 70% (Nasuuna et al., 2018). In Zimbabwe, of 489 children with high VL >1000 copies/ml enrolled for enhance adherence counseling, 69% had repeat VL test result of whom only 31% achieved viral suppression. In this study, children with initial VL >5000 copies/ml were less likely to suppress (Bvochora et al., 2019). In Kenya, of the unsuppressed adolescents, only 8% had repeat VL test results at 3 months and 29% at 6 months. The median time between the first and the repeat VL was 6 months (Mugo et al., 2020).

In Swaziland, out of 12,063 patients who underwent routine VL monitoring, 1,941 (16%) had detectable VL. In this study, children and adolescents were 2.6 times and 3.2 times more likely to have detectable VL compared to adults. Additional predictors included last CD4 count of >350 cells/ml, WHO stage 3 or 4 disease and patients on ART for longer. In this study, it was noted that 54% (450) of those retested after enhance adherence counseling achieved viral re suppression. Children and adolescents were less likely to re suppress as were those with last CD4 count of <350 cells/ml (Jobanputra et al., 2015). Current Information on proportion of children on NNRTI based regimen diagnosed with suspected treatment failure who get a timely repeat VL is not readily available. The objective of this study was to address this research gap as well as document time to repeat VL test for this population.

2.4.5 Regimen switch to second line ART after confirmed first line treatment failure.

With increasing access to antiretroviral treatment, increasing numbers of children are likely to experience treatment failure and require second line regimens as defined by WHO. Approximately one in five children switch to second line ART by 5 years of ART with two thirds being treatment failure related. The proportion of children switched to second line ART varies by region. In Malawi 88% of those with confirmed treatment failure had a regimen switch within 90 days. In this study, use of nevirapine was an independent predictor of virological failure (Tweya et al., 2020). In Lesotho, only 47% of those unsuppressed, suppressed on repeat VL testing and of those who qualified for regimen switch to second line ART, only 45% were ever switched (Muhairwe et al., 2022) . A systematic review of 58 studies reported outcomes of 45,720 viraemic patients mostly from Africa and among patients on first line treatment. Of those with virological failure, only 53.3% were switched to a different regimen. The proportion resuppressing was lower among children at 31.3% compared to adults at 50.4% (Ford et al., 2019).

Factors associated with switch to second line included advance HIV disease, older age, use of NNRTI based regimens and use of routine VL testing for treatment monitoring (Collaborative Initiative for Paediatric & Research Global Cohort, 2019). Current information on proportion of children confirmed to have treatment failure who undergo regimen switch and time to switching is not readily available.

This study aimed to provide information on proportion of children on NNRTI based regimen with confirmed treatment failure who had a regimen switch and median time to effecting regimen switch to second line ART.

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Introduction

This chapter deals with methodology including study site, research design, target population, and sample size. Also captured in this chapter are data collection instruments and procedure, validity, and reliability as well as data analysis methods.

3.2 Study sites

The study was carried out in 7 counties in Western Kenya regions. The counties included Homabay, Migori, Kisumu, Siaya, Busia, Bungoma and Kakamega.

Table 3.1: Number of children infected with HIV in counties under study.

excel	**Total number of people <49 yrs. living with HIV**	**Number children living with HIV**	**Children contribution to PLHIV**
Homabay	138,921	10,722	7.7%
Siaya	123,107	9,501	7.7%
Kisumu	122,301	9,439	7.7%
Migori	85,765	6,619	7.7%
Kakamega	52,976	4,224	8.0%
Busia	38,608	3,078	8.0%
Kisii	34,950	2,923	8.4%
Bungoma	30,044	2,396	8.0%
Total	626,672	48,902	7.8%

Source National AIDS control council 2018

Table 3.1 shows estimated number and proportion of children living with HIV by county

The study was done in the context of program implementation where data collection was done under an approved non research determination. Standard data collection tools were developed centrally where the investigator was a technical lead for the paediatric data collection tools. These were then developed into modules that were programmed into electronic medical records for use at site level. The study was done at 46 faith affiliated sites that had implemented use of the electronic medical records for data management. Patient management across all sites followed standard Ministry of Health (MOH) guidelines. Routine data quality assurance was done to validate data entry and monthly reports submitted to MOH. The sites have a facility level data backup system that is updated daily and a central data backup system for all facilities under this program that is updated quarterly.

3.3 Study design

This was a retrospective cohort study of children initiated on NNRTI based first line ART between 1st January 2010 to 31st December 2014 at faith affiliated health facilities in Western Kenya. This design enabled the researcher to gain understanding of the accurate portrayal and/or account of the characteristics of the study participants.

3.4 Study population

The study was done in two stages. The first stage involved HIV infected children accessing HIV treatment services at 46 faith affiliated health facilities in Western Kenya. Patients at these sites receive a standard package of care that include assessment for ART eligibility, ART initiation, adherence support and evaluation for treatment failure among others. Routine adherence assessment is done that include self-reports, use of appointment diaries, use of pharmacy records and pill count to assess missed ARV doses. Patients are managed according to national guidelines and access VL testing through blood sample transport to central testing laboratories through a sample transport network.

The second stage involved review of all children who had VL >1000 copies/ml who were active on treatment but missing a documented repeat VL in the client records. A

total 136 children had samples taken for repeat VL testing but only 112 were expected to have documented results in client records at the time of the study and were included in the analysis. Date of analysis was extended by 9 months to allow for return of VL results to facilities. A total of 4,250 children formed the target population of the study however, 1,132 children exited from care due to death, transfer and lost to follow up hence, the target population for the study was 3,118.

3.4.1 Assumptions

1. All children initiated on ART for more than 12 months should have had a documented VL as per national guidelines.
2. Children newly initiation treatment should have a documented VL results at month 3 after ART initiation.
3. All children with VL >1000copies/ml should have a documented repeat VL test after 3 months of enhanced adherence counseling.

3.4.2 Sample size

The study included all the children who met the inclusion criteria. This constituted 8.7% of all children living with HIV in the 7 counties of study as shown in table 3.2.

Table 3.2: Number of children on ART included in the study by county.

	Total	**% contribution**
Homabay	1,712	40.3%
Migori	676	15.9%
Kisumu	607	14.3%
Kakamega	503	11.8%
Siaya	236	5.6%
Bungoma	235	5.5%
Kisii	172	4.0%
Busia	109	2.6%
Total	4,250	100%

3.4.3 Inclusion criteria

This was done in two stages. The first stage included all treatment naïve HIV infected children aged between 6 weeks and 14 years and had attended their clinic appointments within the previous 90 days (Active on treatment). The children were initiated on either Nevirapine or Efavirenz based first line ART regimen between 1st January 2010 and 31st December 2014.

The second stage included individual charts review. This included children who were active on treatment, but missing a documented repeat VL test result following a previous high VL of >1000 copies/ml.

3.4.4 Exclusion criteria

The first phase excluded children aged less than 6 weeks or more than 14 years, those on non NNRTI based first line regimen and those on second line ART regimens.

The second phase, individual chart review excluded those with documented repeat VL test result following an initial VL>1000c/ml.

3.4.5 Variables

Dependent variables

Viral load testing outcome

3.4.6 Independent variables

Gender

Age

HIV care status

Duration on ART

Referral source

WHO clinical staging

Baseline CD4 count

Time of ART initiation

Reasons for missing documentation of repeat VL tests for children with virological failure.

Proportion of children with confirmed treatment failure who had regimen switch to second line ART.

3.5 Sampling framework

Sampling was done in two stages. In the first stage, a total of 4,250 participants made up the sample for the study. The sample was drawn from the 8 counties under study with a total population of 48,902 HIV infected children as shown on table 3.2. The target population for the study was 3,118 children who had attended their last clinic days within 90 days of their appointment date. This was used for analysis of VL testing cascade under objective 1 and 3. The second stage involved review of 112 individual chart review of children expected to have documented VL results which were missing in client records

A total of 1,107 government and faith affiliated health facilities that offered HIV care and treatment in the Western Kenya regions that received support from different organizations were reviewed for consideration. All government affiliated health facilities used manual records for client management and consistency in documentation could not be guaranteed due to frequent staff rotations. Record keeping also at government affiliated health facilities had gaps in retrieval of client records and multiple facilities had duplication of client records. Faith affiliated sites on the other hand had implemented use electronic medical records and data collection tools were programmed in the electronic medical records modules. The system could only save data only when mandatory fields have been filled.

Site selection was hence done using purposive sampling based on the knowledge of the program. All faith affiliated facilities that received technical support from KCCB - KARP program during the study period were included. The program supported 46 (4%) of facilities that offered comprehensive HIV care and treatment in the former Nyanza and Western provinces and were distributed across all the current administrative counties. In total, the facilities contributed 14% of all children on antiretroviral treatment in Western Kenya

3.6 Data management

3.6.1 Data collection tools

In the first stage, a data abstraction guide with variables of interest was used to retrieve information from electronic medical records. In the second stage a chart abstraction guide with information of interest was used to abstract data from individual record of clients with missing repeat VL results who had a previous VL test result of >1000c/ml.

3.6.2 Data collection

Data was retrieved from the electronic medical records database using a data abstraction guide after defining relevant variables. Information in the abstraction guide included; date of birth, date of enrolment into HIV care, referral source, baseline WHO clinical stage, baseline CD4 count, date the patient was started on ART, current regimen, initial VL result (VL1), date of VL1, second VL result (VL2), date of VL2, date the patient was started on second line ART, current status (Active in care or exited), and date of exit (transfer out, lost to follow up or death). All children who attended at least one clinic consultation within the previous 90 days were categorized as active while those who missed their clinic appointment for the immediate period equal to or more than 90 days were categorized as lost to follow up. Those with documented information of transfer of services to another facility were categorized as transfer out. It was expected that since the launch of revised guidelines that introduced routine VL testing in June 2014, all children included in this analysis were eligible for VL testing and should have received results by the

time of data abstraction. Children with documented VL results were categorized as either having achieved viral suppression or not achieved viral suppression as defined by cut off <1000 copies/ml by the Kenya national guidelines. Information obtained was transferred to Microsoft excel 2010 after removing individual patient identifiers in preparation for data analysis. Data was then stored in a password protected computer and in an external hard drive which was encrypted, and password protected for back up purposes. Access to data was limited to few relevant staffs only.

3.6.3 Patients with missing repeat viral load results

WHO guidelines recommend a repeat VL testing for all patients with VL results of more than 1000 copies/ml three months after enhanced adherence. Children who were active on treatment but missing VL2 results after VL1 of >1000 copies/ml per site were identified. The investigator worked in collaboration with KCCB – KARP program staff to institute a program level quality improvement initiative to ensure access to repeat VL testing and appropriate management and to better understand reasons for missing repeat VL results. Individual chart reviews of patients with undocumented VL2 were done using a structured chart abstraction guide with the following questions.

1. VL test done but results not documented. If VL test results were available, the date of VL test result was noted.
2. Patient was transferred out/LTFU/Dead. For each affected chart, the date of exit from care was to be noted.
3. Patient had ongoing adherence challenges and VL sample had not been collected.
4. VL sample taken but no results. For each affected chart, the date of sample collection was to be noted.
5. No adherence challenges, viral load sample yet to be taken from the patient.

Support staff were taken through the tool to ensure they understood inclusion criteria, all the required variables and data sources. The tool underwent pretesting to be sure that the questions in the chart abstraction guide could be easily understood and to be sure that all the elements required were available.

After obtaining the relevant information, the list of all children with missing repeat VL results was shared with individual facilities so that identified gaps could be addressed including flagging of files for sample collection during the patient's next clinic appointment.

3.7 Data analysis

Data cleaning was done to ensure only eligible children based on inclusion criteria were included in the analysis. Analysis was done using descriptive statistics. Analysis of the collected data was done using Stata Version 13.1, 1985 – 2013 Stata Corp LP, USA. Descriptive statistics were calculated to examine the distribution of demographic characteristics of the study population. Cox proportional hazard ratio was used explore the relationship between viral suppression and other variables while controlling for confounding factors.

3.8 Ethical considerations

KARP program had an approved non-research determination protocol that permitted analysis and sharing of routinely collected program data. The proposal for this study was also submitted to and approved by University of Nairobi - Kenyatta National Hospital ethics review committee (UON - KNH ERC). Permission to access patient records was granted by facility in charges and KCCB - KARP board of management. The patient's electronic medical records (EMR) databases are password protected and only accessible to a few authorized staffs with user rights. Data obtained from the databases was stripped off all individual patient identifiers before transfer to excel sheets for analysis.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1. Introduction

This chapter presents the result of the study based on information obtained from central medical records and individual chart review. The aim of the study was to determine access to VL testing, VL testing outcomes and reasons for missed opportunities for children on NNRTI-based first line ART regimen at selected health facilities in western Kenya. The study also sought to document proportion of children with confirmed treatment failure who had a regimen modification. Data was analyzed and reported using frequency tables, pie charts and bar graphs. This was followed by a brief interpretation and a discussion on research findings, Data analysis was based and guided by the study objectives.

4.2. Baseline characteristics

4.2.1 Distribution of data from the 46 health facilities

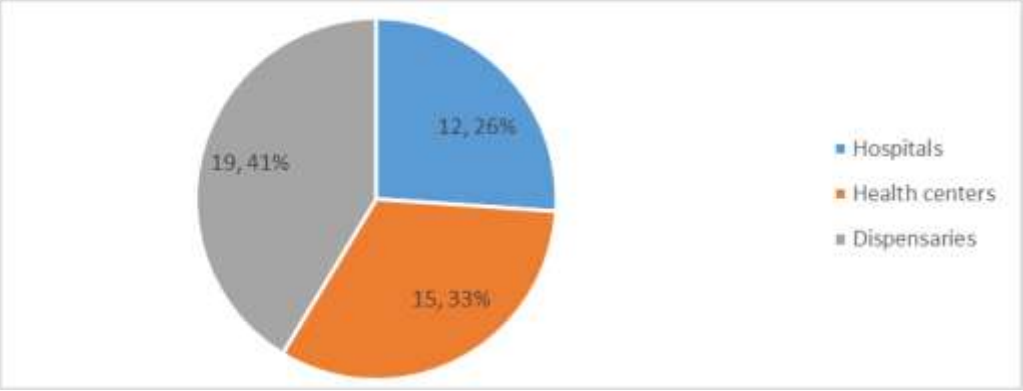

Figure 4.1: Distribution of facility type.

Figure 4.1 shows distribution health facilities. Data from 46 health facilities was obtained of which 12 (26.1%) were hospitals, 15 (32.6%) were health centers and 19 (41.3%) were dispensaries.

4.2.2 Preferred health facility to receive care.

In total, 8.7% of sites had more than 200 children, 32.6% had 100 – 200 children, 26.1% had 50 – 100 and 32.6% had less than 50 children on treatment. Of the 4,267 children who were ever initiated on treatment, 4,250 (99.5%) had complete records and met the inclusion criteria for analysis.

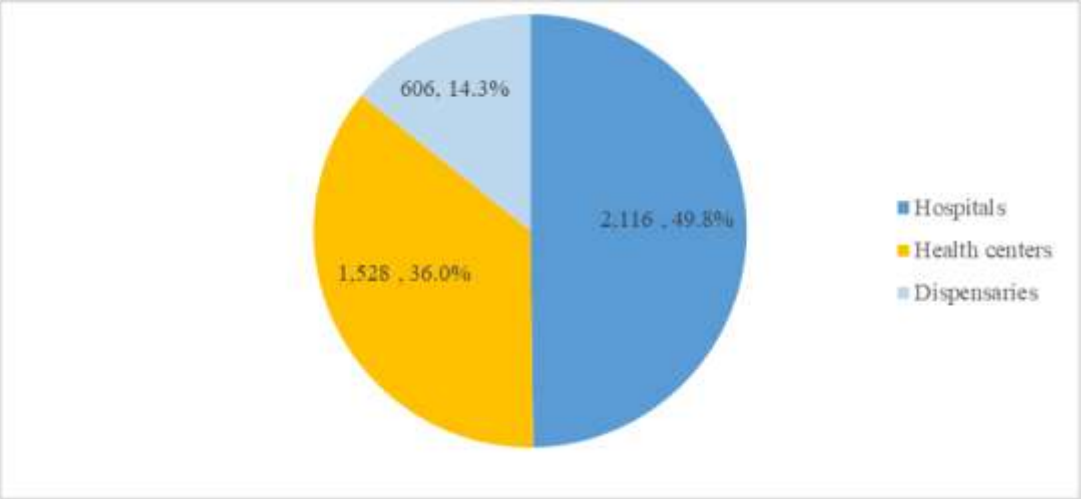

Figure 4.2: Preferred health facility of choice to receive care

Figure 4.2 shows distribution of children by facility type. In total, 49.8% of the children were receiving care in hospitals 36.0% were receiving care in health centers while 14.3% received care in dispensaries.

4.2.3 Age categories of those included in the analysis.

Of the 4250 children, 22.4%, 27.7%, 33.6% and 16.3% were aged less than 2 years old, 2 – 5 years, >5 – 10 years and more than 10 years respectively. Cumulatively, 51.3% were males. 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).

4.2.4 Referral source for HIV positive children

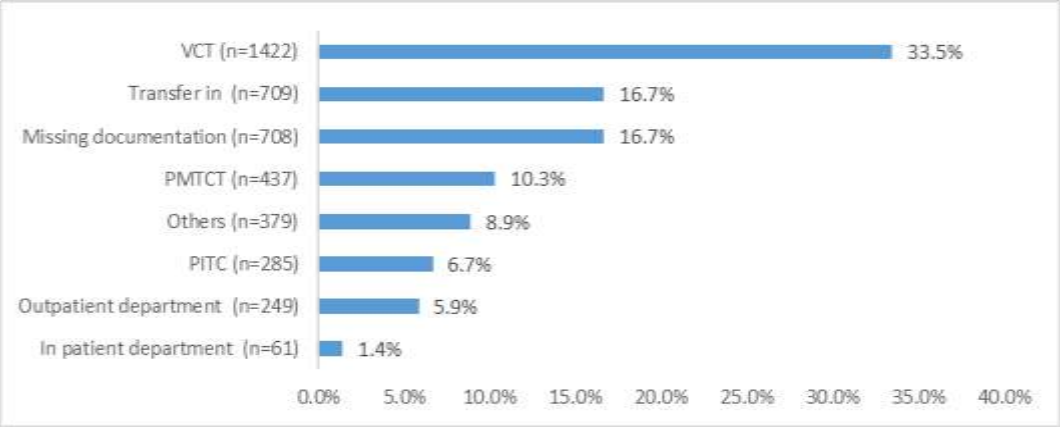

Figure 4.3: Referral source to HIV services for children included in the analysis

Figure 4.3 shows referral source of children enrolled for care at various health facilities. Approximately one third of the children had referral source as voluntary counseling and testing (VCT) while 10.3% were referred from maternal and child health clinics following failed PMTCT interventions.

4.2.5 WHO clinical staging by age category

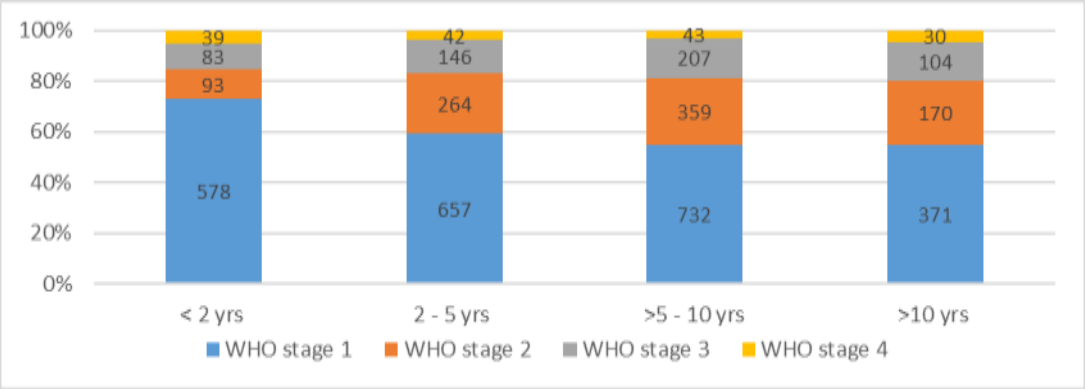

Figure 4.4: WHO clinical stage categorization by age category

Majority, 75.9% (3,224) of the children were categorized as early-stage HIV disease, (WHO clinical stage 1 or 2). Figure 4.4 shows categorization by WHO clinical staging by age category. Children aged < 2 years had a slightly higher proportion under WHO clinical stage 1 compared to other WHO clinical stages.

Table 4.1: Baseline characteristics of children included in the analysis.

Variable	Total (n=4,250)	Percent (%)
Facility type		
Hospital	2,116	49.8
Health centers	1,528	36.0
Dispensaries	606	14.2
Gender		
Male	2,068	48.7
Female	2,182	51.3
Age at enrolment		
< 2 years	953	22.4
2 – 5 years	1,179	27.7
>5 – 10 years	1,426	33.6
>10 years	692	16.3
Duration on ART		
Less than 24 months	1698	39.9%
>24 – 60 months	1771	41.7
More than 60 months	781	18.4
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 clinical Staging		
Stage 1 and 2	2338	55.0
Stage 2	886	20.8
Stage 3	540	12.7
Stage 4	154	3.6
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	1,557	36.6
Missing data	1,294	30.4

4.2.6 HIV care status

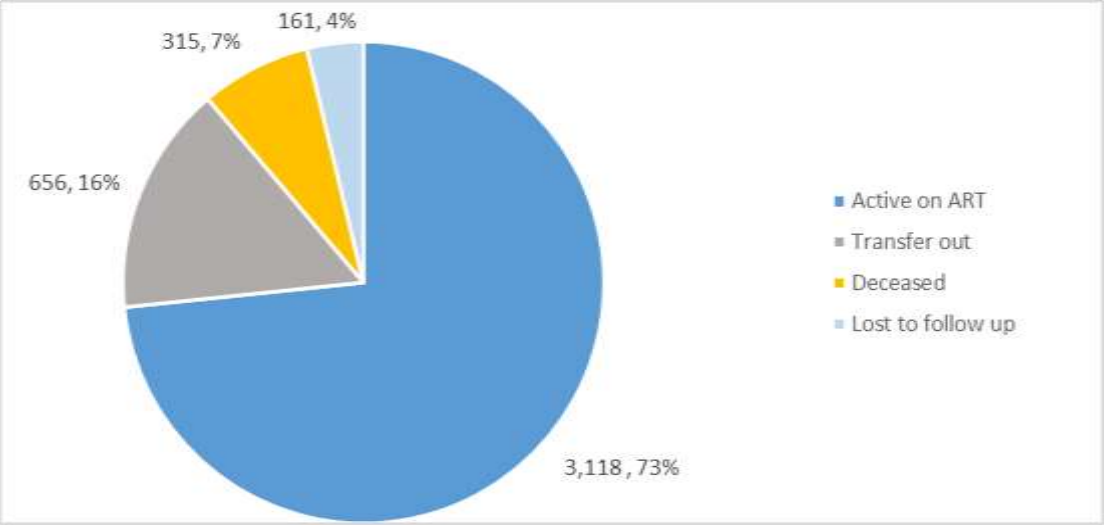

Figure 4.5: ART care status of children included in the analysis.

Figure 4.5 shows care status of children included in the analysis. Overall, out of the 4,250 children, 3,118 (73.4%) had attended their clinic appointment within the previous 90 days and were considered to be active on treatment. Cumulatively, 656 (15.4%) had transferred out of their primary health care facility, 315 (7.4%) were deceased and 161 (3.8%) were lost to follow up (LTFU).

Analysis of the 315 children reported as deceased found the median age at enrolment to be 36 months (IQR 11 – 87) while the median duration on ART was 5.4 months (IQR 1.1 – 17.5). Of the 288 (91.4%) with information on WHO clinical stage, 27.1% had advanced HIV disease (WHO clinical stage 3 or 4) at enrolment while of the 177 (56.2%) with documented baseline CD4 test results, 41.8% had CD4 <200 cells/mm^3.

4.2.7 Median time to event

Table 4.2: Medium time to event based on date of enrolment and ART initiation.

	Median (months)	Interquartile range
Enrolment to ART initiation	2.1	0.6 - 9.3
Enrolment to death	9.8	4.4 - 21.7
ART initiation to death	6.0	1.8 – 18.5
Enrolment to LTFU	14.0	8.0 - 30.0
ART initiation to LTFU	10.6	5.6 - 20.9
Enrolment to transfer out	18.2	8.0 - 30.0
ART initiation to transfer out	13.8	5.2 - 25.3

Table 4.2 shows median time to event based on date of enrolment into HIV care and date of initiation on ART. The median time from enrolment to ART initiation was 2.1 months (IQR 0.6 – 9.3). There was approximately 3-month delay in ART initiation for those reported to be deceased and a 4-month delay for those reported as lost to follow up.

Table 4.3: Median time from enrolment to exit by facility type.

	Hospitals Median (Interquartile range)	Health Centers and dispensaries Median (Interquartile range)
Transfer out	18.9 (9.3 – 34.9)	18.1 (9.2 – 31.3)
Deceased	10 (4.9 – 27.1)	9 (3.6 – 20.0)
Loss to follow up	18.2 (9.7 – 45.4)	11.6 (7.4 – 20.8)

Table 4.3 shows median time from enrolment to exit based on facility type.

Whereas the median time from enrolment to transfer out and death was similar for the two levels of care, the median time to LTFU for the hospitals was slightly higher at 18.2 months compared to primary health facilities at 11.6 months.

4.3 HIV infected children with documented VL test results

4.3.1 Access to VL testing for eligible children on ART.

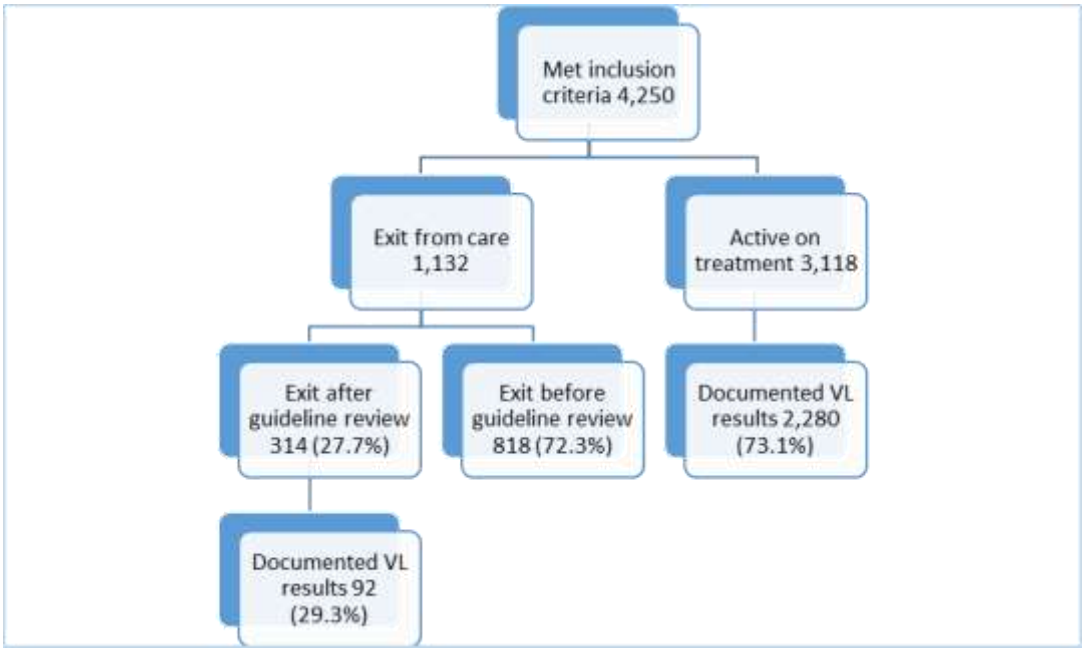

Figure 4.6: Proportion of children with documented VL results based on eligibility and care status

Overall, of the 3,118 children who were active on treatment by June 2016, 73.1% had documented VL results. It was also noted that of the 1,132 children who had exited from care, 314 (27.7%) should have had a VL test result given that they exited after introduction of routine VL testing following guideline review. Of the 314 children, only 92 (29.3%) had a documented VL result. Cumulatively therefore, of the 3,432 (3,118 plus 314) children eligible for viral load test but, 2,372 (69.1%) (2280 plus 92) had documented VL results as shown in figure 4.5.

4.3.2 Access to VL testing by facility type

Table 4.4: Proportion of children accessing VL testing by facility type

	Total active (n=3118)	With VL results
Hospital	1,595	1,200 (75.2%)
Health centers	1,060	786 (74.2%)
Dispensaries	463	294 (63.5%)

Table 4.4 shows access to VL testing by facility type. Although all facilities included in this analysis had access to VL testing through a sample transportation network, the proportion of children receiving care at hospitals and health centers who had a documented VL test results were slightly higher at 75.2% and 74.2% respectively compared to dispensaries at 63.5%.

4.3.3 Proportion of children accessing VL tests by gender

Table 45: Proportion of children with documented VL results based on gender

Variable	Total active (n=3118)	With VL results (n=2280)	Odds ratio OR (95% CI)	Adjusted Odds
Female	1,632	1,176 (72.1%)	Ref	Ref
Male	1,486	1,104 (74.3%)	1.12 (0.96, 1.31)	

The proportion of children with VL results based on gender was similar at 72.1% (n=1632) for females and 74.3% (n=1486) for males.

4.3.4 Proportion of children accessing VL test by age

Table 4.6: Proportion of children with documented VL results by age category

Variable	Total active (n=3118)	With VL results (n=2280)	Odds ratio	Adjusted Odds
< 2 years	613	458 (74.71%)	Ref	Ref
2 – 5 years	846	614 (72.58%)	0.90 (0.71, 1.13)	
>5 – 10 years	1161	841 (72.44%)	0.89 (0.71, 1.11)	
>10 years	498	367 (73.69%)	0.95 (0.72, 1.24)	

Figure 4.6 shows proportion of children with documented VL results by age category. The proportion of children with documented VL results was also similar across age categories at 74.7% for age < 2 years, 72.6% for age 2 – 5 years, 72.4% for age >5 – 10 years and 73.7% for age > 10 years.

4.3.5 Proportion of children accessing VL test by referral source

Table 4.7: Access to VL testing based on referral source

Variable	Total active (n=3118)	With VL results (n=2280)	Odds ratio	Adjusted Odds
PITC	244	174 (71.3%)	Ref	Ref
VCT	1020	789 (77.4%)	1.37 (1.01, 1.88)	0.94 (0.67, 1.31)
Transfer in	522	350 (67.1%)	0.82 (0.59, 1.14)	0.57 (0.40, 0.81)
PMTCT	288	215 (74.6%)	1.18 (0.81, 1.74)	0.75 (0.50, 1.13)
Others	267	217 (81.3)	1.75 (1.15, 2.64)	1.36 (0.89, 2.09)
Outpatient department	204	153 (75.0%)	1.21 (0.79, 1.84)	0.99 (0.64, 1.53)
In patient department	44	34 (77.27%)	1.37 (0.64, 2.92)	0.91 (0.42, 1.98)
Missing documentation	529	348 (65.78%)		

Table 4.7 shows proportion of children with documented VL results based on referral source. A higher proportion of children referred from VCT and other HIV testing modalities had documented VL results compared with those referred from PITC. The difference was not statistically significant.

4.3.6 Proportion of children accessing VL testing by duration on ART

Table 4.8: Proportion of children with VL results based on duration on ART

Variable	Total active (n=3118)	With VL results (n=2280)	Odds ratio	Adjusted Odds
<24 months	807	486 (60.2%)	Ref	Ref
>24 – 60 months	1537	1175 (76.5%)	2.14 (1.78, 2.58)	1.69 (1.17, 2.45)
> 60 months	774	619 (79.8%)	2.64 (2.11, 3.30)	1.82 (1.23, 2.68)

Figure 4.8 shows proportion of children with documented VL results based on duration on ART. The proportion of children who had been on ART for less than 24 months who had documented VL results was significantly lower compared to those who had been on ART for more than 24 months. The odds of having documented VL results was 1.7 times higher for those on ART for 24 – 60 months (aOR 1.69, 95% CI 1.17 – 2.45) and 1.8 times higher for those on ART for > 60 months compared to those on ART for < 24 months (aOR 1.82, 95% CI 1.23 – 2.68).

4.3.7 Proportion of children accessing VL testing VL tests by WHO stage

Table 4.9: Proportion of children with VL results based on WHO clinical staging

Variable	Total active (n=3118)	With VL results (n=2280)	Odds ratio	Adjusted Odds
WHO Staging				
WHO Stage 1	1713	1253 (73.2%)	Ref	Ref
WHO Stage 2	665	470 (70.7%)		
WHO Stage 3	398	294 (73.9%)	1.18 (0.94, 1.48)	
WHO Stage 4	90	75 (83.3%)		
Missing data	252	188 (74.6%)		

Cumulatively, 72.5% of those in early-stage HIV disease (WHO stage 1 and 2) and 75.6% of those with late-stage HIV disease (WHO stage 3 and 4) had documented VL results. The difference was not statistically significant.

4.3.8 Proportion of children accessing VL tests by baseline CD4 count

Table 4.10: Proportion of children with VL results by on baseline CD4 count.

Variable	Total active (n=3118)	With VL results (n=2280)	Odds ratio	Adjusted Odds
< 350 cells/mm3	660	511 (77.4%)	Ref	Ref
350 – 500 cells/mm3	355	277 (78.0%)	1.04 (0.76, 1.41)	
> 500 Cells/mm3	996	746 (74.9%)	0.87 (0.69, 1.10)	
Missing data	1107	746 (67.4%)		

Likewise, the proportion children with VL results based on CD4 count was 77.4%, 78.0% and 74.9% for those with CD4 <350 cells/ml, CD4 350 – 500 cells/ml and CD4 >500 cells/ml respectively. There was no difference in proportion of children with documented VL results based on CD4 count.

4.3.9 Proportion of children accessing VL test by time of guideline change

Table 4.11: Access to VL testing based on time of implementation of routine VL testing.

Variable	Total active (n=3118)	With VL results (n=2280)	Odds ratio	Adjusted Odds
After routine VL testing	589	344 (58.4%)	Ref	Ref
Before routine VL testing	2529	1936 (76.6%)	2.33 (1.93, 2.81)	1.62 (1.17, 2.12)

In total a higher proportion of children who started treatment before implementation of routine VL testing had documented VL test results compared with those who initiated treatment after at 76.6% versus 58.4% . The odds of having a documented VL test result for those who initiated treatment before implementation of routine VL testing was 1.6 times higher compared with those who initiated treatment after (aOR 1.62, 95% CI 1.17 – 2.12).

4.3.10. Access to VL testing for children exited from care.

Table 12 shows proportion of eligible children exited form care who had documented VL results. Cumulatively, of 1,132 children discontinued care from their primary site, 314 (27.7%) discontinued care after implementation of routine VL testing and were considered to have been eligible for VL testing. Cumulatively, 92 (29.3%) had documented VL results compared 2,280 (73.1%) who were active on treatment. The odds of having a documented VL result was 6.6 times higher for children who were active on treatment compared to those who had exited from care (Odds ratio 6.6 [95% CI 5.1 – 8.5]).

Table 4.12: Proportion of children exited from care who had VL results

	Total	**On ART at original site and eligible for VL test**	**No with VL results**	**% with VL results**
Transfer out	656	190	62	32.6%
Dead	315	72	21	29.2%
Lost to follow up	161	52	9	17.3%

Table 12 shows proportion of eligible children who had documented VL results at the time of exit from care. The proportion of those with documented VL test results for those transferred out, deceased, and lost to follow up was suboptimal at 32.6%, 29.2% and 17.3% respectively.

4.4 Viral load testing outcomes for children on NNRTI based first line ART

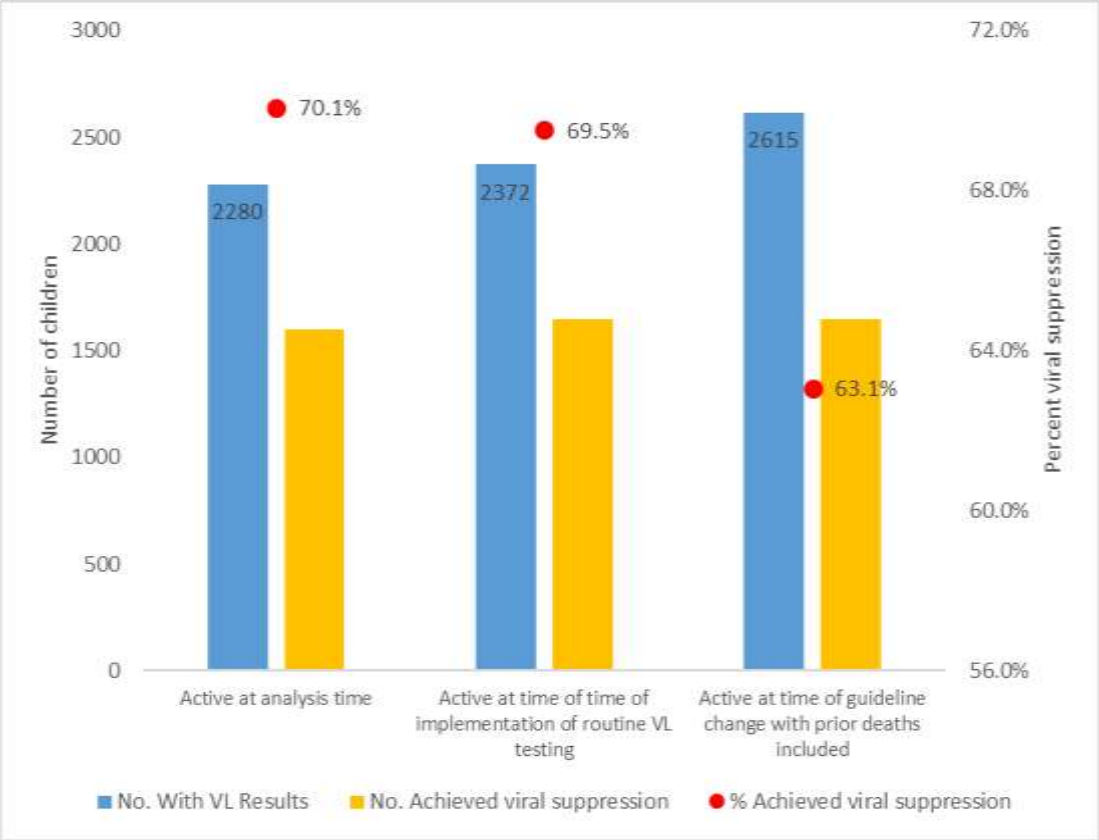

Figure 4.7: Proportion of children achieving viral suppression based on time of guideline revision.

Figure 4.7 shows proportion of children who achieved viral suppression. Overall, of the 2,280 children who were active on ART with documented VL results at the time of analysis (June 2016), 1,598 (70.1%) achieved viral suppression while of the 92 children with VL results at the time of exit, only 51 (55.4%) had achieved viral suppression. The odds of achieving viral suppression was 1.9 times higher for children who were active on treatment (OR 1.88, 95% CI 1.24 – 2.87) compared to those who had exited from care.

If however the 92 children with documented VL results who had discontinued care from their primary site are considered total number with VL results would be 2,372 (2280 plus 92) while those virally suppressed would increase to 1,649 (1598 plus

51). The proportion that would achieve viral suppression would reduce from 70.1% to 69.5%.

Likewise, if the 243 children who died prior to introduction of routine viral testing are assumed not to have been virally suppressed and included in the denominator (2,372 plus 243), the adjusted proportion of children who achieved viral suppression (1,649) would reduce further to 63.1%.

Although the proportion of children accessing care in hospitals who had VL test results was higher compared to primary health facilities, The proportion that achieved viral suppression was similar at 71.0% and 69.1% of those accessing care at hospitals and primary health facilities (Health centers and dispensaries) respectively.

4.4.1 Viral suppression by timing of routine VL testing

Table 4.13: Proportion of children achieving viral suppression by time of implementation of routine VL testing

Variable	Total active (n=3118)	With VL	VL <1000 copies/ml	Odds ratio (95% CI)	Adjusted Odds (95% CI)
Started ART after routine VL testing	589	344 (58.40%)	285 (82.85%)	Ref	Ref
Started ART before routine VL testing	2529	1936 (76.55%)	1313 (67.82%)	0.44 (0.32, 0.59)	0.83 (0.39, 1.78)

Table 4.13 shows proportion of children who achieved viral suppression based on time of implementation of routine VL testing. Although 67.8% of children who initiated ART before implementation of routine VL testing compared with 83.1% of those initiated on treatment after, achieved viral suppression. The difference was not statistically significant.

4.4.2 Viral suppression by gender

Table 4.14: Proportion of children achieving viral suppression by gender

Variable	Total active (n=3118)	With VL	VL <1000 copies/ml	Odds ratio (95% CI)	Adjusted Odds (95% CI)
Female	1,632	1,176 (72.1%)	852 (72.5%)	Ref	Ref
Male	1,486	1,104 (74.3%)	746 (67.6%)	0.79 (0.66, 0 .95)	0.82 (0.64, 1.05)

Table 4.14 shows VL testing outcomes by gender. Although the proportion of females who achieved viral suppression was slightly higher at 72.4% compared to males at 67.6% the difference was not statistically significant.

4.4.3 Viral suppression by duration on ART

Table 4.15: Proportion of children achieving viral suppression by duration on ART

Variable	Total active (n=3118)	With VL	VL <1000 copies/ml	Odds ratio (95% CI)	Adjusted Odds (95% CI)
Less than or equal to 24 months	807	486 (60.22%)	386 (79.4%)	Ref	Ref
>24 – 60 months	1537	1175 (76.45%)	793 (67.5%)	0.54 (0.42, 0.69)	0.58 (0.30, 1.13)
More than 60 months	774	619 (79.79%)	419 (67.7%)	0.54 (0.41, 0.72)	0.53 (.27, 1.06)

Table 4.15 shows VL testing outcomes by duration on ART. A lower proportion of children who had been ART for > 24 months achieved viral suppression compared to those who had been or ART for < 24 months at 67.5% of those who had been on ART for 24 – 60 months and 67.7% for those who had been on ART for more than 60 compared to 79.4% of children who had been on ART for less than 24 months. The difference however was not statistically significant.

4.4.4 Viral suppression by age

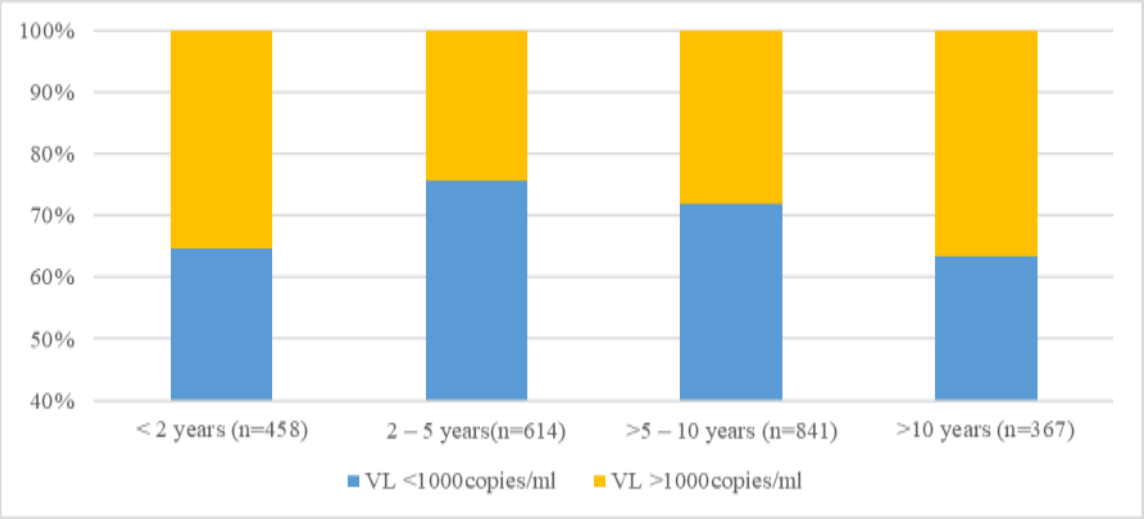

Figure 4.8: Proportion of children achieving viral suppression by age

Figure 4.8 shows VL testing outcomes by age category. The proportion of children who achieved viral suppression was lower for the very young and older children at 64.6% for age < 2years and 63.5% for age > 10 years compared to 75.6% for age 2 – 5 years and 71.9% for age 5 – 10 years. The difference however was not statistically significant.

4.4.5 Viral suppression by WHO clinical stage

Table 4.16: Proportion of children achieving viral suppression by WHO clinical stage

Variable	Total active	With VL	VL <1000 copies/ml	Odds ratio (95% CI)	Adjusted Odds (95% CI)
WHO Stage 1	1713	1253 (73.2%)	894 (71.4%)	Ref	Ref
WHO Stage 2	665	470 (70.7%)	329 (70.0%)		
WHO Stage 3	398	294 (73.9%)	209 (71.1%)	0.95 (0.74, 1.21)	
WHO Stage 4	90	75 (83.3%)	49 (65.3%)		

Table xx shows VL testing outcomes by WHO clinical stage. The proportion of children who achieved viral suppression by WHO clinical stage was 71.4%, 70.0%, 71.1% and 65.3% for WHO stage 1,2,3 and 4 respectively. Cumulatively 69.9% (n=369) of children with advanced HIV disease (WHO stage 3 and 4) compared to 70.9% (n=1,723) of those in early-stage HIV disease at enrolment achieved viral suppression. The difference in proportion of children who achieved viral suppression based on WHO clinical stage was not statistically significant.

4.4.6 Viral suppression by baseline CD4

Table 4.17: Proportion of children who achieved viral suppression by baseline CD4 count

Variable	Total active	With VL	VL <1000 copies/ml	Odds ratio (95% CI)	Adjusted Odds (95% CI)
< 350 cells/mm3	660	511 (77.42%)	334 (65.4%)	Ref	Ref
350 – 500 cells/mm3	355	277 (78.03%)	206 (74.4%)	1.54 (1.11, 2.13)	1.32 (0.93, 1.88)
> 500 Cells/mm3	996	746 (74.90%)	552 (74.0%)	1.51 (1.18, 1.93)	1.39 (1.03, 1.89)

Table 4.17 shows VL testing outcomes by baseline CD4 count. The proportion of children who achieved viral suppression was 65.4%, 74.4% and 74.0% for CD4 <350 cells/mm^3, CD4 = 350 – 500 cells/mm^3, and CD4 >500cells/mm^3 respectively. The odds of achieving viral suppression for those with baseline CD4 >500 cells/mm^3 was 1.4 times compared to those with baseline CD4 <350 cells/mm^3 (aOR 1.4, 95% CI 1.03 – 1.89).

4.5 Documentation of repeat viral load tests for children with virological failure

Of 4,250 children included in the analysis, 3,118 (73.4%) were active on treatment by June 2016 and 2,828 (66.5%) were active on treatment by December 2016. Cumulatively, 95.9% of the 2,828 had documented VL test results of whom 809 (29.8%) had VL >1000 copies/ml and 673 (83.2%) had repeat VL results. In total, 112 children out of the 136 children with missing repeat VL results were expected to have documented results. This took into consideration turnaround time from sample collection, transport to testing laboratories and return of results to health facilities.

The median age of those with missing repeat VL was 9.3 years (IQR 7.0 – 13.2). Individual client record review of the 112 client records with missing repeat VL results found that 87(77.7%) were on first line ART while 25 (22.3%) had already had a regimen switch to second line ART without repeat VL results. Blood samples for VL testing had already been collected from 54 (48.2%) of the 112 children of whom 32 (59.3%) had results available at facilities but not documented in individual client records. Of the 32 children missing documentation, 14 (43.8%) were from hospitals, 19 (59.4%) were not suppressed including 4 children who were on second line ART. In total 9 children (8.0%) had disengaged from care while VL samples had not been collected from 49 (43.8%) children as shown in the figure 4.14.

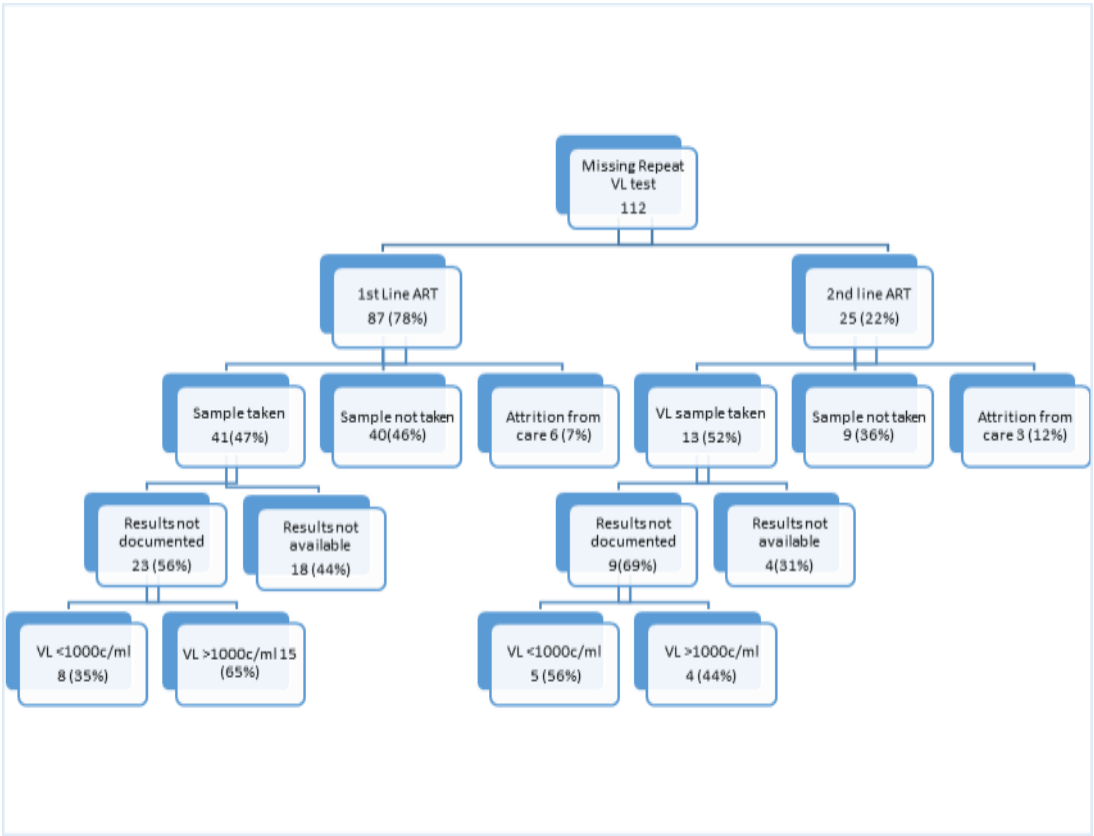

Figure 4.9: Reasons for missing repeat VL results as documented in client records.

4.6 Children with confirmed treatment failure who had regimen switch.

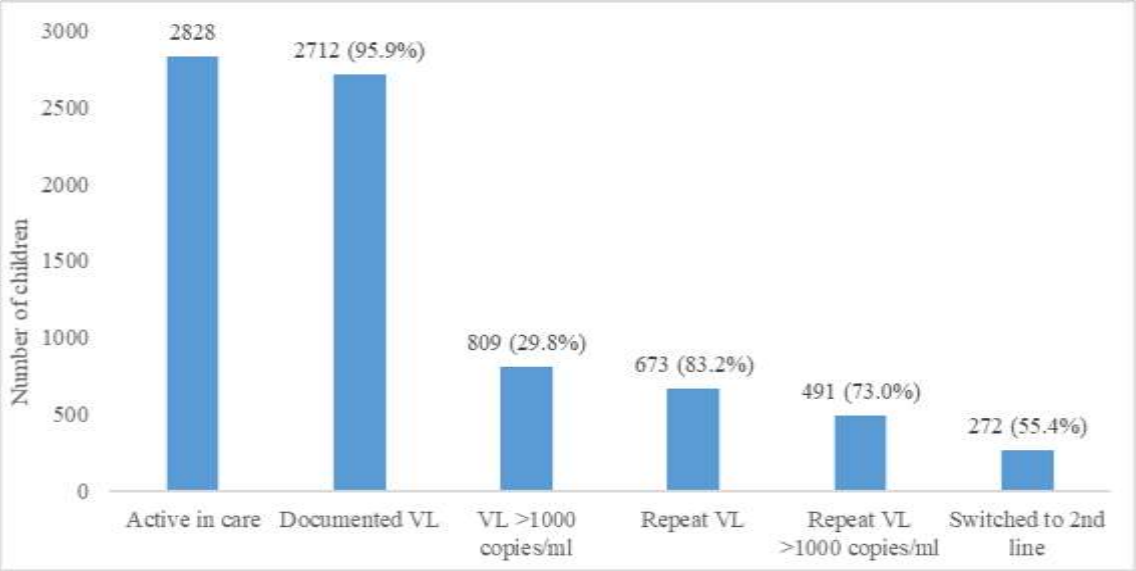

Figure 4.10: Access to VL testing and testing outcomes for children with high VL

In total 491 out of 673 (73.0%) children had repeat VL >1000 copies/ml and were hence confirmed to have treatment failure. Of these, only 272 (55.3%) had been switched to second line ART. The median time from date of first VL result to ARV regimen switch was 13.3 months (IQR 9.8 – 19.2). The odds of achieving re suppression was similar based on gender OR 1.35 (95%CI 0.96 – 1.89), early stage HIV disease (WHO stage 1 and 2) verses late stage HIV disease (WHO stage 3 and 4) OR 1.27 (95%CI 0.82 – 1.99), baseline CD4 count of <350 verses CD4 >500 cells/mm^3 OR 0.77 (95% CI 0.51 – 1.16) and less than verses more than 5 years duration on ART, OR 1.19 (95% CI 0.84 – 1.67). Cumulatively, of the 809 children with VL > 1000 copies/ml, 308 (38.1%) 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. Figure 14 shows the VL testing cascade.

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

This chapter entails discussion of the findings, conclusions from the findings and finally recommendations made based on the findings of the study

5.2. Discussions of the findings

5.2.1 The study sought to establish proportion of children on NNRTI based first line ART with documented VL results

This study whose objective was to document VL testing cascade for HIV infected children on NNRTI-based first line ART regimen between 2010 and 2014 found that overall, 69% of children eligible for VL testing had a documented VL test result. Data on VL testing coverage specifically for children remains scarce as countries scale up access to VL testing and systems to ensure that VL test results are received at user points in a timely manner.

Other studies have equally documented suboptimal VL testing coverage for children. In Uganda, evaluation of incidence and risk factors for first line antiretroviral treatment failure among Ugandan children attending an urban HIV clinic found similar results where 34% of records were excluded due to missing VL test results among others (Sebunya et al., 2013). In Malawi, one study that used quality improvement approach implemented over a period of 13 weeks to address VL testing gap among adults and children noted that although there was an overall increase in VL coverage from 21% to 71%, children aged 0 to 14 years had the lowest coverage throughout the study (Kamwendo et al., 2022). A systematic review conducted in 2016 of 34 studies done to review access to VL testing in the era of test and treat found similar findings. The proportion of children and adolescents with documented VL results was suboptimal at 72% (IQR 47% - 85%). In this study suboptimal uptake of follow-up VL monitoring and low regimen switching rates were also observed (Pham et al., 2022). Review of HIV VL monitoring among patients receiving ART in

eight Sub-Saharan Africa countries between 2013 to 2018 noted significant improvement in access to VL testing across all countries. The proportion of ART patients who had at least one viral load test result increased from 3,8% to 74.1% in Côte d'Ivoire, 8,4 to 85.8% in Kenya, 6% to 51.3% in Malawi and 4.9% to 89% in Uganda. This review however did not provide age disaggregated information (Lecher et al., 2021).

A higher proportion of children accessing care at hospitals who were eligible for VL testing had a documented VL test result compared to those accessing care at primary health facilities. This could be related to logistics support and sample transport networking to central testing laboratories where samples from primary health facilities are first stored at regional hubs before dispatch. Distance to health facilities and infrastructure may also be a contributing factor. Fewer children who had exited from care had documented VL results compared to those who were active on ART. This could be related to mortality while on ART and inability to trace those lost to follow up to have their blood samples taken. Data on proportion of children exited from care who had documented VL test results remains scarce.

Factors affecting VL testing coverage in this study were like other studies and included: inadequate capacity of health care worker to update records, receipt of ART at primary health facilities (Kamwendo et al., 2022; Nakalega et al., 2020)

5.2.2 The study sought to establish proportion of children on NNRTI based 1st line ART with documented VL results who achieved viral suppression

This study found that 70% of children on NNRTI based first line ART regimens achieved viral suppression. This would however reduce to 63% if all those who died were considered to have had virological failure. This is consistent with other studies that have reported suboptimal viral suppression among children on ART. In Zimbabwe, a similar proportion of children and adolescents (69%) accessing ART in public health facilities achieved viral suppression. The proportion of children reported as virally suppressed in the international epidemiology Databases to Evaluate AIDS (IeDEA) collaboration study was found to be suboptimal at 72.4% (Makadzange et al., 2015; Mapangisana et al., 2021). 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% (Boerma et al., 2016). Data from the three studies above however included children who were on NNRTI and non-NNTRI based first line ART. Ongoing adherence challenges was one of the contributory factors identified based on proportion of clients with missing repeat VL results. Indeed, suboptimal adherence to treatment has been associated with treatment failure especially in children on NNRTI based regimens (Bulage et al., 2017).

More children with VL test results after implementation of routine VL testing achieved viral suppression compared to those tested before. Before revision of treatment guidelines, VL testing in Kenya was targeted whereby only those with clinical failure or immunologic failure were eligible for VL testing to confirm treatment failure. These were however a select population and may not accurately give information on the actual proportion of children with virological failure. A retrospective study to evaluate the proportion of true virological failure among patients diagnosed with clinical and immunologic failure in Kenya found the sensitivity of clinical and immunologic criteria in diagnosing virological failure to be 61% and 38% respectively while specificity was 34% and 66% respectively (Joram et al., 2017).

In this study, the proportion of children exited from care who had achieved viral suppression was found to be lower compared to those who were active on ART. Data from other studies on the same remain scarce and not readily available. Similar findings were reported from South Africa where virological non suppression was associated with higher loss to care at 30.3% compared to suppressed children at 9.7% (van Liere et al., 2021). Findings from this study are also in line with findings from India where the proportion of children who had virological suppression was higher in those who stayed in care at 75% compared to those who died at 39% and LTFU at 71 % (Alvarez-Uria, 2014). The findings of this study reinforce WHO recommendation of timely VL testing for all patients and especially children.

This study found that lower proportion of children who had been on ART for longer than 24 months achieved viral suppression compared with those who had been on

ART for less than 24 months. Other studies that have documented similar results. In Zimbabwe, children on ART for ≥4 years had higher treatment failure rates than those on ART for <4 years (39.6% vs. 23.9%). In this study nevirapine based ART regimen was associated with a 3-fold increased risk of failure. (Makadzange et al., 2015). In Cameroon, the proportion of children and adolescents on first line ART who achieved viral suppression decreased from 84% in month 12 to 77% by month 48. (Fokam et al., 2019). The fundings of this findings are also 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 (Sebunya et al., 2013). In south Africa however, shorter duration on ART was associated with higher rates of virological suppression (van Liere et al., 2021).

Children with CD4 >500 cells/mm^3 were more likely to achieve viral suppression compared to those with VL <350 cells/mm^3. Other studies have equally 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 (Yassin & Gebretekle, 2017). A few studies have however failed to demonstrate a correlation between virological failure and immunological failure (Barth et al., 2011). The role of CD4 count in monitoring patients on ART has however been revised and should only be used in settings where routine VL testing is not readily available based on WHO recommendations. Lower proportions of the younger (<2 years) and older (>10 years) compared to other age categories achieved viral suppression. This is consistent with other studies that demonstrated viral suppression to be lower among the youngest and the oldest children (Hoffmann et al., 2009). The findings of this study were regimen specific and were however lower than those observed from routine HIV treatment monitoring by the Kenya Ministry of Health that reported suppression rates of 66%, 82% and 82% for ages less than 2 years, 2 – 9 years and 10 – 14 respectively (MOH, 2014b).

5.2.3 The study sought to document proportion with repeat VL test results among children diagnosed with virological failure and reasons for missing results

This study found that 83% of children with virological failure had documented repeat VL results as per WHO recommendation. Other studies have however found the proportion of children with virological failure who access repeat VL testing to be lower. In Uganda, 79% of children diagnosed with virological failure were found to have repeat VL test results while in Swaziland, only 60% of patients eligible for repeat VL testing had documented VL test results (Jobanputra et al., 2015; Nasuuna et al., 2018). In Lesotho, overall, only 44% of children had a follow up VL within 6 months of first unsuppressed VL. Of these 47% resuppressed (Muhairwe et al., 2022). The most common reasons for missing documentation of repeat VL results were documentation errors, ongoing adherence issues and delayed return of VL results to sites. Data on reasons for missed opportunities for repeat VL testing remains scarce. Inadequate capacity of health care workers in updating client records has equally been documented as barrier to optimal viral suppression in children (Kamwendo et al., 2022). We found that only 27% of those with virological failure achieved viral suppression after enhanced adherence. Findings of this study are in concurrence with other studies that have reported suboptimal re suppression among children with high VL. In South Africa, only 27% of patients with viremia re suppressed 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 (Jobanputra et al., 2015; Lejone et al., 2018). In Uganda, of 345 children who completed three sessions of enhanced adherence counseling and had repeat VL results, only 23% re suppressed (Nasuuna et al., 2018). A systematic review of six databases that reported data from 8 countries, five studies reported on viremic re suppression, with a pooled estimate of 71% re suppression. The study noted clear trend of re suppression and adherence support (Bonner et al., 2013). A systematic review of 58 studies that reported outcomes of 45,720 viraemic patients mostly from Africa, and among patients on first-line antiretroviral therapy found that the proportion that re suppressed was lower among children (31.2%) and adolescents (40.4%) compared to adults (50.4%). Similar to the findings of this study, this study

did not find important differences based on, gender, viral failure threshold, time between VL sample collection. The study concluded that appropriate action on VL results is limited across a range of settings, highlighting the importance of VL cascade analyses to identify gaps and focus quality improvement to ensure that action is taken on the results of VL testing (Ford et al., 2019).

5.2.4. The study sought to establish proportion of children with treatment failure who had a regimen switch.

Cumulatively, 55% of children with confirmed treatment failure had an ART regimen switch. Information on proportion of children who switch to second line ART after confirmed treatment failure is limited.

In one study in Uganda, of the children who had completed the recommended three enhanced adherence sessions and had repeat VL >1000c/ml, the proportion that were switched to second line ART was lower at 41%. (Nasuuna et al., 2018). The finding of this study are similar to those of a systematic review of 58 studies that reported outcomes of viraemic patients on first line ART with confirmed treatment failure where only 53.4% were appropriately switched to a different regimen (Ford et al., 2019). Similar to this study, no important differences were observed based on gender or time between viral loads. In Lesotho, only 45% of children with confirmed treatment failure who had qualified had been switched to second line ART. The proportion switched within 12 weeks of follow up was 7%. In this study, delays were more pronounced in rural facilities (Muhairwe et al., 2022). In Thailand, the cumulative rate of ART regimen switches from first line to second line ART increased from 4% to 20% from 1 to 3 years after treatment. This finding could be similar to this study where lower proportions of children who had on ART achieved viral suppression and could potentially translate to higher proportion switched to alternative regimens. In this study, children aged more than 12 years at ART initiation, those starting with NNRTI based regimen, and baseline CD4% <10% had an increased risk of switching to second-line regimens (Teeraananchai et al., 2017).

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 regimen. Availability of

drug resistance testing (DST) would usually show that the virus could be still susceptible to first line ART drugs, but DST is not routinely available. 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 (Bonner et al., 2013). The findings of this study raises a possibility of ongoing adherence challenges that may have contributed to failure to re suppress prior to change of regimen. This reinforces WHO 2016 recommendation of repeating VL testing after enhanced adherence support for all patients on ART with virological failure prior to ART regimen switch.

5.3 Study strengths and limitations

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 also provides regimen specific viral load testing information including possible reasons of missing results at user points that are critical in patient management. An addition it provides comprehensive information on VL testing cascade from initial testing to establish response to treatment to switch of regimen based on confirmed treatment failure. This information may be essential in understanding gaps in patient care along the VL testing cascade.

This study however relied mainly on secondary data and some client data elements were missing. These were excluded from analysis. Assumptions were also made that national guidelines were followed with fidelity. Any deviations from this could not be verified given that secondary data was used.

Due to the nature of study site which was scared across nine counties in western part of Kenya, time constrains would be an issue due to the large area that was covered to collect the relevant data. There was a question of homogeneity of the data collected since vast study site had various social and demographic differences which could have affected treatment outcomes among the children.

The study did not have a comparison group and focused on faith-affiliated facilities only posing challenges in generalization to other health facilities or study settings.

The number of facilities selected represented a small proportion of facilities and children on ART in Western Kenya and hence results could only be generalized to faith affiliated facilities and not general population.

5.4. Conclusions and recommendations

5.4.1 Conclusions

Overall, 73% of children who were active on ART had documented VL results of whom 70% achieved viral suppression. The study found lower proportion of those who had been on ART for less than 24 had documented VL results compared with those who had been on ART for longer.

The study established that lower proportion of the very young and older children achieved viral suppression. It also established that a higher proportion of children who had been on ART for less than 24 moths achieved viral suppression compared with those who had been for ART for longer. Those with CD4>500cells/mm^3 were more likely to achieve viral suppression as were those active on ART compared with those who had exited from care.

Cumulatively, 83.2% of children with virologic failure had documented repeat VL results.

Blood samples for VL testing had not been collected from almost half of the children and more than half had results available at facility level but not in individual client records.

Of the 73% of children with repeat VL>1000c/ml, only 55% had been switched to second line ART. Almost three quarters of those switched without repeat VL test failed to achieve viral suppression on their follow up test.

5.4.2 Recommendations

Programs should be more vigilant in ensuring timely VL testing for all eligible children especially younger children and those at risk of exit from care.

The very young and older children, those who have been on ART for longer, those at high risk of attrition from care and those with advanced HIV disease may need additional support to achieve viral suppression.

To facilitate individualized client management for those with virological failure, health systems should be strengthened to provide timely access to repeat VL testing as well ensure that results are documented in the patient records.

Management of children with confirmed treatment failure should be prioritized to avoid delays in regimen switch. Capacity building and additional support may however be required to ensure that they achieve viral suppression especially those switched without repeat VL tests.

5.4.3. Suggestions for further studies

Further studies should be done to compare proportion of children who achieve viral suppression on various ART regimens including reasons for delayed interventions given that study was limited to only children on nevirapine or Efavirenz based regimens. Similarly, we recommend further studies to evaluate barriers to regimen modification after confirmed treatment failure given that in this study, only 55% of those eligible had a regime switch.

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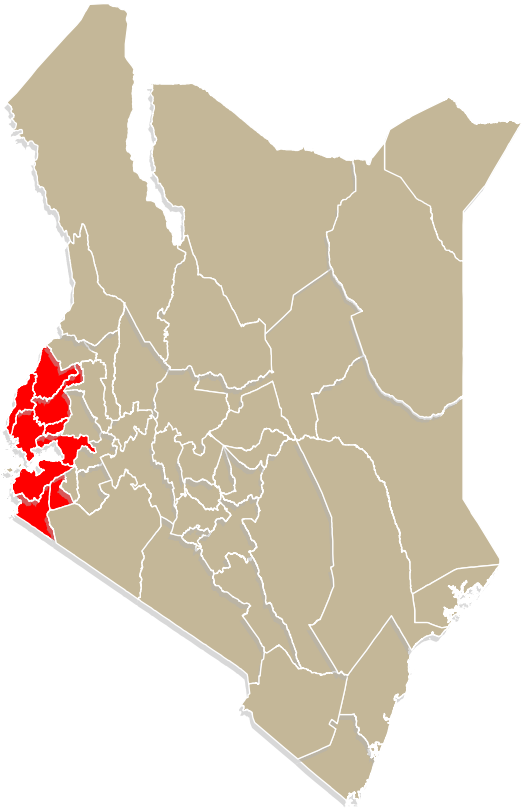
APPENDICES

Appendix I: List of facilities

	Facility	Children on ART		Facility	Children on ART
1	Kendu Adventist Hospital	408	24	Kadem TB & Leprosy Dispensary	66
2	Mukumu Hospital	304	25	Nyangoma Mission Health Centre	64
3	St Camillus Mission Hospital	279	26	Okiki Amayo Health Centre	57
4	St Joseph Mission Hospital	220	27	Arombe Dispensary	57
5	Maseno Mission Hospital	191	28	Angiya Dispensary	56
6	Lugulu Friends Mission Hospital	189	29	Osani Community Dispensary	53
7	Asumbi Health Centre	184	30	Wire Dispensary	53
8	St Elizabeth Chiga Health Centre	182	31	Bukembe Dispensary	50
9	St Monica Rapogi Health Centre	175	32	Verna Health Centre	49
10	Nyabondo Mission Hospital	174	33	Rangala Health Centre	43
11	St Monica Hospital	171	34	St Pius Musoli Health Centre	42
12	Holy Family Nangina Hospital	155	35	Kakamega Forest Dispensary	40
13	Oriang Mission Dispensary	142	36	Vigeze Community Dispensary	37
14	St Marys Hospital (Mumias)	124	37	Lwanda Dispensary	33
15	Homa Hills Health Centre	123	38	Christamarrianne Hospital	32
16	Mirogi Health Centre	117	39	Chwele Health Centre	32
17	Tabaka Mission Hospital	117	40	Mechimeru Dispensary	30
18	St Elizabeth Lwak Mission Health Center	113	41	Sikulu Dispensary	30
19	Shirikisho Dispensary	112	42	Got Nyabondo Dispensary	29
20	Ringa Dispensary	83	43	Ulanda Dispensary	29
21	St Paul's Health Centre	74	44	Mayanja Dispensary	24
22	Mawego Health Centre	67	45	Nyanchwa Dispensary	23
23	St Clare Bolo Health Centre	66	46	St Monica Town Clinic	22

Appendix II: Map of Counties where sites were located



Appendix III: Data abstraction guide

Data was abstracted per cohort year; 2010, 2011, 2012, 2013 and 2014 and content included;

1. Date of birth
2. Date of enrolment
3. Gender
4. Baseline CD4 test result
5. Date of baseline CD4
6. WHO stage at enrolment
7. Weight at enrolment
8. Most current CD4 prior to ART initiation
9. Date of most current CD4 prior to ART initiation
10. Date of ART initiation
11. ART regimen initiated
12. Date of viral load test
13. Viral load result
14. Repeat viral load
15. Date of repeat viral load
16. Care status at the following months: 6, 12, 18, 24, 48, 60
17. Attritions
    a. Transfer out: Date of transfer out
    b. LTFU: Date of LTFU
    c. Dead: Date reported dead
    d. Stop ART: Date of "stop ART"
18. Date of attrition from ART

Appendix IV: Chart abstraction guide to find out reasons for missing follow up viral load test for patients with VL >1000 copies/ml.

1. Was the patient active on ART at the time of eligibility for repeat VL testing? Yes ….., No ……
    a. If no please provide details
        i. Transfer out
        ii. Lost to follow up
        iii. Dead
2. Was blood sample collected for repeat VL test? Yes ……., No …….
    a. If yes, note date of sample collection …..dd/mm/yy…..
    b. If no, please give reason
        i. Adherence challenges
        ii. Psychosocial reasons
        iii. No good reason. Gaps in health systems. Sample yet to be taken
        iv. Others
3. If blood sample was taken, were results received at the facility? Yes …….., No …….
4. Were VL test results documented in the client file Yes: ……., No ……..

Appendix V: WHO Clinical Staging

WHO Stage 1

Asymptomatic

Persistent generalized lymphadenopathy

WHO stage 2

Unexplained persistent hepatosplenomegaly

Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

Herpes zoster

Lineal gingival erythema

Recurrent oral ulceration

Papular pruritic eruption

Fungal nail infections

Extensive wart virus infection

Extensive molluscum contagiosum

Unexplained persistent parotid enlargement

WHO Stage 3

Unexplained moderate malnutrition not adequately responding to standard therapy

Unexplained persistent diarrhoea (14 days or more)

Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month)

Persistent oral candidiasis (after first six weeks of life)

Oral hairy leukoplakia

Lymph node tuberculosis; pulmonary tuberculosis

Severe recurrent bacterial pneumonia

Acute necrotizing ulcerative gingivitis or periodontitis

Unexplained anaemia (<8 g/dL), neutropaenia (<0.5 × 109/L) or chronic thrombocytopaenia (<50 × 109/L)

WHO stage 4

unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis (jirovecii) pneumonia

Recurrent severe bacterial infections

Chronic herpes simplex infection

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Extrapulmonary tuberculosis

HIV encephalopathy

Extrapulmonary cryptococcosis, including meningitis

Cerebral or B-cell non-Hodgkin lymphoma HIV-associated nephropathy or cardiomyopathy

Appendix VI: Published manuscripts and abstracts

1. Paul Wekesa, Jaquin Kataka, Kevin Owuor, **Lennah Nyabiage,** Fredrick Miruka, Stella Wanjohi, Samuel Omondi (2020). Time to HIV testing of sexual contacts identified by HIV-positive index clients in Siaya County, Kenya. PLoS One. Sep 8;15(9):e0238794. doi: 10.1371/journal.pone.0238794. eCollection 2020. https://pubmed.ncbi.nlm.nih.gov/32898159/
2. **L. Nyabiage**, P. Musingila, M. Omondi, J. Mutwiri, D. Rono, L. Manwa, B. Otieno-Nyunya and K. Ngure (2018). 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. East African Medical Journal Vol. 95 No. 12. https://www.ajol.info/index.php/eamj/article/view/194561
3. Jayne Lewis Kulzer, Jeremy A Penner, Reson Marima, Patrick Oyaro, Arbogast O Oyanga, Starley B Shade, Cinthia C Blat, **Lennah Nyabiage**, Christina W Mwachari, Hellen C Muttai, Elizabeth A Bukusi, Craig R Cohen (2012). Family model of HIV care and treatment: a retrospective study in Kenya. Journal of the International AIDS society. Feb 22;15(1):8. doi: 10.1186/1758-2652-15-8. https://pubmed.ncbi.nlm.nih.gov/22353553/
4. Julia W Gargano 1, Kayla Laserson, Hellen Muttai, Frank Odhiambo, Vincent Orimba, Mirabelle Adamu-Zeh, John Williamson, Maquins Sewe, **Lennah Nyabiage**, Karen Owuor, Dita Broz, Barbara Marston, Marta Ackers (2012). The adult population impact of HIV care and antiretroviral therapy in a resource poor setting, 2003-2008. AIDS. 2012 Jul 31;26(12):1545-54. doi: 10.1097/QAD.0b013e328353b7b9. https://pubmed.ncbi.nlm.nih.gov/22441254/

IAS 2021 Virtual. Accepted Abstracts

1. Anne Wasilwa, Amadi Emmanuel, Habib Omari Ramadhani, Angela Ndaga, Violet Makokha, Kepha Abuya, Daniel Oneya, **Lennah Omoto Nyabiage**, Caroline Ng'eno. Impact of enhanced adherence counselling on viral re-suppression among adolescents and young persons with persistent high viremia

in selected health facilities in Kisii and Migori county, Western Kenya. https://theprogramme.ias2021.org/Abstract/Abstract/615

2. Violet Makokha, Emmanuel Amadi, Habib Omari Ramadhani, Duncan Obunge, Florence Ogero, Daniel Oneya, **Lennah Omoto Nyabiage**, Caroline Ng'eno. Viral suppression among adolescents and young adults on ART before and after structured transition to adult care in rural Western Kenya. https://theprogramme.ias2021.org/Abstract/Abstract/786
3. David Ogiti, Emmanuel Amadi, Roseline Oyuga, Vivian Ousso, D. Onea, **Lennah Omoto Nyabiage,** Caroline Ng'eno, Emily Koech, Natalia Blanco, Marie-Claude Lavoie. Impact of a family-centered care model on viral suppression among HIV-infected children in Migori, Kenya. https://theprogramme.ias2021.org/Abstract/Abstract/1131

ICASA 2021 Virtual. Accepted abstracts

1. **Lennah Nyabiage**, Immaculate Mutisya, Paul Musingila, Rachael Joseph, Jacquin Kataka, Caroline Ngeno, Francesca Odhiambo, James Wagude, Appolonia Aoko, Lucy Ng'ang'a. Lessons Learnt from paediatric treatment optimization implementation in four counties in western Kenya. Abstract No. PEB040.
2. **Lennah Nyabiage**, James Wagude, Leonard Kingwara, Joseph Rachael, Millicent Achieng, Elizabeth Katiku, Ernest Makokha, Appolonia Aoko. Lessons earnt from ART optimization of children failing protease inhibitor-based regimens in four counties in Western Kenya. Abstract No. PEB036

Appendix VII: Ethics and Research Committee (ERC) approval

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Ref: KNH-ERC/A/112

29th March, 2016

Dr. Lennah Nyabiange Omoto
TM310/1930/2013
JKUAT

Dear Dr. Omolo

Revised Research Proposal: Outcomes of HIV infected children ever initiated on nevirapine or efavirenz based first line antiretroviral treatment regimen at selected health facilities in western Kenya (P586/09/2015)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and approved your above proposal. The approval period is from 29th March 2016 – 28th March 2017.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal)
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an executive summary report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

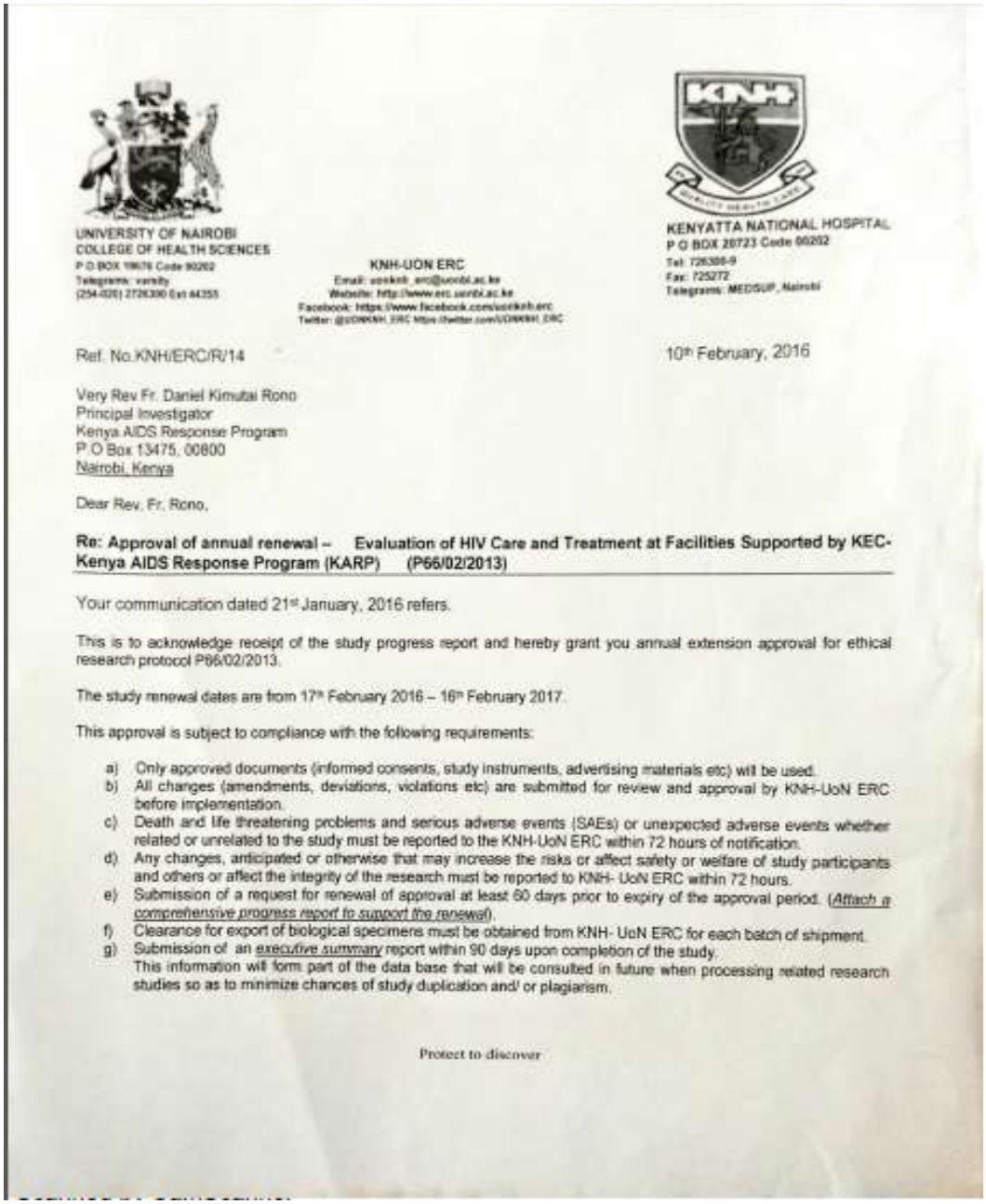
"Protect to discover"

Yours sincerely,

PROF. M.C. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chair, KNH-UoN ERC
Supervisors: Dr. Kenneth Ngure, KJUAT
Dr.Christina Mwachari, KEMRI
Prof.B.Otieno- Nyunya, Division of Global HIV and AIDS

Appendix VIII: KCCB – KARP Non research determination



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Ref: No.KNH/ERC/R/14

10th February, 2016

Very Rev Fr. Daniel Kimutai Rono
Principal Investigator
Kenya AIDS Response Program
P.O Box 13475, 00800
Nairobi, Kenya

Dear Rev. Fr. Rono,

Re: Approval of annual renewal – Evaluation of HIV Care and Treatment at Facilities Supported by KEC-Kenya AIDS Response Program (KARP) (P66/02/2013)

Your communication dated 21st January, 2016 refers.

This is to acknowledge receipt of the study progress report and hereby grant you annual extension approval for ethical research protocol P66/02/2013.

The study renewal dates are from 17th February 2016 – 16th February 2017.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study.
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

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Appendix IX: Publication

East African Medical Journal Vol. 95 No. 12 December 2018

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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Corresponding author: Dr. Lennah Nyabiage, MPH Student, Jomo Kenyatta University of Agriculture and Technology, School of Public Health, P.O Box 3408, Kisumu, 40100, Kenya, E-Mail Address: lnyabiage@yahoo.com.

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

L. Nyabiage, P. Musingila, M. Omondi, J. Mutwiri, D. Rono, L. Manwa, B. Otieno-Nyunya and K. Ngure

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 $p \leq 0.05$ 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/mm³ compared to age < 2 years and CD4 <350 cells/mm³ 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

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

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.

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).

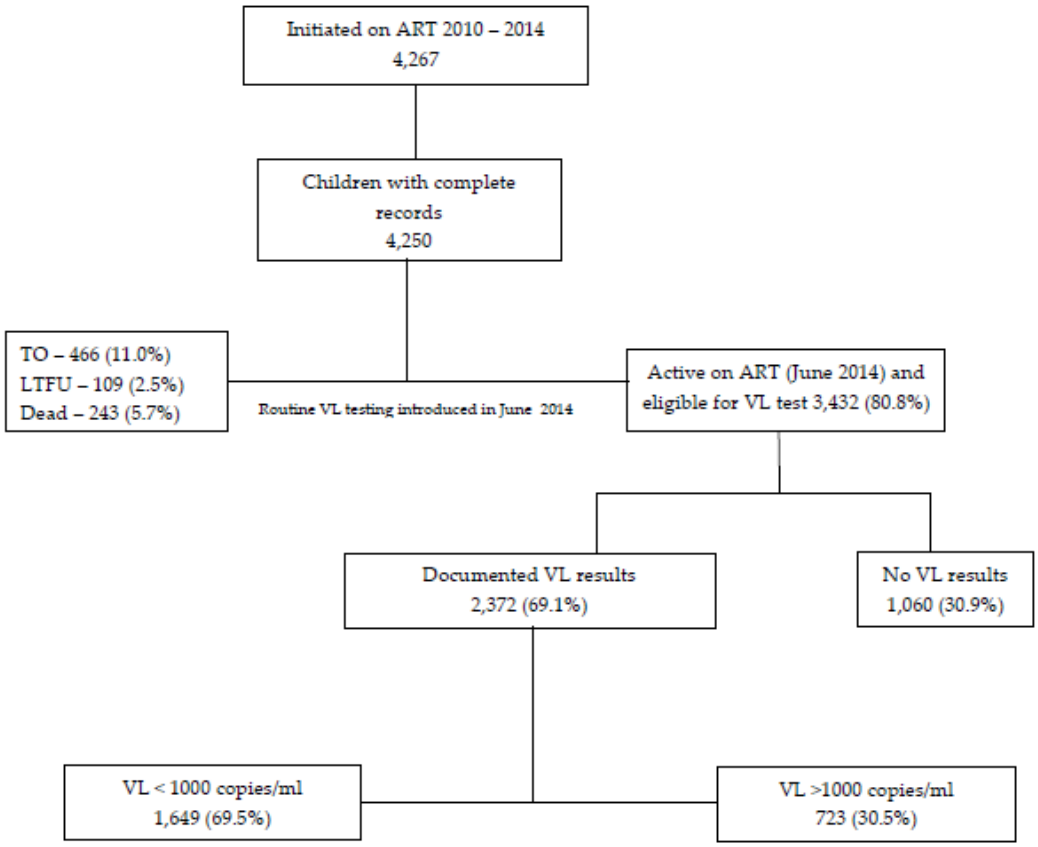

Figure 1. Flow chart on proportion of records included and excluded at each stage of analysis

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 ≤ 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 ≤ 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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