DETERMINANTS OF FORECAST ACCURACY FOR PAEDIATRIC ANTIRETROVIRAL DRUGS IN KENYA

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DEDICATION

I dedicate this work to my husband Dr. Stephen Njogo and my children John, Isabel and Solomon for their support and perseverance during my study.

I also dedicate this work to my dear mother Lucy Githaiga and dad Suleiman Githaiga who laid foundation for success in my education and also formed me to aim high in life.

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ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ADFT	Augmented Dickey-Fuller test
AIDS	Acquired Immunodefficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
d4T	Stavudine
DHMT	District Health Management Team
EFV	Efavirenz
FDC	Fixed Dose Combination
FPLM	Family Planning Logistics Management
HIV	Human Immunodefficiecy Virus
LPV/r	Lopinavir with ritonavir
MAPE	Mean Absolute Percentage Error
MSH	Management Science for Health
NASCOP	National AIDS and STI Control Program
NVP	Nevirapine
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease inhibitor
TDF	Tenofovir
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

DEFINITION OF TERMS

Forecasting: With regards to products, it is the process of estimating quantity required of particular products to meet demand for the specified period of time.

Forecast accuracy: Is the degree of closeness of the forecast quantity to the actual (true) consumed quantity.

Forecast bias: Refers to persistent tendency for forecasts to systematically under or overestimated a value.

Forecast decision tree: Is a tree-like model of decisions and their possible outcomes and their consequences used as a decision support tool.

Forecast error: This is the difference between the actual value and the value predicted for a given period.

Forecast error metric: Is a system of measurements for quantitatively assessing forecast errors.

Logistics Management Information System/Logistics Information Management System: This is a combination of logistics and information systems. Logistics is concerned with ensuring the right quantity of the right item is at the right place at the right time and right cost while Information system gathers, categorizes, stores and shares the information required for decision making by management.

Paediatric: For this study a paediatric patient is a child aged between 0 and 14 years. This is the age category used for indicator monitoring guidelines and tools by World Health Organization and National AIDS/STI Control Program**.**

Supply chain: Is the process of planning and management of all activities involved in sourcing and procurement, conversion, and all logistics management activities.

Supply planning: Is the process of adjusting quantities forecasted to determine quantities to procure and time of delivery of the products**.**

ABSTRACT

Background: Antiretroviral drugs are used for Human Immunodeficiency Virus (HIV) infection prevention as well as long-term therapy. Use of these drugs is essential in reducing HIV infection prevalence and improving the quality of life of people living with HIV infection. Availability and access is thus very important. Uninterrupted supply can be achieved through routine forecasting and supply planning. Forecasting for paediatric antiretroviral (ARV) drugs is complex due to the fact that dosing is weight-based, a suitable range of paediatric drug formulations is lacking and paediatric ARV drugs are not packaged in monthly dosage requirements. Forecast accuracy, consumption monitoring and timely supply planning are key elements to uninterrupted supply.

Objectives: The objectives of the study were to determine forecast accuracy for paediatric antiretroviral drugs in Kenya; determine relative proportions of children at various weight categories and on various antiretroviral regimen and formulations; determine within and between-individual changes over time with regards to weight and formulation; and identify factors that influence choice of ARV formulations dispensed to paediatric patients from the pharmacy personnel perspective.

Methodology: Forecast accuracy was calculated using Mean Absolute Percentage Error (MAPE) for periods 2010/11, 2011/12 and 2012/13. Retrospective longitudinal cohort design was used to determine effect of age, weight and sex on antiretroviral formulations dispensed to children at a selected public health facility in Kenya. In-depth interviews were done to establish factors that influence choice of ARV formulation dispensed to children. Forecast and consumption data was collected. Univariate, bivariate and repeated measures logistic regression data analysis was done. A point of concept saturation approach was used for qualitative data analysis.

Results: Forecast accuracy for seven paediatric ARV formulations was established for 2010/11, 2011/12 and 2012/13 forecast periods. Forecasts were found to be inaccurate for abacavir/lamivudine 60/30mg; zidovudine/lamivudine 60/30mg; zidovudine/ lamivudine/nevirapine 60/30/50mg; efavirenz 200mg; Lopinavir/ritonavir 80/20mg and zidovudine 10mg/ml where MAPE ranged between 11.8% and 2198.9%. NVP 10mg/ml

was the only product that recorded reasonable forecasts where MAPE of "41.6%, 49.1% and 24.4% was observed in 2010/11, 2011/12 and 2012/13, respectively". Forecast errors were found to be non-random. For repeated measures data, majority of the children were males and constituted 171(55.0 %), 171(55.9 %) and 169(55.8 %) in July 2010, 2011 and 2012, respectively. Median and interquartile (IQR) range for age were 9.2(6.8, 12.0), 9.6(7.3, 12.0) and 10.3(7.5, 12.5) years in July 2010, 2011 and 2012, respectively. Median and IQR range for weight were 26(20, 32), 27(21, 32) and 28(21, 34) Kg in July 2010, 2011, 2012, respectively. 55.0 %, 61.5% and 64.9 % of children were in the ≥25 Kg weight category in July 2010, 2011 and 2012, respectively. Only 19.0 %, 30.3 % and 32.6 % of children were on paediatric formulations for period 2010/11, 2011/12 and 2012/13. The study revealed that children were likely to turn 25 Kg at age 8 years. Male children were found to be more likely to use adult formulation than female children. Dispensing staff reported weight, age, paediatric ARV drug availability; and preference to dispense paediatric ARV formulation as factors that influenced choice of drug dispensed to children below 15 years.

Conclusion: Forecasts for abacavir/lamivudine 60/30mg; zidovudine/lamivudine 60/30mg; zidovudine/ lamivudine/ nevirapine 60/30/50mg; efavirenz 200mg; lopinavir/ ritonavir 80/20mg and zidovudine10mg/ml were inaccurate in 2010/11, 2011/12 and 2012/13. Only nevirapine 10mg/ml had accurate forecast across the three periods. The forecast errors were found to be non-random. The forecast did not take into account sex and age as important variables that determine formulations dispensed to children. Dispensing staff reported drug availability and their preference to dispense particular formulations as factors that influenced choice of ARV drug they dispensed to children.

Recommendations: There is need for evidence based forecasting where data on variables that are required for forecasting are continually collected and reviewed against consumption patterns. In addition, it would be necessary for forecast performance to be monitored on quarterly or bi-annual basis for early detection and correction of errors. Use of different forecasting approaches and models would be important in comparing forecast performance.

CHAPTER 1: INTRODUCTION

1.1. Background to the study

The number of people estimated to have Human Immunodeficiency Virus (HIV) infection globally was 35.3 million in the year 2012 (UNAIDS, 2013). An increase in number of people living with HIV has been observed over time and this has been attributed to increased access and use of life-saving antiretroviral therapy (UNAIDS, 2013). Children who are newly with HIV infected in 2012 were 260,000 in the low and middle income countries (UNAIDS, 2013). In 2009, over 90 per cent of new infections in children were attributed to mother-to-child transmission (WHO, 2010). The number of children less than 15 years on antiretroviral therapy (ART) in under-developed countries increased from 566 000 in 2011 to 630 000 in 2012 (WHO, 2013).

The prevalence of HIV infection in Kenya in the year 2012 was 5.6 per cent among adults aged 15 to 64 years and 0.9 per cent among children aged 18 months to 14 years. This corresponded to about 1,192,000 people living with HIV. A reduction in HIV prevalence was observed in adults from 7.2 per cent in 2007 to 5.6 per cent in 2012. A national, population-based survey for children was first undertaken in year 2012 where only children aged between 18 months to 15 years were considered. The national HIV prevalence among children below 18 months remains unknown. The proportion of people living with HIV and eligible for antiretroviral treatment was estimated at 58 per cent. However, it was shown that only 63 per cent of the 58 per cent were on treatment in the year 2012 (NASCOP, 2013). As at June 2013, there were 619,669 patients on antiretroviral drugs comprising 561,774 adults and 57,895 children (NASCOP, 2013).

1.2. Roll-out of antiretroviral therapy in Kenya

In Kenya, antiretroviral therapy was launched in the public sector towards the end of 2003. The antiretroviral therapy was first rolled out to the county referral and county

hospitals previously called provincial and district hospitals, respectively. Before then, only about 7,000 patients were receiving antiretroviral therapy from the private sector and some non-governmental organizations. Prevention, care and treatment HIV infection management services have been decentralized to all levels of health sector in an effort to improve access, equity and adherence to treatment (NASCOP, 2009).

Decentralization has been defined as "the sharing of responsibilities of providing HIV prevention, care and treatment services at multiple levels of health care service provision within the Kenya health system with the goal of expanding access to quality HIV services". Decentralization model adopted in Kenya encompasses downwards and upwards patient referrals; capacity building where high level facilities support lower level facilities; products and information flow. Downward referral is the transfer of stable patients from high level facilities to lower level facilities to decongest high level facilities to create room for complicated and specialized cases. Upward referral is the transfer of patients who require specialized management that cannot be handled at lower levels such as treatment failures and some adverse events (NASCOP, 2009).

A three level decentralization model has been used for distribution of antiretroviral drug product from national stores to health care provision facilities. Information flow takes a reverse channel (Figure 1). Level one is the national procurement, warehousing and distribution agencies; level two includes central sites, district stores and stand-alone sites while level three is the satellite sites (Figure 1). The national procurement, warehousing and distribution agencies procure, warehouse and distribute antiretroviral drugs to the level two, that is, central sites, district stores and stand-alone sites. There are two national procurement, warehousing and distribution agencies for antiretroviral drugs: Kenya Medical Supplies Agency (KEMSA) and Kenya Pharma project. The activities of the two agencies are coordinated by national AIDS/STI Control Program (NASCOP) which is a unit in the ministry of health (NASCOP, 2009).

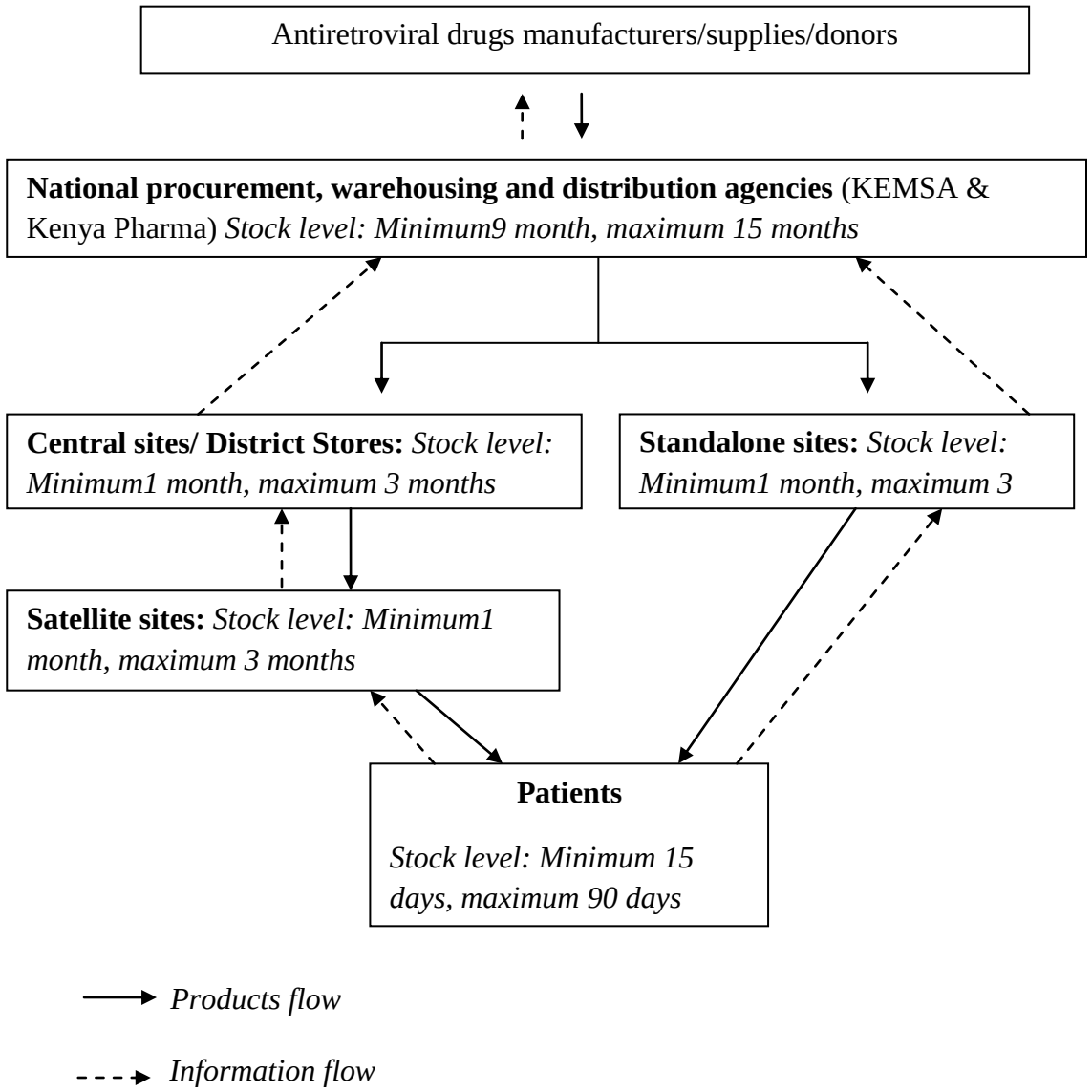

Figure 1: Product and Information flow for antiretroviral drugs (adopted from NASCOP, 2009)

Central sites, district stores and stand-alone sites form the second level in the decentralized model for in the antiretroviral supply chain. Central sites and stand-alone sites were the previously known as provincial and district hospital but now known as county referral and county hospitals, respectively in the devolved government. Some of the high volume primary care facilities previously known as health centers especially in

the high HIV infection prevalence areas are also central sites or stand-alone sites. Central sites and district/sub-county stores are assigned satellite sites to distribute antiretroviral drugs to as well as collect logistic information. The logistic information from the satellites is aggregated by the central sites and district/sub-county stores and is transmitted to NASCOP. The difference between central sites, district/sub-county stores and stand-alone sites is operational by design. Central and stand-alone sites are health facilities that offer clinical services to patients and dispensing of antiretroviral drugs is done. In addition to dispensing to patients, central sites also store and distribute antiretroviral drugs to other health facilities assigned to them in the decentralization model while stand-alone sites only store and dispense antiretroviral drugs to the patients who receive clinical services from the facilities. District/sub-county stores are regional storage facilities for both pharmaceutical and non-pharmaceutical products. District/sub-county stores are not dispensing points for antiretroviral drugs (NASCOP, 2009).

Satellite sites are the third and last level of the decentralized model. They receive antiretroviral drugs from the central sites or district store. Satellite sites are required to transmit a monthly report before receiving the products they require. The monthly reports are aggregated by respective central sites and district stores and transmitted to national level. The key logistic data items reported include consumption, stock on hand and any losses, expiries or damages. Data on patient numbers per regimen is also reported (NASCOP, 2009).

Pull system has been used for supply of antiretroviral drugs. This is a system where facilities order drugs according to their needs to fill-up stocks to the set maximum stock levels. What is supplied to the ordering entity is supported by the reported data in the monthly reports. As such quality of data is essential in the resupply of antiretroviral drugs. NASCOP has set the minimum and maximum stock levels for the different levels of the decentralization. Minimum stock level and maximum stock levels for satellite sites are one and two months, respectively and; one month and maximum three months for central sites, district stores and stand-alone sites. National stores have a minimum stock level of nine months and maximum stock level of fifteen months (NASCOP, 2009).

All health facilities offering antiretroviral therapy use national standardized data collection and reporting tools. The data collection tools are either manual or electronic with majority of the district, provincial and referral hospitals using electronic tools. Health facilities order drugs on a monthly basis as well as report on logistic data items that include quantity received, quantity issued, consumption, stock on hand and losses. Additional data collected and reported to the national level include patient numbers per regimen. Satellite sites are expected to report to the central sites by second day of every month while central sites and stand-alone by tenth day of every month (NASCOP, 2009). The average monthly reporting rate for antiretroviral drugs by health facilities has been over 90 per cent (NASCOP, 2013). Consumption is adjusted depending to the reporting rate to cater for non-reporting sites. The national stores process the orders and supply facilities within the same month (NASCOP, 2009).

Antiretroviral therapy has been provided free of charge to the patients in the public health facilities and faith based health facilities supplied by the two national agencies. Financing for antiretroviral drugs is mainly by the government of Kenya, Global Fund and President's Emergency Plan for AIDS Relief (PEPFAR). Previously, the Clinton Health Access Initiative (CHAI) was financing paediatric antiretroviral drugs but this was handed over to Global Fund in 2011 (NASCOP, 2012)

1.3. Forecasting for antiretroviral drugs in Kenya

In Kenya, forecasting for antiretroviral drugs has been done consistently for the last five years. Forecasting ensures uninterrupted supply of products in support of adherence to treatment and achievement of strategic plans in fight against HIV and AIDS. The forecasting process has been done through a consultative process where all relevant stakeholders are involved (NASCOP, 2013).

Morbidity-based method has been used to forecast demand for antiretroviral drugs in Kenya. Epidemiological data on number of people expected to receive treatment and that already on treatment is used for this method. The number expected to receive treatment

is computed on monthly basis to give a linear trend of a time series over forecast year. Program data, standard treatment guidelines, strategic plans, survey reports and evidence-based research findings are used as source of data for forecasts. Where data is lacking or is inadequate, assumptions are made. Assumptions are developed based on research findings from within the country, other countries and expert opinions. For morbidity-based forecasting method, it is assumed that treatment guidelines will be fully implemented and program strategies such as treatment coverage will be achieved as envisaged (NASCOP, 2012). Both prescribing and dispensing practices should conform to the guideline recommendations. Prescribing practices not changing as anticipated have been reported to affect forecast accuracy (Laila *et.al*, 2011). Assessment of prescribing practices as one of the early warning indicator for HIV drug resistance in Kenya revealed that 81% and 88% of health facilities adhered to standard treatment guidelines for prescribing to adults and children, respectively (Ngugi et al, 2013). Assessment of dispensing practices among practitioners in the private sector revealed that 58% of pharmacists did not dispense in accordance with the guideline recommendations (Dawn, 2007). Studies for dispensing practices for antiretroviral therapy in the public sector are limited

Forecasts for adult and paediatric patient population are developed separately. This is because adult and paediatric patient use different formulations and the dosing requirements are different. During forecasting, patients aged 0 to 14 years are categorized as paediatric while those above 15 years are categorized as adults during the forecasting process (NASCOP, 2011; NASCOP; 2012 and NASCOP, 2013). This age categorization is used internationally and locally in collection and reporting of indicators in HIV care and treatment patient monitoring systems (WHO, 2006). The monitoring and evaluation tools by NASCOP use this categorization and epidemic projections for Kenya are also based on this categorization (NASCOP, 2011 and NACC, 2014).

Forecasting for paediatric antiretroviral medicines has been challenging due to the complex nature of the Paediatric antiretroviral therapy. The challenges are due to the fact that children formulations and dosages change over time as the child grows, there are

limited paediatric fixed dose combinations thus necessitating the combination of different formulations, like liquid and solid to complete a regimen. Adult antiretroviral drug formulations are sometimes used for children where tablets are split to meet the dose requirements, unlike adult antiretroviral drugs that are packed in monthly dose schedules, packaging paediatric antiretroviral drugs in monthly dosages is challenging as dosing depends on weight of the child, most of the paediatric antiretroviral drugs are not palatable and liquid formulations may require use of high volumes and adherence in children is often a challenge due to many caretakers. This complexity poses a challenge in forecasting for paediatric antiretroviral (USAID/DELIVER PROJECT, 2009). In addition, data on antiretroviral drug formulations in use by children has been lacking. This is because data on weight and formulation in use has not been collected as routine program data.

Antiretroviral drugs approved for use in children are few compared to those for adults. However, the market has been highly fragmented in terms of paediatric formulations available (WHO, 2012). Both solid and liquid formulations exist for use in children. Initially, only liquid formulations were available. Their bulkiness and complexity in measuring dose by care givers affected adherence. Development of paediatric fixed dose formulations provided some relief from challenges caused by bulky liquid formulations. Transition from liquid formulations to fixed dose tablet formulation in Kenya took place in 2009 and 2010 (NASCOP, 2010).

Paediatric fixed dose tablet formulations are available as either duo or triple combinations. There are two types of paediatric duo fixed dose combinations tablet formulation; abacavir/lamivudine and zidovudine/lamivudine and one triple fixed dose combination of zidovudine/lamivudine/nevirapine. Due to the unavailability of triple abacavir fixed dose tablet formulation, children on first line requiring abacavir based regimen have to use nevirapine liquid formulation or nevirapine adult tablet formulation to complete the regimen. It is assumed that only few children use the nevirapine liquid formulation (NASCOP, 2013).

Antiretroviral drug options recommended for children depend on age, weight, exposure to nevirapine in prevention of mother to child transmission, a paediatric indication and an appropriate formulation (NASCOP, 2011). Weight has been used to determine dose requirements in children. Therefore weight is a key consideration in forecasting for antiretroviral drugs. In Kenya, data on weight has not been part of routine data collected by NASCOP. As such, assumptions are made to guide the forecasting process. Three weight categories (8, 12 and 20Kg) have been assumed for children on first line treatment and two weight categories (15 and 20Kg) those on second line treatment (Table 1). It is assumed that children on second line are older children who have been on first line treatment for some time and therefore expected to have higher weights thus the difference for children on first and second line. The assumed weights have been based on judgment guided by dosing chart for children in the national standard treatment guidelines.

Table 1: Assumptions on proportion of children at various weight categories

	First line regimen			**Second line regimen**	
	8 Kg	**12 Kg**	**20 Kg**	**15 Kg**	**25 Kg**
2010 report	15%	35%	50%	50%	50%
2011 report	6%	38%	56%	50%	50%
2012 report	14%	16%	65%	50%	50%

The assumed weights have been used to develop the forecasting decision tree (Figure 2). The decision tree is informed by past trends as well as experts' opinion. To get the proportion of children on a particular drug, the allocated proportions are multiplied (NASCOP, 2012). For instance, from the 2012 report (Table 1) the proportion of children assumed to weigh 8 Kg was 14 per cent. To determine the proportion of children on first line regimen zidovudine + lamivudine + nevirapine and assumed weigh 8 Kg, decision tree (Figure 2) is used. To apply the decision tree, proportion of patients on first line (A_1), proportion of children on zidovudine (B_2); proportion of children on nevirapine (C_4); and proportion of children assumed to weigh 8 Kg are multiplied as follows: A_1%

x B_2% x $C_{4\%}$ x 14%. Lamivudine is ignored in the calculation as it exists as a fixed dose combination with zidovudine or zidovudine and nevirapine. Once this multiplication is done for all the ARV products, the data is entered into the forecasting software package.

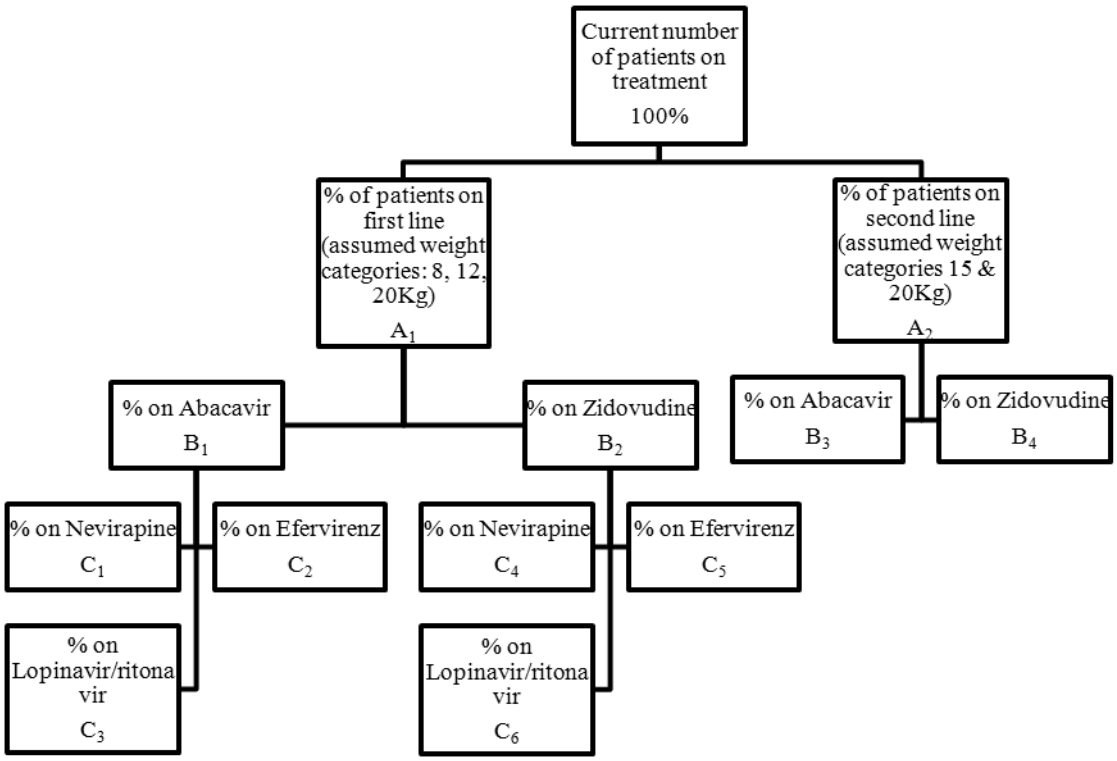

Figure 2: Demonstration of a Forecasting Decision Tree

An analysis of the weight categorization using dosing chart in the Guideline for Antiretroviral Therapy in Kenya, 4th edition, 2011 (appendix 1) revealed that the weight can broadly be categorized into six weight bands. 3 to 5.9 Kg, 6 to 9.9 Kg, 10 to 13,9 Kg, 14 to 19.9 Kg, 20 to 24.9 Kg and above 25 Kg. This is guided by the fact that children in the same weight band have the same dosage requirements. However, average weights assumed during forecasting seem to ignore this categorization. Example of assumptions used for year 2010, 2011 and 2012 forecasting reports are summarized in Table 1. For children 25Kg and above, it is assumed that they will use adult formulations. However, the proportion of children using adult formulations remains unknown (NASCOP, 2013).

Inconsistencies in assumptions made on proportions of children on various weight categories; 8, 12, 20 Kg (Table 1) is enough evidence that there exists some information gap.

Forecasts for antiretroviral drugs have been developed using various software packages including Microsoft Office Excel. The software package mainly used for developing forecasts for antiretroviral drugs is called Quantimed. Quantimed is a software package developed by Management Sciences for Health's Rational Pharmaceutical Management Plus Project. It designed to develop quantity and costs of products. Quantimed can be used to quantify products using three forecasting methodologies; consumption based method, morbidity based method, and adjusted consumption based method (MSH, 2006). These methods are discussed further in Chapter 2.

CHAPTER 2: LITERATURE REVIEW

2.1. Introduction to forecasting

Forecasting is the process of estimating required quantity of selected products. Forecasts are generally done to minimize planning uncertainty (Raja and Mohammad, 2005). Forecasting has also been defined as the ability to predict the future. According to Jain and Malehorn (2005), forecasting refers to "numerical estimates by date of the future that can be achieved with a specified level of support". It is further argue that reproducibility of the predictions is important through a system of logic. Forecasts depend on the future resembling the past; the closer the resemblance, the more accurate the forecast. A combination of forecasting and supply planning is referred to as quantification. Supply planning is the process of adjusting quantities forecasted to determine quantities to procure and time of delivery of the products. The steps in quantification process are as outlined in Figure 3. The output derived from quantification exercise include quantity of required commodities, funding needs and gaps for procurement of the required commodities, sources of the available funds, timing of funding commitments and expected ordering and/or delivery of products. Quantification report is used as an advocacy tool for funding and other resources such as storage facilities for drugs and human resource to deal with the huge amounts of funds and commodities (FPLM, 2000).

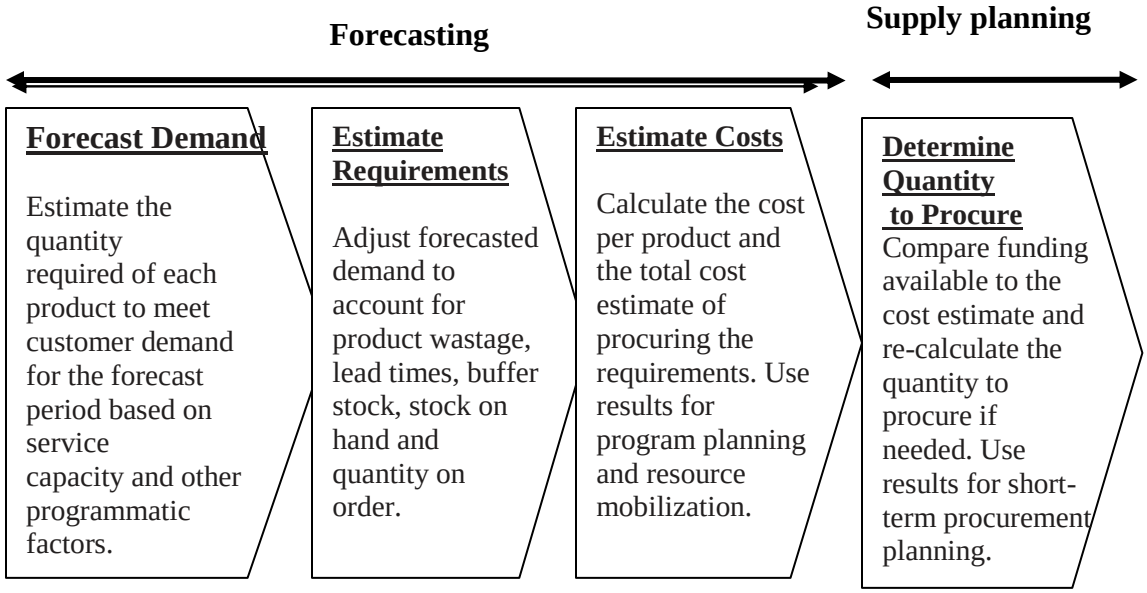

Figure 3: Steps in Quantification process (adopted from Claudia and Chandani, 2006)

Forecasts provide information on future demand and therefore form a basic input in the decision making processes of operations management. According to Jain and Malehorn (2005), the mission of forecasting is to provide a reasonable future demand estimation upon which organization can draw strategic plan. Demand forecast is useful in determining how much capacity or supply is needed to meet demand. Expected level of demand and forecast accuracy are the two important aspects of forecast. The expected level of demand can be a function of some structural variation, such as a trend or seasonal variation while forecast accuracy is the potential size of forecast error and is a function of the ability of forecasters to correctly model demand, random variation, and sometimes unforeseen events (Stevenson, 2009). Forecasts are made for a defined time horizon which can be short, intermediate of long term (Stevenson, 2009). Forecasting differs from scenario planning. Scenario planning is a systemic method for creative thinking about possible complex and uncertain futures. It is a technique for decision making in circumstances of uncontrollable and irreducible uncertainty. It provides conservationists a method for developing more resilient conservation policies (Peterson et.al, 2003). On the other hand, forecasting focuses on a dominant view of the future market and business environment has a time horizon for achievability of forecast. Results in a plan are based on a dominant set of market assumptions and has a financial orientation as opposed to just qualitative descriptive (Raspin and Terjesen 2007).

2.2. Forecasting approaches and techniques

Forecasting approaches have been classified using various dimensions. According to Stevenson (2009) there are generally two approaches to forecasting; qualitative and quantitative. Under each approach, there are various forecasting techniques. Qualitative approaches are based on human judgment and opinions. They are subjective and non-mathematical. However, they bear the strength of being able to incorporate latest changes in the environment. The main weakness of qualitative method is that it can bias the forecast thus reducing forecast accuracy. Quantitative approaches are objective and mathematical. They rely on existing historical data to make projections or the

development of associative models that attempt to utilize causal or explanatory variables to make a forecast. Quantitative methods have the strength of being consistent and objective.

Stevenson (2009) further describes three main forecasting techniques: (i) judgmental forecasts which rely on analysis of subjective inputs obtained from source such as customer surveys, the sales staff, managers and panels of experts; (ii) time-series forecasts which use historical data to project the future. In time series, various models are used. Some models attempt to smooth out random variations in historical data; others attempt to identify specific patterns in the data and extrapolate those patterns into the future; (iii) associative models use equations where explanatory variables are used to predict demand. Braekkan (2010) demonstrated that judgmental forecasting is characterized by biases inherent in human decision making and people's inability to process information in large quantities. However, the technique is recommended where there is limited access to quantifiable information, highly uncertain environments and limited access to software.

Armstrong (2001) classifies forecasting approaches as judgmental and statistical. Techniques based on judgment are mainly qualitative and include role playing, intentions and experts opinions. The accuracy of forecasts based on experts' opinion can be improved through the use of structure approaches, such as the Delphi procedure (Stevenson 2009). Techniques in the statistics approach include univariate and multivariate methods. These methods are based on time series approach. Little evidence exists on benefits derived from multivariate method. Univariate methods use extrapolation where historical data is used to predict the future. Exponential smoothing is the most popular and cost effective of the extrapolation methods (Armstrong and Brodie, 1999).

Forecasting approach is also classified as either top-down or bottom-up approach. In top-down approach, forecasts are made for a group such as patient group and drug class. The group is then broken further into lower level of individual item forecast. Methods used to break down group forecast into individual items include equal share across all

components, components share based on historical demand and component share based on forecast demand. In bottom-up approach, each of the lower level items is separately forecasted and the forecast are then aggregated to a group forecast (Jain and Malehorn, 2005).

Raspin and Terjesen (2007) categorizes forecasting into modes. In this approach, three modes are identified: formal, focused and intuitive forecasting. These forecasting modes are based on two major dimensions of forecasting activities: formality and breadth. In formality dimension, managers adopt a formal and systematic approach to forecasting. There is deliberate effort to search for information using pre-determined methods and mediums. Breadth dimension refer to the broadness of gathering strategic information for forecasting. With high breadth, many types of information are gathered and broad trends are discerned. Formal forecasting mode use external secondary information and thus broad range of forecasting information can be obtained. Focused forecasting mode is similar to formal forecasting in terms of formality of approach. However, focused forecasting is more necessitated by an emerging specific need due to change in the environment. In intuitive forecasting mode, conversational and anecdotal evidence is used. Personal sources both internal and external are used as opposed to external secondary information. Formal forecasting mode has high formality and breadth, focused forecasting mode has high formality but low breadth while intuitive forecasting has low formality and breadth.

Forecast models are stochastic in nature where the probability of future value is computed. In stochastic models can either be stationary or non-stationary. Fir stationary models, processes are assumed to remain in statistical equilibrium with probability properties that do not change over time. In such cases, constant mean level with constant variance is assumed. In non-stationary models, no constant mean level over time is assumed. Stochastic models are needed if forecast is to be considered optimal and in control in time series (Box *et.al*, 2008).

2.3. Forecasting approaches for health commodities

A combination of various forecasting approaches and techniques are used in forecasting for pharmaceutical products. This is because forecasting is more of imagining what the future holds rather than placing models in spreadsheets (Cook, 2006). In addition, a combination of objective data used in quantitative techniques and use of personal judgments in qualitative techniques reduces bias that may be caused by one technique (Stevenson, 2009).

In the health sector, forecasting methodology is classified from the dimension of type of data. The main types of data used to forecast for health products are data on consumption and on morbidity. As such there are two main forecasting methods applied for health products: consumption based method and the morbidity based method (Cook, 2006). These two methods are used to forecast for new potential patients and for the existing patients (Cook, 2006). According to Raja and Mohammed (2005), adjusted consumption-based method can be considered as a third method. This is a mix of the two methods and is used when neither data for consumption or morbidity methods is particularly reliable. Choice of the forecasting method is based on quality and usefulness of the data available (USAID/ DELIVER PROJECT, 2008). In addition, different forecasts require differing types and/or levels of data both at the input and output level. Lack of sufficient data to predict the future necessitates combination of both consumption and morbidity based methods to allow comparison of the forecast output (Cook, 2006).

The consumption-based method uses data on product consumption to estimate the future consumption of each product for a specified period of time. In this method, historical consumption trends are analyzed and assumptions made about factors expected to influence the demand for individual products during the specified time (USAID/ DELIVER PROJECT, 2008). On the other hand, the morbidity-based method uses existing best-case scenario approach where epidemiological data showing shifts in disease incidence with the number of people expected to receive treatment is used and assumptions are made that treatment guidelines will full be implemented (Adesina, 2010). Service, morbidity and demographic data and programmatic targets are used as

starting points in the morbidity-based method. This information in addition expected product unit usage per patient is used to get the consumption forecast (USAID/ DELIVER PROJECT, 2008).

Morbidity based method uses a top-down approach to forecasting (Figure 4). According to Cook (2006), forecasting in the pharmaceutical industry can be categorized as either patient or prescription based methods. The patient based method is a morbidity-base in method, the theoretical maximum number of patients with a given disease state is first defined and then the market is filtered to arrive at the number of patients who currently are receiving therapy. Prescription based method uses a different approach where first the number of patients currently receiving therapy is established. This forms the baseline and is expanded to reach the theoretical maximum. Cook (2006) argues that the patient-based method is the preferred method because it allows the user to identify the theoretical maximum for a product and the pressure points along that way that are constricting the market. On the other hand, he argues that users of prescription-based method prefer the method because current measures of treatment activity are more accurate than epidemiology data and that symptomatic and diagnosis rates are difficult to obtain. In addition, prescription-based forecaster argues that use of the data related to current drug usage as the starting point is a stronger keystone upon which to build the forecast than the epidemiology data. Regardless of the method, the same information is required with the only difference being the starting point.

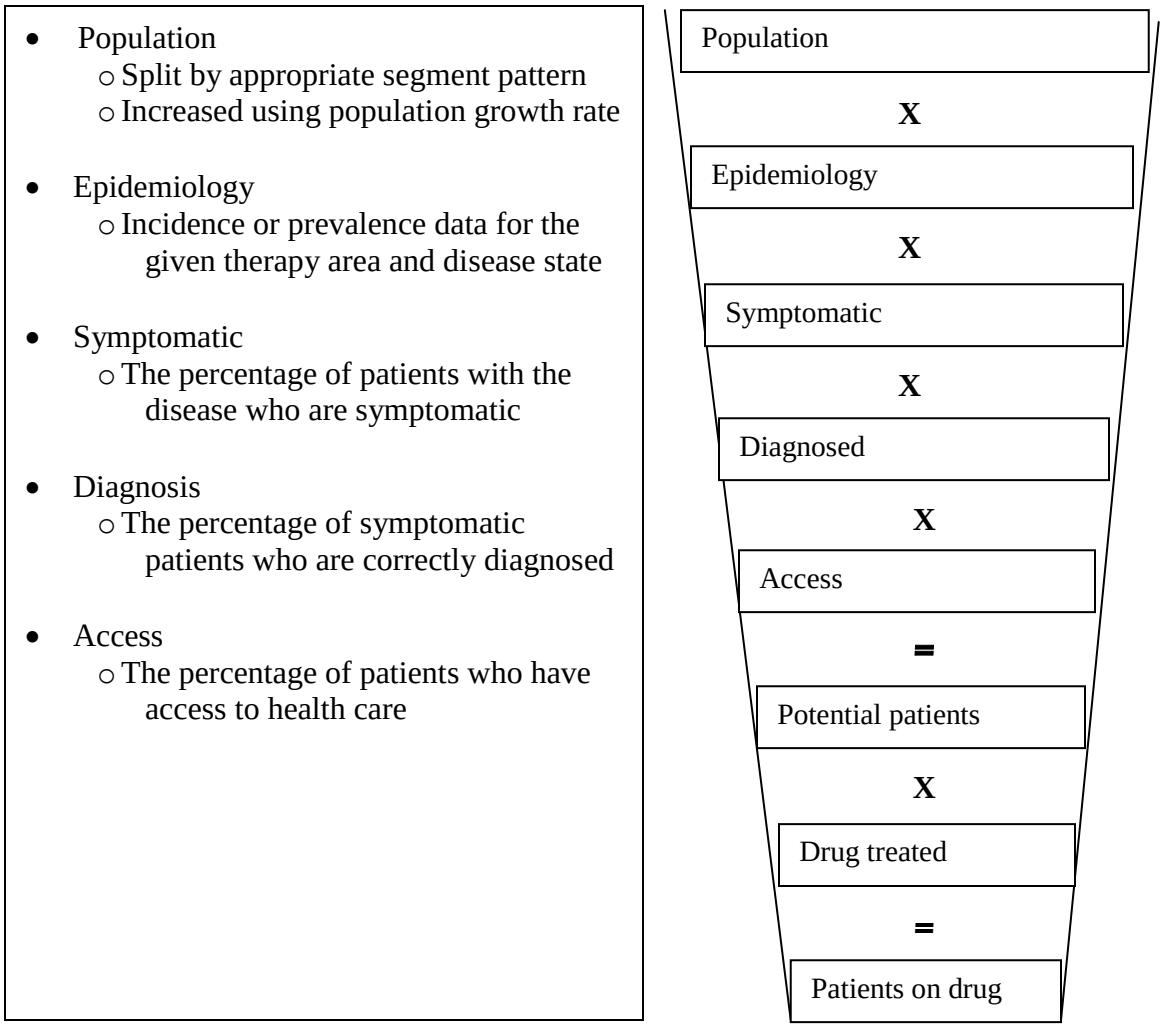

Figure 4: Morbidity based methods algorithm (adopted from Cook, 2006)

Regardless of the approach or technique used, forecasts exhibit certain common features. Forecast generally assumed that the same underlying causal system that existed in the past will continue to exist in the future; forecasts are not perfect and discrepancies between actual results and predicted values exist; forecasts for groups of items tend to be more accurate than forecasts for individual items and forecast accuracy decreases as the time horizon increases (Stevenson, 2009).

A properly prepared forecast should exhibit elements of timeliness; accuracy; reliability; meaningful units; easy to understand and use; cost-effectiveness and should be in writing.

Time in forecast is important as adequate time is required to respond to the information contained in a forecast. Therefore, forecasting horizon must cover the time necessary to implement possible changes. Forecast errors should be stated as this helps forecast users to plan for possible errors and provide basis for comparing alternative forecasts. The forecast should be reliable and therefore should work in a consistent manner. The technique and process should give consistent results. Inconsistencies may erode users' confidence in the forecast output. The forecast should be expressed in meaningful units. Financial planners need to know how much funds are required and this should be expressed in a standard currency while operations managers need to know how many units need to be ordered. A forecast that is documented allows objective basis for evaluation as well as reference for future forecast processes (Stevenson, 2009).

2.4. Factors that affect forecast accuracy

Accuracy refers to the extent to which a measurement or an estimate based on measurements agrees with true the value (Kirch, 2008). Accuracy has also been defined as the absence of error. As the error gets closer to zero percent, the more accurate a measure becomes and vice versa. Positive errors result when the forecast is too low while negative errors result when the forecast is too high forecast (Stevenson, 2009). According to Winklhofer and Diamantopoulos (2002) accuracy is synonymously used with forecast performance. To understand the concept of forecast accuracy, it should be divided into potential accuracy and achieved accuracy. Potential accuracy refers to the maximum obtainable accuracy for a given forecast situation, that is, accuracy threshold might be accurate for an organization in a volatile market, but inaccurate for one in a stable market (Winklhofer and Diamantopoulos, 2002).

Forecast accuracy is further defined as a measure of how closer the forecasted quantities correspond to the quantities that are actually consumed. In real life, the forecasted situation is often times different from the actual situation. However, if the differences between forecasts and actuals are significant, the reasons should be investigated (Laila

et.al, 2011). Forecast accuracy is said to be a function of the forecaster's ability to correctly model demand, random variation as well as unforeseen events (Stevenson, 2009). According to Walther and Moore (2005), accuracy is the overall distance between the estimated value and the true value. It is stated that accuracy is a factor of both bias and precision which when combined define the performance of an estimator. It is further stated that the overall ability to make accurate point estimation is worse if an estimator is more biased and the less precise. Forecast accuracy can therefore be evaluated in terms of size and direction of an error. Size of a forecast error is the difference between the actual value and the forecasted error while the direction of the error is the degree by which forecast model over or under estimates the actual values (Lawrence and Klimberg, 2011). The latter is referred to as bias. According Winklhofer and Diamantopoulos (2002), accuracy and bias relate to the magnitude and direction of the forecast error, respectively.

Monitoring forecast accuracy should be part of the critical activities by managers that enables swift corrective action to avoid imbalance of supply. Periodic review of forecasting accuracy show important patterns such as periods of accuracy and inaccuracies and this may potentially lead to forecasting and/or review process changes (Laila *et.al*, 2011). Tracking forecasts is a means of checking how well the actual observations compare with forecasted values. The primary goal of forecast monitoring is determinations of if and when forecast should be reviewed (Jain and Malehorn, 2005). Winklhofer and Diamantopoulos (2002) argued that "forecasting should not be judged on the simple accuracy criterion but its role should be enlarged and be concerned with its ability to improve the decision making within organizations''.

Several factors have been attributed as determinants of the accuracy of forecasting. These include good logistics information management system that support availability of quality data, well trained and motivated staff, a rigorous and regular multiple data sources review, use of large and diverse forecasting teams. In healthcare system, high forecasting errors for antiretroviral drugs have been attributed to delays in implementation of policy changes in line with forecast, prescribing practices not adjusting as anticipated, the complexities of pediatric antiretroviral therapy, lack of insufficient data for use in

forecasting, unpredictability of timing of fund disbursement and in-country distribution challenges (Laila *et.al*, 2011). Reliable logistics database have been cited as one of the primary requirement for accurate forecasts. In addition, demographic data should be examined and used where necessary (FPLM, 2000). Forecasting methods is also an important contributing factor to forecast accuracy. Use of two different forecasting methods is important to improving forecast accuracy since it allows comparison of forecast output (Raja and Mohammad, 2005).

Stevenson (2009) states that the possible sources of forecast errors may be due to inadequacies in the model used such as omission of an important variable, shift in the variable that the model cannot deal with and/or appearance of new variable; irregular variations may occur due to several phenomenon such as temporary shortages; incorrect use of forecasting technique or misinterpretation of results; and random variations, that is, the inherent variation that remains in the data after all causes of variation have been accounted for. A forecast is considered to be in control if errors exhibit only random variations. Randomness of errors is an indication that errors cannot be predicted and they do not exhibit any pattern. Where forecast errors are not random, it means the model used in forecasting is inadequate and a better one needs to be developed. Forecast errors are considered random if no patterns are exhibited; there is constant variance over time; errors points do not persistently stay either above or below a centerline for a large number of consecutive periods; and data points do not oscillate rapidly above or below the centerline. If errors are non-random, investigations should be carried out at on the source and how to correct the problem (Lawrence *et. al*, 2009).

Demand forecasting for pediatric antiretroviral drugs is more complex than for adult antiretroviral drugs. This is because the level of detail required in paediatric ARV drugs is greater. The key factors to be considered in forecasting for paediatric ARVs include: combined use of liquid, capsule, and tablet formulations; formulations need to be changed and dosages need to be adjusted over time as the child grows; adult ARV drug formulations are used for children and may need to be cut or crushed to meet pediatric dosing requirements; patient adherence is difficult because of the complicated dosing, the

large volumes, and the foul taste of some formulations, as well as the children's inability to swallow pills; selection and availability of ARV drug formulations for children are limited; and paediatric ARV drugs are not packaged according to dosing regimens, which complicates prescribing and dispensing (Claudia and Chandani, 2006).

2.5. Measuring forecast accuracy

Forecasts are unlikely to be 100 per cent accurate. Depending on the forecast model used, forecasts may be slightly higher or less than the actual value. A good practice in forecasting is to set upper and lower limits upon which the forecast errors monitoring can be based on (Lawrence and Klimberg, 2011). Stevenson (2009) states there always exists random variation due to some residual error despite the attempt to account for all other factors. It is therefore advisable to always include an indication of the extent to which the forecast might deviate from the actual value so as to provide the forecast user with a better perspective on how far-off a forecast might be.

Size of the forecast errors is measured using a forecast error metric. This is a mathematical measure used to evaluate forecast bias and accuracy. Commonly used metrics for forecast accuracy include the mean absolute deviation (MAD); the mean squared error (MSE); and the mean absolute percent error MAPE). MAD is the average absolute error, it is the easiest to compute and it weights all errors evenly. However, it does not put errors into perspective and it is not easily understood. MSE is the average of squared errors; it weights errors according to their squared values and thereby giving more weight to the larger errors. MAPE is the average absolute percent error and it weights errors according to relative errors (Stevenson, 2009).

MAPE is the measure of choice where there is needs to put the errors into perspective. These measures are to compare the accuracy of alternative forecasting methods and to track error performance over time to decide if attention is needed. MAPE should be used when there is a need to put errors in perspective (Stevenson, 2009). MAPE is the most commonly used measure to determine forecast accuracy (Rayer, 2007). Percentage errors

have the advantage of being scale independent, and can be used to compare forecast performance across different data sets. However, they have the disadvantage of being infinite or undefined (Hyndman and Koehler, 2006). As a rule, the smaller the MAPE value, the higher the accuracy of the forecast (Asrah and Djauhari, 2013). A scale of judgment of forecast errors based on MAPE was developed by Lewis in 1982. According to the scale, forecasts with MAPE of 10%, 11% to 20%, 21% to 50% and 51% and above are classified as highly accurate, good forecast, reasonable forecast and inaccurate forecast, respectively (Lawrence *et.al,* 2009).

Bias or direction of errors can be monitored using visual inspection tools and statistical test. Visual inspection tools used for detecting non-randomness include tracking signal and control charts. A tracking signal chart is based on ratio of cumulative forecast errors to the corresponding value of mean absolute deviation. The resulting values are compared to predetermined limits. The limits range between ±3 to ±8 and they are established based on experience and judgment. For control charts, individual forecast errors are computed instead of cumulative errors. The limits are multiples of estimated standard deviation of forecast which is computed by getting square root of mean squared error. Standard deviations of 2 or 3 are often used to set the limits. In both tools errors plotted over the monitoring period with a centerline of the chart represents an error of zero (Shim and Siegel, 1999; Stevenson, 2009).

Unit root tests are used as the statistical tests that test for randomness of forecast error in a time series setup. The null hypothesis is that errors or data is non-stationary in a time series while alternative hypothesis is that errors are stationary. Parametric unit root tests applied include Dickey-Fuller and Philipps-Perron tests (Ullrich, 2009). Run test, a nonparametric test is also used to test for stationary. In the test, it is assumed that data points do not persistently stay either above or below a centerline for a large number of consecutive periods and neither oscillate rapidly above or below the centerline. If errors are non-random, investigations should be carried out to find the source and how to correct the problem (Lawrence *et.al,* 2009).

Any forecast with errors that are persistently above or below a trend line in the time series are considered to be biased. In addition, forecast with errors that exhibit trends and patterns such as seasonality and cycles are also considered inadequate (Stevenson, 2009). A good forecast is one devoid of both inaccuracies and bias (Brandimarte and Zotteri, 2007).

Forecasting is characterized by a complex nature where existing variables makes it almost impossible to correctly predict future values on a regular basis. In addition, random variation exists that cause some residual error in in situations where all possible factors necessary for forecasting have been accounted for. It is important therefore to include an indication of the extent to which the forecast might deviate from the value of the variable that actually occurs. These provide a better perspective on how far off a forecast might be (Stevenson, 2009). Laila *et.al* (2011) used a threshold of 25 percent error (over- and under-forecast) as a measure of being accurate, to evaluate forecast accuracy of antiretroviral drugs in four African countries. In Zimbabwe, a forecast errors threshold of 25 per cent was piloted over one year as one of the pharmaceutical supply management indicator. Actions were taken to correct the errors. It was noted that the errors reduced over the quarters (WHO, 2011).

The sole aim of forecasting endeavor is to have error free and unbiased forecasts. Forecast inaccuracies are associated with substantial costs. Over-forecasting can lead to lost opportunities due to tying funds in over-forecasted products and loss due to expiries. Under-forecasting can lead to lack of clients' satisfaction, loss of goodwill and waste of time and funds in planning for the gap (Leong, 2012).

2.6. Forecast accuracy for antiretroviral drugs

Few studies and reports exist on forecast accuracy for health commodities. In a study carried out across four countries; Zambia, Ethiopia and two others (X and Y) that opted to remain anonymous, forecast were reported to be inaccurate. Calculation of Mean Absolute Percentage Errors (MAPE) by combining forecasts and actual consumption of

all the ARV products per country revealed that country X had a MAPE of between 75 to 275%; MAPE for country Y was 100 to 2000%; Ethiopia had MAPE of 220 to 340% and Zambia had MAPE of 20 to 180%. Greater forecast errors were observed with pediatric antiretroviral drugs than those for adult in three countries. MAPE for paediatric antiretroviral drugs reached a high of 520% for country X, 3800% for country Y and 270% for Zambia. Reasons cited as contributing factors to the forecast inaccuracies included; prescribing practices not changing and failure of drugs to be delivered as anticipated; and poor quality data used for forecasting. In country X an improvement in forecast accuracy was observed over time. This was attributed to the countries efforts to routinely collect data on weight and using it to review consumption patterns during forecast monitoring as well as in annual forecasting exercise (Laila *et.al,* 2011).

In Zimbabwe, mean absolute percentage error (MAPE) was includes as one of the indicators in pretesting of the pharmaceutical supply management indicators. The indicator was monitored on quarterly basis and necessary adjustments made to the forecast to correct the error. It was noted that the MAPE reduced over the quarters thus leading to improved accuracy (WHO, 2011). As such periodic monitoring of forecasts is critical to an organization management as it provides avenues to detect errors and make the necessary adjustments.

Monitoring forecast accuracy has not been a routine practices for health commodities in Kenya. Despite forecasting for antiretroviral drugs being conducted annually for over five years consecutively, information on forecast accuracy is lacking. According to Laila *et.al* (2011), achievement of forecast accuracy can be attributed to rigorous review process. Other factors that contribute to forecast accuracy include use of experienced staff and institutionalization of practices; use of multiple data sources and availability of robust logistic management information systems that provide quality data. Laila *et.al* (2011) further state that high MAPE are observed when there are delays in implementation of policy changes, where prescribing practices do not change as anticipated, and where discrepancies in available data for use in forecasting exist. As

such it is important to determine the forecast accuracy for antiretroviral drugs in Kenya to address the existing gap.

2.7. Problem statement

The National HIV and STI Control Program (NASCOP) carry out national forecasting for antiretroviral drugs and other products for HIV testing, prevention, care and treatment on annual basis. This process has been carried out consistently on annual basis since 2009. The program uses the demand forecasting to plan for procurement in an effort to ensure uninterrupted supply of products as well as a tool for resource mobilization (NASCOP, 2012).

Demand forecasting for both adult and paediatric antiretroviral drugs is done using morbidity-based forecasting method. Accuracy of forecasts heavily relies on quality of data in terms of completeness and reliability. Data availability is also crucial for forecast accuracy as unavailability of data leads to use of assumptions. Heavy reliance on assumptions has been one of the contributing factors to forecast inaccuracy. The accuracy of forecast using the morbidity-based method depends on the degree to which standard treatment guidelines are adhered to and on the availability of prescribed drugs for dispensing. As such both prescribing and dispensing practices should conform to the guideline recommendations. Prescribing practices not changing as anticipated have been reported to affect forecast accuracy (Laila *et.al*, 2011). In Kenya, 81% and 88% of health facilities offering antiretroviral therapy were found to adhered to expected prescribing practices for adults and children, respectively (Ngugi et al, 2013). Assessment of dispensing practices among practitioners in the private sector revealed that 58% of pharmacists did not dispense in accordance with the guideline recommendations (Dawn, 2007). Studies for dispensing practices for antiretroviral therapy in the public sector are limited. Due to availability of an array of formulations (both adult and paediatric) for dispensing to children, the choice of drug dispensed to children is at the discretion of the

dispensing staff in consultation with the child's care giver. There is therefore mixed use of drugs formulated for use by children and adults among children.

Forecasting for pediatric antiretroviral drugs is more complex than for adult antiretroviral drugs. Factors that contribute to these include combined use of different ARV formulations; changes in child's weight over time that may necessitate change of formulations and dosages over time; and drugs formulated for use in adult patients are used by children (Claudia and Chandani, 2006). In Kenya, forecasting for paediatric antiretroviral drugs has been reported to have large discrepancies from the actual demand. A review of stock analysis done on monthly basis by NASCOP to determine national monthly consumption and stock levels revealed overstocking or under stocking of majority of the paediatric antiretroviral drugs (NASCOP, 2013).

The dosing for paediatric antiretroviral medicines is based on weight. As such, weight is a crucial data item that needs to be considered in forecasting for paediatric antiretroviral drugs. Dosing charts are provided in the standard treatment guidelines as well as in form of job aids to ease prescribing and dispensing of antiretroviral drugs. According to the dosing chart, children from 9 Kg can use some antiretroviral drugs formulated for adult use. This requires splitting of the tablets to acquire paediatric dosage (NASCOP, 2011). However, in the forecast it is assumed that all children less than 25 Kg use the paediatric formulations (NASCOP, 2012). An information gap exists on the best weight categories to be used for calculation of dosages for children aged between 0 to 14 years.

Health facilities report drug consumption on monthly basis to the national level where the consumption is aggregated per drug (NASCOP, 2009). These consumption data is not disaggregated into adults and children thus posing a challenge of determining what proportion of children use drugs formulated for adults. The data on drug consumption among children is therefore inadequate to inform annual forecasting for paediatric antiretroviral drugs.

Based on the above discussion, there is need to determine the accuracy of forecast for paediatric antiretroviral drugs and determine factors that may affect the accuracy from the dispensing records as well as from the dispensing staff perspective.

2.8. Research question

This study aims to answer;

1. What is the accuracy of the paediatric antiretroviral drugs forecast?
2. What is the relative proportion of children within various weight categories and on various regimens and formulations of antiretroviral drugs?
3. Are there within-individual and between-individual changes over time with regards to weight, regimen and formulation;
4. What are possible factors that influence the dispensing practices for paediatric antiretroviral drugs?

2.9. Justification of the study

Forecasting is an important activity in supply chain management. It supports uninterrupted supply of essential goods and services as well as support planning by an organization management. Management of HIV infection calls for uninterrupted supply of products due to the dynamic nature of the virus. Uninterrupted supply therefore is essential in supporting adherence and compliance of antiretroviral therapy.

NASCOP conducts forecasting for antiretroviral drugs on annual basis. However, the forecast accuracy is neither determined nor monitored. Accuracy and control are vital aspect of forecasting. Forecast errors can lead to interrupted supply of essential health products which can have untoward effects on management of a disease condition especially HIV infection. Accuracy should be considered as a factor when planning for

supplies, in choosing among different forecasting techniques as well as cost associated with the forecasting exercise. Routine monitoring of forecasts accuracy should therefore be adopted as a key activity of an organization.

Forecasting for paediatric antiretroviral drugs in Kenya has been characterized by complex nature of special requirements and existing challenges in paediatric antiretroviral therapy. Dosing in children is based on weight and therefore there is no standard dose or category of doses that can be applied to all children. NASCOP lacks data on appropriate weight to use to guide the forecasting process. As a result, 8, 12, 15, 20 and 25 Kg weights have been assumed to be best for use to calculate quantity of drugs required. Assumptions are made on proportion of children thought to have these weights. In addition, appropriate formulations are lacking for children. Unlike for adults, only a few fixed dose combinations exist for use among children. Both solid and liquid formulations also exist for use among children. To make a complete regimen, a combination of at least two drugs has to be made. Some children are also thought to use split tablets of adult formulations. Studies on relative proportion of children with different weights and using various formulations are lacking.

2.10. Study objectives

The overall objective of the study was to evaluate forecast accuracy for paediatric antiretroviral drugs in Kenya and assess determinants of forecast accuracy.

The specific objectives of the study were;

1. Establish the forecast accuracy for paediatric antiretroviral drugs by NASCOP for the period July 2010 to June 2013.

2. Determine the relative proportions of children within various weight categories and on various antiretroviral regimen and formulations at Mbagathi District Hospital.

3. Determine within-individual and between-individual changes over time with regards to weight, regimen and formulation.

4. Identify factors that influence choice of antiretroviral drugs formulations dispensed to paediatric patients at Mbagathi District Hospital from the pharmacy staff perspective.

2.11. Study hypotheses

This study hypothesized that

i. There was no actual difference between actual and forecast consumption of antiretroviral drugs.

ii. Dispensing practices at the study site adhered to the recommended formulations as per the current Guideline for Antiretroviral Therapy in Kenya, 4th edition, 2011.

2.12. Anticipated output and significance for the study

Forecasting is a basic input in the decision processes of operations management. This is because they provide information on future demand. The primary objective of the operations management is to have a good balance between supply and demand. As such, forecast accuracy is a vital aspect of forecasting as it provides important information to the management. Antiretroviral drugs availability and access is crucial to management of HIV infection. HIV infection treatment interruption due to unavailability of drugs, inaccessibility and non-adherence can lead detrimental effects of treatment failure which is more difficult and costly to manage. Accurate forecast is thus key to ensuring adequate allocation of the scarce resources, timely procurements and delivery of products in an effort to have uninterrupted supplies.

The anticipated output of the study is forecast accuracy for paediatric antiretroviral drugs, the relative proportions of children within various weight categories and on various

antiretroviral regimen and formulations as well as potential factors that influence dispensing practices that may have an impact on the forecast accuracy for paediatric antiretroviral drugs.

The findings of this study are intended to inform the ministry of health and the relevant stakeholders on forecast performance in terms of accuracy, and potential factors that may impact on the forecast accuracy. It is hoped that information on forecast accuracy for the period covered by the study will provide insight to the ministry of health and relevant stakeholders on the situation of the forecast for the paediatric antiretroviral drugs.

CHAPTER 3: METHODOLOGY

3.1 Research Design

Different research designs were employed to achieve the objectives of the study. For the first objective, forecast accuracy was determined by computing Mean Absolute Percentage Errors.

A retrospective longitudinal design was employed for the second and third specific objectives. These objectives aimed to determine the relative proportion of children within various weight categories and on various regimens and formulations of antiretroviral drugs and; determine the within-individual and between-individual changes over time with regards to weight, regimen and formulation. The objectives entailed collecting repeated measurements on study cohorts from ART electronic dispensing tool for a three year's period: July 2010 to June 2013. Measures were thus collected repeatedly on the same variables on each sample unit over the study period. Both continuous and categorical variables were collected.

The fourth objective was to determine the factors considered by dispensing staff when dispensing to children on antiretroviral therapy. This objective was achieved through in-depth interviews of dispensing staff as key informants.

3.2 Study site

The study was carried out at the National AIDS/STI Control Program (NASCOP) and Mbagathi District Hospital. Data for the first objective was obtained from NASCOP while data for second to fourth objectives was obtained from Mbagathi District Hospital. Mbagathi District was selected because it is one of the facilities with high number of paediatric patients on antiretroviral therapy, the pharmacy uses ART electronic dispensing tool. It was also less costly to carry out the study in the facilities as no out-of-

home costs were incurred. The facilities may not be representative of all health facilities in Kenya and therefore information gathered would give a baseline for a larger study.

NASCOP is a unit within the Ministry of Health mandated with the responsibility of HIV infection prevention, care and treatment. NASCOP runs various programs namely anti-retroviral therapy for both adults and children; HIV infection prevention of mother-to-child transmission; post exposure prophylaxis against HIV infection; HIV infection testing and counseling; basic education and dissemination of information about HIV infection; male circumcision; development and dissemination of information about behaviour change and mass media campaigns, and treatment for sexually transmitted infections.

The key drug and non-drug products managed by NASCOP include antiretroviral drugs, HIV infection test kits, reagents for measuring CD4 cells and viral load levels, nutrition supplements, drugs for prevention and treatment of opportunistic infections and other products for HIV infection prevention such as condoms and circumcision kits. Antiretroviral drugs are used in antiretroviral therapy, post exposure prophylaxis and prevention of mother-to-child transmission. Antiretroviral drugs play a big role in reducing incidences and prevalence of HIV infection as well as improving the lives of people living with HIV infection.

To ensure products availability and access, NASCOP in collaboration with relevant stakeholders has been carrying out forecasting and supply planning of products on annual basis. NASCOP in collaboration with procurement, warehousing and distribution agencies operate logistic management information system where data on consumption and patients are routinely collected and aggregated. Microsoft excels spreadsheets on aggregated national consumption and patients are updated on monthly basis while forecasting reports are developed annually.

Mbagathi District Hospital is one of the two district hospitals in Nairobi County. From 1995 to 2012, Mbagathi District hospital was the only district hospital in Nairobi Province, now Nairobi City County. Mbagathi District hospital was previously an

infectious disease wing of the Kenyatta National Hospital before being made a district hospital. With the support of Medicins San Frontieres (MSF), the hospital started offering HIV infection interventions in 1997. At the time HIV morbidity and mortality was high in the country. MSF is an international, independent, medical humanitarian non-governmental organization that offers emergency assistance to people affected by armed conflict, epidemics, natural disasters and exclusion from healthcare.

Mbagathi District Hospital started offering antiretroviral therapy in 2003. Before then, the hospital with the support of MSF provided drugs for management of opportunistic infection inpatient ward to the hospitalized patients in an effort to reduce mortality rates. In addition, MSF supported the hospital with operation of a patient support center where psychosocial support and outpatient consultations for people living with HIV were offered.

Mbagathi District hospital offers antiretroviral therapy to patients across Nairobi County and a few from the neighboring counties. The hospital therefore served patients with a wide variety of characteristics. Mbagathi District Hospital was used as a proxy for all the health facilities dispensing paediatric antiretroviral drugs in Kenya.

3.3 Study population

The study population for objective two and three was children aged less than 15 years on long-term antiretroviral drugs by July 2010, 2011 and 2012. Pharmacy technical staff dispensing antiretroviral drugs to children made the study population for objective four.

3.4 Sample size and Sampling Techniques

Objective two and three were related and therefore sample and sample size were the same. Sample size was calculated using Equation 1 (Krejcie and Morgan, 1970), as described below.

Equation 1: Sample size calculation formula

$$n = \frac{Z^2 (P)\ 1-P}{E^2}$$

Where;

n=sample size

Z= Confidence level. A 95% (Z=1.96) level of confidence was used.

P= Proportion of sample anticipated to possess a characteristic of interest. For this study, P was the proportion of children anticipated to be less than 25 Kg. Due to lack of studies on the proportion of children on various weights and/or weight categories, P was assumed to be 50 per cent. Use of 50 per cent yields the maximum required sample size for the study population.

E= Maximum sampling error allowed in the results. This was 0.05 since the confidence interval used was 95 per cent.

Therefore:

$$n = \frac{1.96^2 \times 0.5 \times (1-0.5)}{0.05^2}$$

n=384

The ART electronic dispensing tool at the Comprehensive Support Centre pharmacy was used as the sampling frame for the study. The sample for the study comprised children less than 15 years and actively on antiretroviral therapy by end of June 2010, 2011 and 2012. As per Equation 1, required sample size was 384. A list of all patients receiving antiretroviral therapy as well as drugs for management of opportunistic infections was generated and was exported to Microsoft Office Excel work sheet. The list of children

less than 15 years and actively on antiretroviral therapy by end of June 2010, 2011 and 2012 was then filtered out using the age and the date of next appointment columns, respectively.

Objective four was qualitative in nature. Purposeful sampling technique was used. Criterion sampling technique of the purposeful sampling was employed where criterion was all pharmacy technical staff involved in dispensing antiretroviral drugs to children on long-term antiretroviral therapy in the study site. The pharmacist in-charge was consulted to help identify these staff. There were 14 technical dispensing staffs in Mbagathi District hospital, 13 pharmacists and one pharmaceutical technologist. At the time of the study there were two pharmaceutical technologist interns. All the dispensing staff including the interns rotated in the comprehensive Support Centre pharmacy where antiretroviral drugs were dispensed to both the adults and children. Data saturation approach was used to determine the sample size. This is the point of theme saturation where new themes or explanations stop emerging from the data. A sample size of 12 was achieved through an iterative process which included 11 pharmacists and one intern. Data was analyzed after every 2 or 3 interviews in order to assess data saturation.

3.5 Research Instruments and data collection techniques

Three different data collection forms were used. For objective one, data on actual and forecast consumption was populated into a Microsoft Office Excel work sheet for each product for the three forecast periods. Sample of the data is provided in Appendix 5. The actual consumption data was generated from national stock status spread sheets while forecasted consumption was generated from Quantimed software and the NASCOP forecast annual reports.

For objective two and three data on demographic characteristics and repeated measures data on dispensing history were collected. The continuous variables collected were age, weight and date of dispensing while categorical variables were regimen and ARV drug

dispensed. Other categorical variables generated from the variables collected were ARV combination, age category, and weight category and weight bands.

In-depth interviews were done for objective four. Informed consent was obtained before the start of each interview. The pharmacy staffs were allowed to select an interview date, time and venue that were convenient for them. The interviews were done in the Comprehensive Care Centre pharmacy and outpatient drug storage area depending on the preference of the interviewee. . These rooms were lockable, quiet and had restricted access to unauthorized staff. During the interviewing sessions, notice was put on the door for not to interrupt. The interviews were carried out between 8th and 30th May 2014. The interviewees were given codes and their names were not documented. Probing questions were used to guide the interviews. Through these in-depth interviews, factors that influence dispensing staff on choice of antiretroviral drugs dispensed to children were explored. The interviews were documented manually by pen and paper.

3.6 Data analysis

Mean absolute percentage error (MAPE) was used as the metric to measure the forecast accuracy (objective 1). Equation 2 below was applied in calculation of MAPE. Forecast accuracy analysis for paediatric antiretroviral drugs was done for three forecast periods 2010/11, 2011/12 and 2012/2013. The periods were running from July to June of each period. MAPE was calculated using 12-month and quarterly forecast and consumption data across the three forecast periods for all products.

For the quarterly based MAPE, products were weighted equally using a three month moving average. Only paediatric antiretroviral drugs were considered in the analysis and they included abacavir/lamivudine (ABC/3TC) 60/30mg; zidovudine/lamivudine (AZT/3TC) 60/30mg; zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) 60/30/50mg; efavirenz (EFV) 200mg; lopinavir/ritonavir (LPV/r) 80/20mg; nevirapine (NVP) 10mg/ml and zidovudine (AZT) 10mg/ml.

Equation 1: Mean absolute percentage error (MAPE)

$$MAPE = \frac{\sum \left\{ \left| \frac{\text{Actual consumption} - \text{Forecast consumption}}{\text{Actual consumption}} \right| \right\} \times 100}{n}$$

Where;

$\sum \left| \frac{\text{Actual consumption} - \text{Forecast consumption}}{} \right|$ is the absolute error.

n= forecast periods which was 3 and 12 for the quarterly and 12-months MAPE, respectively.

Randomness of forecast errors was tested to evaluate adequacy of the forecast model. The randomness criteria tested was (i) lack of patterns and trends in forecast errors; (ii) constant variance (homoscedasticity) for errors over time; (iii) errors points not persistently staying either above or below a centerline for a large number of consecutive periods and (iv) errors not oscillating rapidly above or below the centerline. Augmented Dickey-Fuller (ADF) test and Run test were used to test for randomness of forecast errors. The period covered was July 2010 to June 2013 and this comprised 36 months.

Augmented Dickey-Fuller (ADF) test was used to test criteria (i) and (ii), i.e. (i) no patterns and trends in forecast errors and; (ii) forecast errors were homoscedastic over time. The null hypothesis for ADF test is that errors or data are non-random and a p-value of <0.05 is an indication of significant randomness in errors or data.

Run test was used to test criteria (iii) and (iv), i.e. (iii) forecast errors points did not persistently stay either above or below a centerline for a large number of consecutive periods and; (iv) forecast errors oscillating rapidly above or below the centerline. Since the forecast errors were not normally distributed, median was used as the centerline. The null hypothesis for Run test is that the forecast errors are random, i.e. same number of runs appeared above and below the median; and that the number of runs is within the required critical value range (Appendix 2). The null hypothesis of randomness is rejected ($p<0.05$) at the 95% confidence level if the number of runs (r) is less than or equal to the

first critical value or greater than or equal to the second critical value. The number of runs (r) is determined using number of observations above (n_1) and number of observations below a centerline (n_2) (Appendix 2). Both Augmented Dickey-Fuller test and Run test were done using Stata version 12.

Individual control charts for each product were constructed to help in visual inspection of patterns and trends. To construct the control charts, mean square error (MSE) was computed and its square root used as an estimate of the standard deviation of the distribution of errors. The 95% confidence level was used where 0 ± 2 standard deviations was used to set forecast error upper control limit and lower control limit for each product for the forecast period between July 2010 to June 2013. The upper control limit and the lower control limit were computed as $0+z\sqrt{MSE}$ and $0-z\sqrt{MSE}$, respectively. z=number of standard deviations. Where patterns such as cyclical and trends such as upward or downwards are identified from the charts, it means errors are non-random. In addition, forecasts where charts show errors that outside either the upper or lower limit are considered to be out of control (Lawrence *et. al,* 2009).

Objective 2 and 3 were analyzed using Stata version-12 software and Microsoft Office Excel (2007). Repeated measures data was collected on children less than 15 years on antiretroviral drugs by end June 2010, 2011 and 2012. Both descriptive and exploratory data analysis were explored where for the latter, repeated measures logistic regression was applied. All variables were subjected to univariate data analysis. For continuous variables; age and weight, tests for normal distribution were done and the summary statistics; mean, median, range, interquartile range and standard deviation were determined. Frequencies and percentages were determined for categorical variables. Bivariate analysis to establish relationship various categorical variables was done using chi square test.

Exploratory analysis for binary outcome repeated measures data was done using within-subject effects and population-averaged logistic regression models. Hausman test was run to determine which within-subject effects analysis to perform between fixed-effects or random-effects logistic regression models. Hausman test tested the null hypothesis that

the preferred model is random-effects versus the alternative fixed-effects. Fixed-effects model measures the relationship based on time variation within-subjects while random-effects measures model is the weighted average of the within and between effects. The relationship between ARV combination outcome variable and explanatory variables; age category and weight category was explored. ARV combination was categorized as paediatric ARV combination or represented adult ARV combination. According to the guidelines for Antiretroviral Therapy in Kenya, 4th Edition paediatric formulations are recommended for children weight<25 Kg. Weight was therefore categorized as <25 Kg or ≥ 25 Kg. it was considered that some children may grow to the age 15 years and above in the forecast period. Age was therefore categorized < 15 years and ≥ 15 years.

Objective 4 was qualitative in nature. Data collected was transcribed. The data was then classified into themes and mapped using charts to define concepts. These thematic codes were developed through inductive coding style. An iterative process was used to derive the themes from the early stages of data collection and continued through the interviewing period. Concept of point of saturation was used for the data analysis. Relative importance of codes was used to form the thematic prevalence.

3.7 Ethical considerations

Approval to carry out the study was granted by Kenyatta National Hospital/University of Nairobi Ethics and Research committee (KNH/UoN-ERC) (Appendix 3) approval number P41/01/2014. Participants' name and/or hospital identification numbers were not used and instead study identification numbers were allocated to conceal the participants' identity. All the information acquired on study participants was treated in the strictest confidence.

CHAPTER 4: RESULTS

4.1. Forecast accuracy for paediatric antiretroviral drugs

Forecast accuracy for seven paediatric antiretroviral drugs namely abacavir/ lamivudine(ABC/3TC) 60/30mg; zidovudine/lamivudine(AZT/3TC) 60/30mg; zidovudine/lamivudine/nevirapine(AZT/3TC/NVP) 60/30/50mg; efavirenz(EFV) 200mg; lopinavir/ritonavir(LPV/r) 80/20mg; nevirapine(NVP) 10mg/ml and zidovudine(AZT) 10mg/ml was established. Forecast accuracy analysis for paediatric antiretroviral drugs was done for three forecast periods 2010/11, 2011/12 and 2012/2013. The periods were running from July to June of each period.

Mean absolute percentage error (MAPE) was used as the metric to determine forecast accuracy. MAPE was calculated using 12-month and quarterly forecast and consumption data across the three forecast periods for all products. For the quarterly based MAPE, products were weighted equally using a three month moving average.

4.1.1. Mean absolute percentage error for the 12-months period

Mean absolute percentage errors were observed across all the products (Table 2). MAPE ranged between 11.8% and 2198.9%. Based on Lewis MAPE scale of judgment for forecast errors, forecasts with MAPE of 0-10% are termed as highly accurate, 11-20% as good, 21-50% as reasonable and 51% and above as inaccurate Lawrence *et. al*, 2009).

ABC/3TC-60/30mg, AZT/3TC-60/30mg and AZT/3TC/NVP-60/30/50mg had MAPEs above 51% across all the periods. AZT/3TC-60/30mg recorded the highest MAPE of "2198.6% and 276.1% in 2010/11 and 2011/12, respectively". A drastic drop to 88.9% was observed in 2012/13. Efavirenz 200mg had the least MAPE and therefore good forecast in 2011/12 and 2012/13. MAPE of 11.8% and 13.4% were recorded in 2011/12 and 2012/13, respectively. This was a decrease from 58.5% in 2010/11. Forecast for LPV/r-80/20mg/ml was reasonable in 2010/11 at MAPE of 34.3% in 2010/11. However,

MAPE increased substantially to 268.0% in 2011/12 and then a slight decrease to 188.5% in 2012/13 leading to inaccurate forecast. NVP 10mg/ml recorded reasonable forecasts across the three periods. Mean absolute percentage error "41.6%, 49.1% and 24.4% was recorded in 2010/11, 2011/12 and 2012/13, respectively". Reasonable forecast for AZT-10mg/ml was observed in 2010/11.The MAPE was 38.6% in 2010/11. However, the forecast was inaccurate in 2011/12 and 2012/13 where MAPE of 52.6% and 143.8% was observed for the respective periods.

A graphical representation of the MAPE per product for the three forecast periods is displayed in Figure 5. MAPE for zidovudine/lamivudine 60/30mg was not plotted due to very high MAPE especially in period 2010/11.

Table 2: Twelve month Mean Absolute Percentage Errors per product

Product	**2010_11**	**2011_12**	**2012_13**
ABC/3TC 60/30mg	80.5%	65.3%	88.9%
AZT/3TC 60/30mg	2198.6%	276.1%	88.9%
AZT/3TC/NVP 60/30/50mg	91.1%	133.0%	74.9%
EFV 200mg	58.5%	11.8%	13.4%
LPV/r 80/20mg/ml	34.3%	268.0%	188.5%
NVP 10mg/ml	41.6%	49.1%	24.4%
AZT 10mg/ml	38.6%	52.6%	143.8%

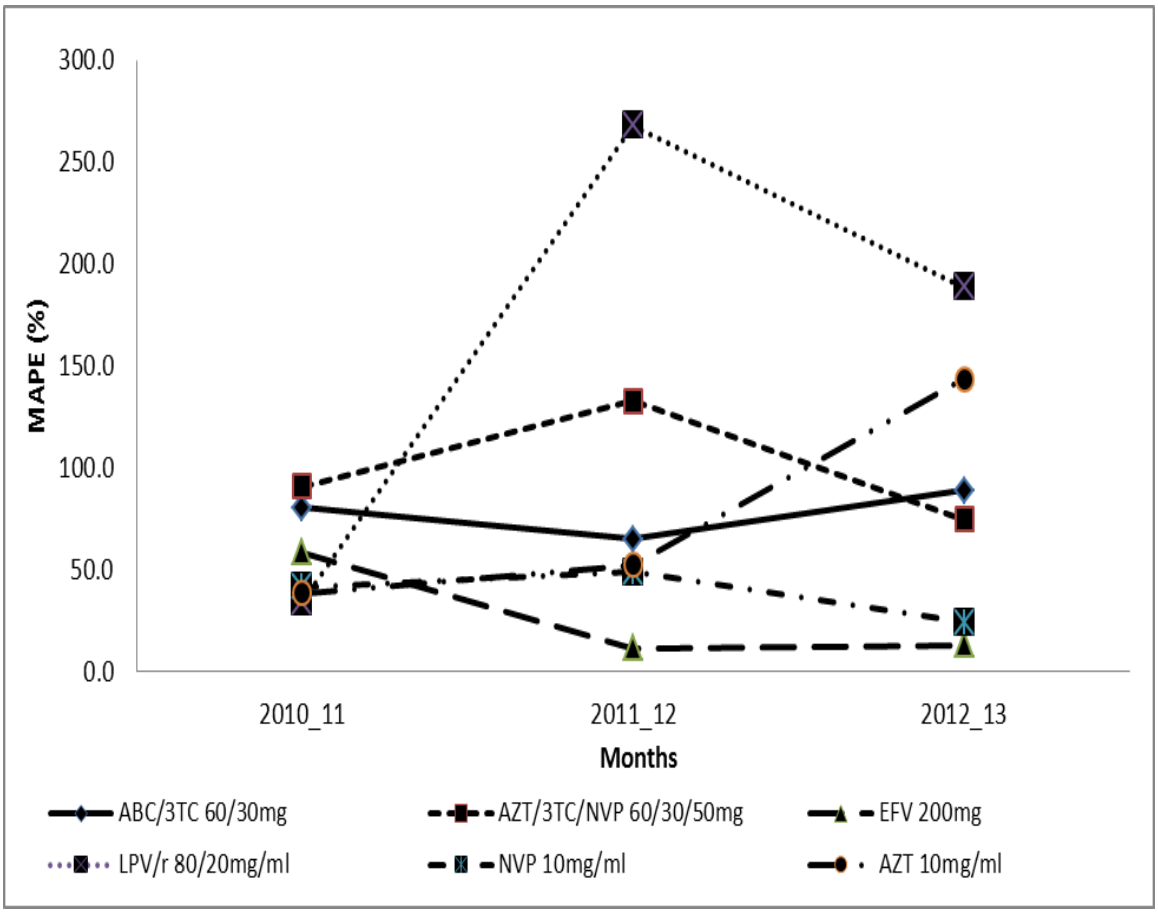

Figure 5: 12-month Mean Absolute Percentage Errors (MAPE) per product

MAPE for LPV/r 80/20mg/ml, AZT/3TC/NVP 60/30/50mg and NVP 10mg/ml increased in 2011/12 and then decreased in 2012/13. On the other hand, MAPE for ABC/3TC 60/30mg and EFV 200mg decreased in 2011/12 and then increase in 2012/13. MAPE for AZT 10mg/ml increased across the three periods.

4.1.2. Mean absolute percentage error for quarter period

Quarterly MAPEs for ABC/3TC-60/30mg remained above 51% category for all the quarters except quarter 3, 6 and 8. All the MAPEs for AZT/TC-60/30mg, AZT/3TC/NVP-60/30/50mg and LPV/r-80/20mg/ml were above 51% category in all the quarters. MAPEs for EFV-200mg were inaccurate at "51.8%, 62.8%, 62.2% and 57.0% in quarter 1, 2, 3 and 4, respectively". These were quarters for period 2010/11. MAPEs for EFV-200mg in quarter 5 to 12 ranged between 8.6% and 20.1%. For NVP-10mg/ml, MAPE of 62.9% was observed in quarter 8. This was the only quarter with inaccurate forecast for NVP-10mg/ml. AZT-10mg/ml had MAPE of 10.2% in quarter 1 and this increased substantially to 314.7% in quarter 12 (Table 3).

Table 3: Quarterly Mean Absolute Percentage Errors per product

Quarter	Month	ABC/ 3TC 60/30mg	AZT/ 3TC 60/30mg	AZT/ 3TC/ NVP 60/30/ 50mg	EFV 200mg	LPV/r 80/20mg/ml	NVP 10mg/ml	AZT 10mg/ml
Q1	Sep-10	142.3%	2058.6%	150.7%	51.8%	75.5%	40.2%	10.2%
Q2	Dec-10	74.0%	2769.6%	83.5%	62.8%	251.0%	47.2%	12.9%
Q3	Mar-11	13.7%	1780.3%	32.4%	62.2%	306.4%	43.6%	59.8%
Q4	Jun-11	92.1%	720.3%	97.7%	57.0%	481.9%	35.6%	71.8%
Q5	Sep-11	114.2%	289.6%	142.6%	17.8%	219.8%	40.8%	50.0%
Q6	Dec-11	44.2%	321.5%	138.2%	12.2%	276.5%	41.4%	19.4%
Q7	Mar-12	57.6%	242.0%	116.7%	8.7%	270.5%	51.4%	35.3%
Q8	Jun-12	45.2%	251.4%	134.6%	8.6%	305.4%	62.9%	105.6%
Q9	Sep-12	76.2%	106.4%	58.1%	13.5%	154.0%	40.5%	83.4%
Q10	Dec-12	94.6%	150.3%	72.6%	3.9%	223.8%	32.3%	34.7%
Q11	Mar-13	97.7%	159.9%	87.9%	16.0%	178.6%	14.3%	142.4%
Q12	Jun-13	87.0%	161.6%	81.2%	20.1%	197.5%	10.5%	314.7%

4.1.3. Randomness of forecast errors for paediatric antiretroviral drugs

4.1.3.1. Statistical test for randomness

Test for randomness revealed that forecast errors were not random. Forecast errors are considered random if no patterns are exhibited; if there is constant variance over time; if errors points do not persistently stay either above or below a centerline for a large number of consecutive periods; and data points do not oscillate rapidly above or below the centerline.

It was observed that all the products failed to meet the four criteria for randomness of errors. As such the forecast errors exhibited trends and had heteroscedasticity. The error points persistently stay either above or below the zero thresholds for a large number of consecutive periods and/or data points meandered rapidly above or below the zero thresholds.

From Augmented Dickey-Fuller (ADF) test, forecast errors for ABC/3TC 60/30mg, AZT/3TC-60/30mg, AZT/3TC/NVP-60/30/50mg, EFV-200mg, LPV/r-80/20mg/ml and NVP-10mg/ml were found not to be statistically significant ($p>0.05$) at 95% confidence level (Table 4). The forecast errors for these products were non-random and therefore had trends and heteroscedasticity over time. Forecast errors for AZT 10mg/ml were the only ones that demonstrated statistically significant ($p=0.00$) randomness and homoscedasticity at 95% confidence level. A p-value of <0.05 is an indication that significant randomness in data exists. The null hypothesis for ADF test, i.e. forecast errors are non-random was therefore rejected for AZT 10mg/ml liquid.

Table 4: Summary statistics for forecast errors using Augmented Dickey-Fuller test

Product	z-test*	p-value
ABC/3TC 60/30mg	-0.976	0.762
AZT/3TC 60/30mg	-2.833	0.054
AZT/3TC/NVP 60/30/50mg	-1.867	0.348
EFV 200mg	-2.124	0.235
LPV/r 80/20mg/ml	-2.243	0.191
NVP 10mg/ml	-2.178	0.214
AZT 10mg/ml	-6.144	0.000**

**z-critical= -2.972 at 95% confidence level **significant at p<0.05*

For the Run test, there were 36 months (observations) representing months for the forecast periods between July 2010 and June 2013. The number of observations required to be above and below a centerline was 18, i.e. $n_1 = n_2 = 18$. Based on the $n_1 = n_2 = 18$, the numbers of runs were required to fall within the acceptable critical value range of 12 to 26 runs at 95% confidence level.

There were 4 runs for LPV/r-80/20mg/ml; 7 runs for NVP-10mg/ml; 8 runs for ABC/3TC-60/30mg and AZT/3TC/NVP-60/30/50mg; 9 runs for EFV-200mg; and 10 runs for AZT/3TC-60/30mg and AZT-10mg/ml. The runs for all the products were outside the acceptable critical value range of 12 to 26 runs at 95% confidence level and the p value was <0.05 (Table 5). For Run test, a $p<0.05$ is an indication that non-randomness in data exists. The null hypothesis for Run test, i.e. forecast errors are random was therefore rejected for all products. As such, forecast errors for all the products were nonrandom.

Table 5: Summary statistics for forecast errors using Run test

Product	**No of runs (r)***	**z-test**	**p-value**
ABC/3TC 60/30mg	8	-3.72	0.00**
AZT/3TC 60/30mg	10	-3.04	0.00**
AZT/3TC/NVP 60/30/50mg	8	-3.72	0.00**
EFV 200mg	9	-3.38	0.00**
LPV/r 80/20mg/ml	4	-5.07	0.00**
NVP 10mg/ml	7	-4.06	0.00**
AZT 10mg/ml	10	-3.04	0.00**

**r: >12 and <26* ***significant at p<0.05*

4.1.3.2. Visual inspection for randomness of forecast errors

The individual product control charts for the seven products showed various patterns and trends over time ABC/3TC-60/30mg, EFV-200mg, NVP-10mg/ml and LPV/r-80/20mg/ml exhibited downward trends in forecast errors over time. No significant trends were evident for AZT/3TC-60/30mg, AZT/3TC/NVP-60/30/50mg and AZT-10mg/ml. All the products exhibited seasonal patterns (Figure 6).

ABC/3TC-60/30mg, AZT/3TC-60/30mg, AZT/3TC/NVP-60/30/50mg and LPV/r-80/20mg/ml had errors that were persistently below the centerline for almost all the forecast period July 2010 to June 2013. NVP 10mg/ml had errors above the centerline from July 2010 to June 2011 and above zero line from July 2011 to June 2012. This was an indication of under-forecast for July 2010 to June 2011 and over-forecast from July 2011 to June 2012. Efavirenz 200mg had errors persistently above the centerline while errors for zidovudine liquid were below the centerline for majority of the months. This was an indication of over-forecast for these months (Figure 6)

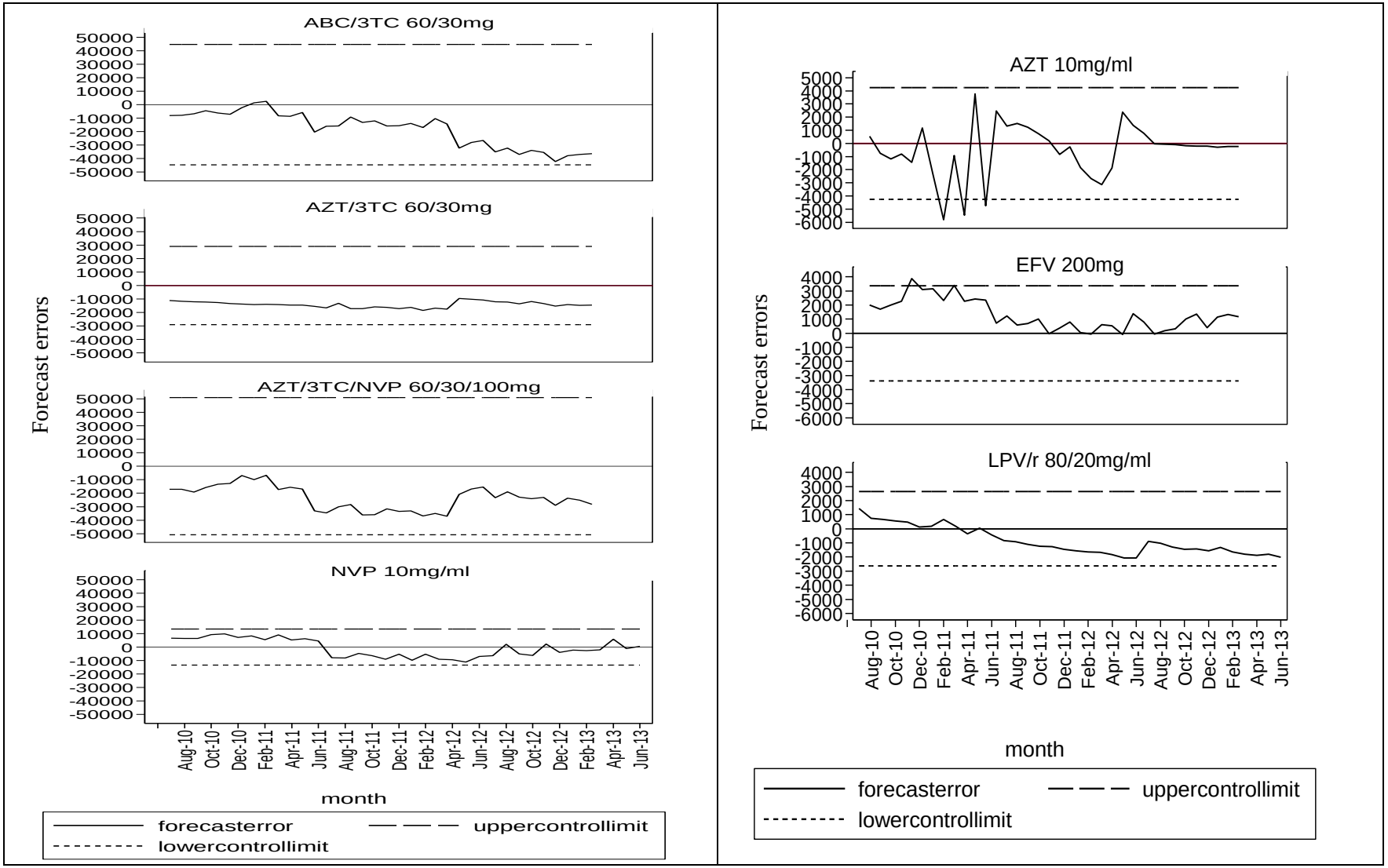

Figure 6: Individual control charts for paediatric antiretroviral drugs on forecast error

4.2. Determinants of forecast accuracy for paediatric antiretroviral drugs

4.2.1. Baseline characteristics of the study population

There were 311, 306 and 285 children actively on antiretroviral therapy by end June 2010, 2011 and 2012, respectively. There were 3622, 3506 and 3242 observations generated from repeated measurements for the 311, 306 and 285 children, respectively for the corresponding periods July 2010 to June 2011, July 2011 to June 2012 and July 2012 to June 2013.

The baseline characteristics of the study children are summarized in Table 6. Majority of the children were males and constituted 171(55.0%), 171(55.9%) and 169(55.8%) in July 2010, 2011 and 2012, respectively. The median and interquartile range (in brackets) for age were 9.2(6.8, 12.0), 9.6(7.3, 12.0) and 10.3(7.5, 12.5) years in July 2010, 2011 and 2012, respectively. The median and interquartile range (in brackets) for weight were 26(20, 32), 27(21, 32) and 28(21, 34) Kg in July 2010, 2011, 2012, respectively. For the three years, age and weight were found to be positively skewed through the test for skewness and kurtosis normality test in Stata version-12. Analysis of weight category (< 25 Kg and ≥25 Kg) revealed that 55.0%, 61.5% and 64.9% of the children were in the ≥25 Kg, weight category in July 2010, 2011 and 2012, respectively.

There were more children on adult formulations; 82.6%, 72.9% and 63.9% in July 2010, 2011, 2012, respectively than paediatric formulation (17.4%, 27.1% and 36.1% in July 2010, 2011, 2012, respectively). This revealed a decreasing trend in proportions for adult formulation and an increasing trend for paediatric formulations. There were 9, 11 and 12 regimens identified for July 2010, 2011, 2012, respectively. The d4T/3TC/NVP regimen had the highest proportion (60.8%) of children followed by AZT/3TC/NVP; 24.8% and ABC/3TC/NVP; 6.8% in 2010. Decreasing trends in proportion of children on d4T/3TC/NVP regimen was observed as that of children on AZT/3TC/NVP and ABC/3TC/NVP regimen increased over the next two years 2011 and 2012 (Figure 7). Proportions for all regimens identified as at July 2010. 2011 and 20112 are captured in Appendix 6

A wide range of drugs combinations either as fixed dose combinations or single combinations were available for dispensing to children (Appendix 7-9). It was observed that four drug combinations formed at least three quarter of the drug combinations dispensed to children at the beginning of the study periods. The four combinations were d4T/3TC/NVP 30/150/200mg; AZT/3TC/NVP 300/150/200mg; AZT/3TC/NVP 60/30/50mg and ABC/3TC 60/30mg + NVP 200mg (Table 6).

Table 6: Baseline characteristics as at July 2010, 2011 and 2012

Characteristic	Median (IQR)		
	July 2010	**July 2011**	**July 2012**
Age (years)	9.2(6.8,12.0)	9.6(7.3, 12.0)	10.3(7.5,12.5)
Weight (Kg)	26(20,32)	27(21, 32)	28(21, 34)
		N (%)	
	July 2010	**July 2011**	**July 2012**
Sex: Male	171(55.0)	171(55.9)	169(55.8)
Female	140(45.0)	135(44.1)	126(44.2)
Weight category:< 25 Kg	140(45.0)	118(38.5)	100(35.1)
≥25 Kg	171(55.0)	188(61.5)	185(64.9)
Weight bands(Kg)			
3.0-5.9	0(0.0)	0(0.0)	0(0.0)
6.0-9.9	0(0.0)	2(0.7)	3(1.1)
10.0-13.9	13(4.2)	12(3.9)	6(2.1)
14.0-19.9	57(18.2	45(14.7)	41(14.4)
20.0-24.9	70(22.5)	59(19.3)	50(17.5)
25.0-29.9	63(20.3)	70(22.9)	64(22.5)
30.0-34.9	55(17.7)	56(18.3)	56(19.6)
35.0-39.9	16(5.1)	26(8.5)	27(9.5)
≥40 Kg	37(11.9)	36(11.8)	38(13.3)
ARV formulation			
Adult formulation	257(82.6)	223(72.9)	182(63.9)
Paediatric formulation	54(17.4)	83(27.1)	103(36.1)
Regimen*			
d4t/3TC/NVP	189(60.8)	153(50.0)	70(24.6)
AZT/3TC/NVP	77(24.8)	87(28.4)	131(46.0)
ABC/3TC/NVP	21(6.8)	36(11.8)	46(16.1)
ARV drug combinations**			
d4T/3TC/NVP 30/150/200mg	189(60.8)	147(48.0)	70(24.6)
AZT/3TC/NVP 300/150/200mg	32(10.3)	39(12.7)	68(23.9)
AZT/3TC/NVP 60/30/50mg	25(8.0)	47(15.4)	62(21.8)
ABC/3TC 60/30mg + NVP 200mg	10(3.2)	18(5.9)	24(8.4)

**Only 3 regimens are presented in this Table. Whole list of regimen is presented in appendix 6.*

***Only 4 ARV drug combinations are presented in this Table. Whole list of regimen is presented in Appendix 7-9.*

Slash (/) means combination is fixed dose: Plus (+) means combination is not fixed dose e.g. ABC/3TC 60/30mg is fixed dose combination plus NVP 200mg

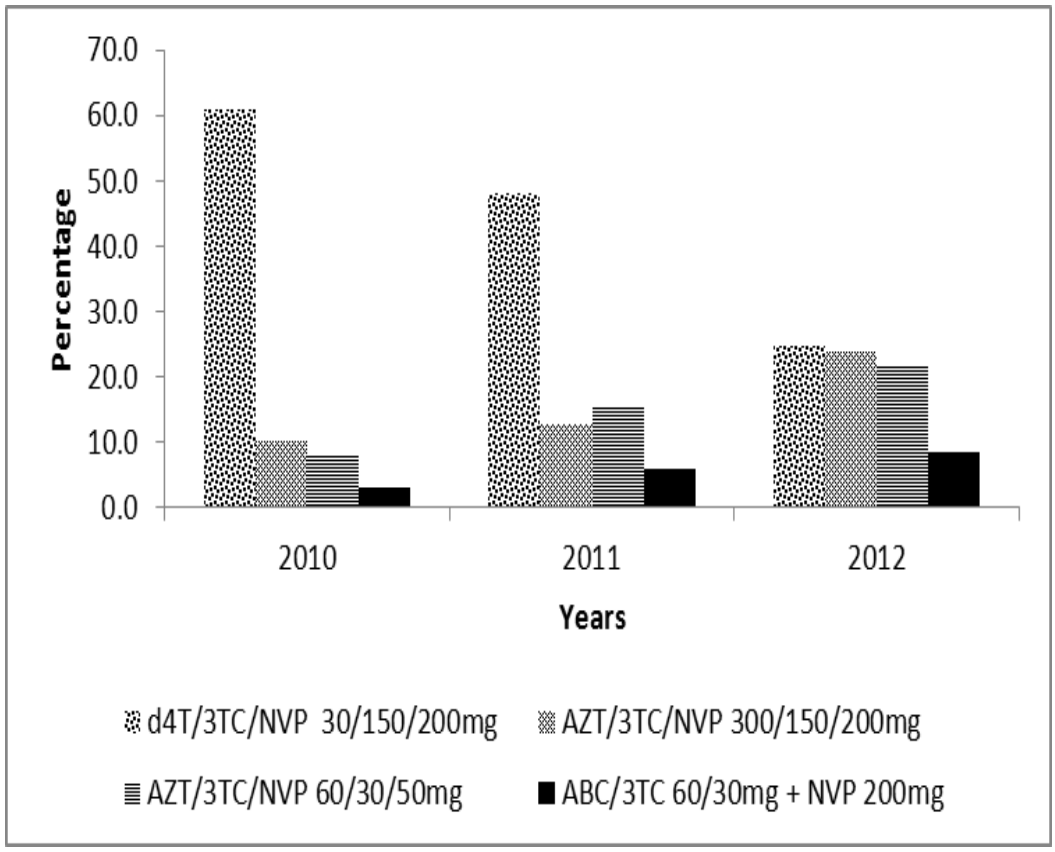

Figure 7: Proportion of children on the four more commonly used ARV drug combinations at baseline

From Figure 7 above, it was observed that proportion of children on d4T/3TC/NVP 30/150/200mg decreased over the years while that of AZT/3TC/NVP 300/150/200mg, AZT/3TC/NVP 60/30/50mg and ABC/3TC 60/30mg + NVP 200mg increased. The proportion of children on d4T/3TC/NVP 30/150/200mg, AZT/3TC/NVP 300/150/200mg and AZT/3TC/NVP 60/30/50mg was almost equal in 2012.

4.2.2. Univariate analysis

At the 12 months follow-up, 289(92.9%), 275(89.9%) and 251(88.1%) children were dispensed antiretroviral drugs for 12 month period while 22(7.1%), 31(10.1) and 34(11.9) were dispensed ARVs for a period ranging 1 to 11 months (Appendix 10). There were 3622, 3506 and 3242 observations generated from the repeated measurements for the three periods 2010/11, 2011/12 and 2012/13, respectively.

4.2.2.1. Weight category and weight bands

The univariate data analysis revealed that in all of the dispensing months, there were more children in the ≥25 Kg weight category. On average, there were 58.9% , 65.4% and 68.5% children in the ≥25 Kg weight category for the periods 2010/11, 2011/12 and 2012/13, respectively. The proportion for the ≥25 Kg weight category increased across the months as the one for the < 25 Kg decreased (Figure 8).

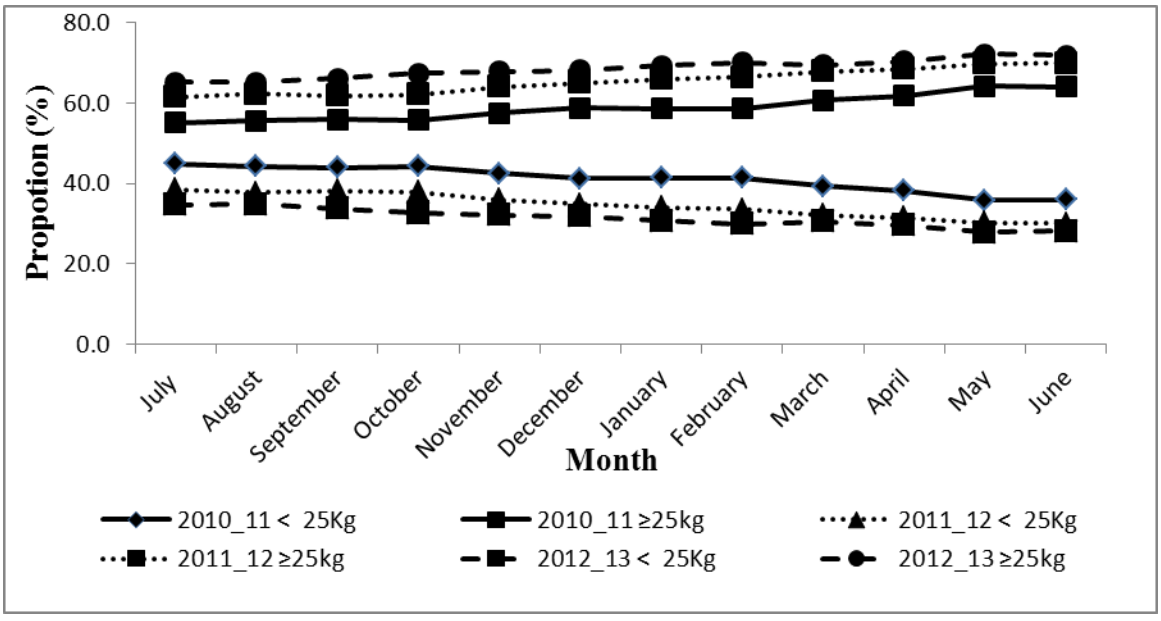

Figure 8: Proportion of children with < 25 Kg and ≥25 Kg weight category across the months

Analysis of proportion of children on various weight bands revealed that there were no children below 10 Kg for period 2010/11 while only 0.3% and 0.4% were below 10 Kg in 2011/12 and 2012/13. Majority of children were in the 20 to 24.9 Kg weight band (Table 7).

Table 7: Average proportion of children per weight band

Year	6.0-9.9Kg	10.0-13.9Kg	14.0-19.9Kg	20.0-24.9Kg	≥25Kg
2010/11	0.0%	2.80%	16.40%	21.90%	58.90%
2011/12	0.30%	2.70%	14.40%	17.20%	65.40%
2012/13	0.40%	2.30%	12.30%	16.50%	68.50%

4.2.2.2. Regimen

Majority of children were on d4T/3TC/NVP, AZT/3TC/NVP and ABC/3TC/NVP regimen across the three forecast periods; 2010/11, 2011/12 and 2012/13. The total proportion of children on d4T/3TC/NVP, AZT/3TC/NVP and ABC/3TC/NVP regimen together was 91.4%, 89.4% and 85.7% for periods 2010/11, 2011/12 and 2012/13, respectively. In 2010/11, 58.9%, 25.7% and 6.8% were on d4t/3TC/NVP, AZT/3TC/NVP and ABC/3TC/NVP regimen, respectively. A decrease in proportion of children on d4T/3TC/NVP regimen was observed as that of those on AZT/3TC/NVP and ABC/3TC/NVP regimen increased for the year 2011/12 and 2012/13 (Table 8).

Table 8: Average proportion of children by regimen

Regimen	2010/11	2011/12	2012/13
d4t/3TC/NVP	58.90%	38.90%	22.80%
AZT/3TC/NVP	25.70%	38.40%	47.70%
ABC/3TC/NVP	6.80%	12.10%	15.20%
ABC/3TC/LPV/r	2.80%	0.50%	1.80%
ABC/DDI/LPV/r	2.30%	3.40%	2.20%
AZT/3TC/EFV	0.90%	1.70%	2.60%
TDF/3TC/NVP	0.90%	1.00%	1.10%
d4t/3TC/EFV	0.70%	0.10%	0.20%
ABC/3TC/AZT	0.30%	1.30%	-
TDF/3TC/EFV	0.30%	1.70%	1.90%
d4t/3TC/LPV/r	0.30%	-	-
AZT/3TC/LPV/r	0.30%	0.70%	1.50%
TDF/3TC/LPV/r	0.30%	0.20%	1.10%
ABC/3TC/EFV	-	-	1.90%

Comparison between proportion of children forecasted and observed on the three leading regimens; d4t/3TC/NVP, AZT/3TC/NVP and ABC/3TC/NVP (Table 9) revealed that there was underestimation for d4t/3TC/NVP regimen across the three years and overestimations for ABC/3TC/NVP regimen across the three years. For AZT/3TC/NVP, overestimation was observed in year 2010/11 and 2011/12 and underestimation in 2012/13. For the period 2010/11, it was assumed that there would be 13.8% children on d4t/3TC/NVP regimen and no children on the regimen in period 2011/12 and 2012/13. However, 58.9%, 38.9% and 22.8% were observed to be on the regimen for the year 2010/11, 2011/12 and 2012/13, respectively. The overall net effect was underestimation of 18.7%, 18.1% and 14.9% in 2010/11, 2011/12 and 2012/13, respectively for three regimens (Table 9).

Table 9: Comparison of forecasted and observed proportions for d4t/3TC/NVP, AZT/3TC/NVP and ABC/3TC/NVP regimen

Regimen	Forecast	observed	Difference (Observed minus Forecast)	Comments
2010/11				
d4T/3TC/NVP	13.80%	58.90%	45.10%	underestimate
AZT/3TC/NVP	46.80%	25.70%	-21.10%	overestimate
ABC/3TC/NVP	14.80%	6.80%	-8.00%	overestimate
Total	**75.40%**	**91.40%**	**16.00%**	underestimate
2011/12				
d4T/3TC/NVP	0.00%	38.90%	38.90%	underestimate
AZT/3TC/NVP	50.30%	38.40%	-11.90%	overestimate
ABC/3TC/NVP	21.60%	12.10%	-9.50%	overestimate
Total	**71.90%**	**89.40%**	**17.50%**	underestimate
2012/13				
d4T/3TC/NVP	0.00%	22.80%	22.80%	underestimate
AZT/3TC/NVP	34.80%	47.70%	12.90%	underestimate
ABC/3TC/NVP	34.80%	15.20%	-19.60%	overestimate
Total	**69.60%**	**85.70%**	**16.10%**	underestimate

4.2.2.3. ARV drug formulations and combinations

On average, the proportion of children on adult formulations was higher than those on paediatric formulations. There were 81.0%, 69.7% and 67.4% children on adult formulation while only 19.0%, 30.3% and 32.6% were on paediatric formulations for period 2010/11, 2011/12 and 2012/13, respectively. There was a difference on the number of ARV drug combinations dispensed to the children across the three years.

For d4T/3TC/NVP regimen, there were two ARV drug combinations dispensed d4T/3TC/NVP 30/150/200mg adult fixed dose combination (FDC) and d4T/3TC/NVP 12/60/100mg paediatric FDC. In 2010/11 and 2012/13, all the observations on d4t/3TC/NVP regimen were dispensed d4T/3TC/NVP 30/150/200mg adult fixed dose combination (FDC).Of the 38.9% on d4T /3TC/NVP regimen in 2011/12, 94.9% were dispensed d4T/3TC/NVP 30/150/200mg adult FDC and 5.1% were dispensed d4T/3TC/NVP 12/60/100mg paediatric FDC.

For AZT/3TC/NVP regimen, there were ten ARV drug combinations dispensed to children in 2010/11 and three in 2011/12 and 2012/13. However, AZT/3TC/NVP 60/30/50mg paediatric FDC and AZT/3TC/NVP 300/150/200mg adult FDC comprised the highest proportion of 45.7% and 44.2%, respectively for year 2010/11; 47.7% and 52.3%, respectively for year 2011/12 and 41.1% and 58.7% for year 2012/13.

For ABC/3TC/NVP regimen, there were six, four and two ARV combinations for the year 2010/11, 2011/12 and 2012/13, respectively. ABC/3TC 60/30mg + NVP 200mg and ABC 300mg + 3TC 150mg + NVP 200mg comprised the highest proportion. In 2010/11, 59.7% and 37.8% were dispensed ABC/3TC 60/30mg + NVP 200mg and ABC 300mg + 3TC 150mg + NVP 200mg, respectively. In 2011/12, 54.2% and 42.4% were dispensed ABC/3TC 60/30mg + NVP 200mg and ABC 300mg + 3TC 150mg + NVP 200mg, respectively while in 2011/12 the proportions were for ABC/3TC 60/30mg + NVP 200mg and ABC 300mg + 3TC 150mg + NVP 200mg were 50.3% and 49.0%, respectively (Table 10). Details of all ARV drug combinations dispensed for the three years are in Appendix 11.

Table 10: Average proportion for selected ARV combination

ARV drug combination	2010/11	2011/12	2012/13
d4T/3TC/NVP 30/150/200mg	100.0%	94.9%	100.0%
d4T/3TC/NVP 12/60/100mg		5.1%	
Total	***100.0%***	***100.0%***	***100.0%***
AZT/3TC/NVP 60/30/50mg	45.6%	47.5%	41.1%
AZT/3TC/NVP 300/150/200mg	44.3%	52.3%	58.7%
AZT 10mg/ml + 3TC 150mg + NVP 200mg	6.0%	-	0.0%
AZT 300mg + 3TC 150mg + NVP 200mg	1.4%	-	0.1%
AZT/3TC 300/150mg + NVP 200mg	0.4%	-	-
AZT 10mg/ml + 3TC 10mg/ml + NVP 10mg/ml	1.1%	-	-
AZT 10mg/ml + 3TC 150mg + NVP 10mg/ml	0.7%	0.1%	-
AZT 10mg/ml + 3TC 10mg/ml + NVP 200mg	0.2%	-	-
AZT 300mg + 3TC 150mg + NVP 10mg/ml	0.2%	-	-
AZT/3TC 60/30mg+NVP 200mg	-	-	0.1%
Total	***100.0%***	***100.0%***	***100.0%***
ABC/3TC 60/30mg + NVP 200mg	59.8%	54.4%	50.6%
ABC 300mg + 3TC 150mg + NVP 200mg	37.8%	42.5%	49.4%
ABC 20mg/ml + 3TC 10mg/ml + NVP 200mg	0.8%	0.0%	0.0%
ABC/3TC 60/30mg + NVP 10mg/ml	0.8%	1.2%	0.0%
ABC 20mg/ml + 3TC 10mg/ml + NVP 10mg/ml	0.4%	1.9%	0.0%
ABC 20mg/ml + 3TC 150mg + NVP 10mg/ml	0.4%	0.0%	0.0%
Total	***100.00%***	***100.0%***	***100.0%***

4.2.3. Bivariate analysis

4.2.3.1 Relationship between ARV formulations and weight category

Bivariate analysis using chi square test revealed that significant relationship (p=0.00) existed between ARV formulation and weight category across all the years. It was observed that in majority of the dispensing observations across the three periods, adult formulations were dispensed to children ≥25 Kg. 99.2%, 98.7% and 97.0% of the observations had adult formulations in the ≥25 Kg weight category. For the <25 Kg weight category, year 2011/12 and 2012/13 had majority of the observations with paediatric ARV formulations. 85.0% and 97.1% of the observations had paediatric ARV formulations in 2011/12 and 2012/13, respectively. In 2010/11 there were slightly more observations with adult formulations, that is, 55.0% had adult formulations and 45.0% paediatric formulations (Table 11).

Table 11: Relationship between ARV formulation and weight category

	N (%)		
	<25 Kg	**≥25 Kg**	**P value**
2010/11			
Adult	820(55.0)	2113(99.2)	0.00*
Paediatric	671(45.0)	18(0.84)	
2011/12			
Adult	182 (15.0)	2,261 (98.7)	0.00*
Paediatric	1,033(85.0)	30 (1.3)	
2012/13			
Adult	30 (2.9)	2,156 (97.0)	0.00*
Paediatric	990 (97.1)	66 (3.0)	

**=significant at p<0.05; N=observations*

4.2.3.2 Relationship between sex and ARV formulations

Chi square test was used for analysis of relationship between sex and ARV formulations A significantly higher number of both male and female children received adult formulations for all three periods considered ($p < 0.05$) (Table 12).

It was also observed that, for the periods 2010/11 and 2012/13, there were higher proportions of females (52.4% and 52.2% for the two periods, respectively) among those children receiving paediatric formulations. In 2011/12, there were equal proportions for females and males dispensed paediatric formulations (Table 12).

However, there were higher proportions of males among those children receiving adult formulations. This was consistent for all periods, i.e. 55.4%, 59.8% and 58.8% of the children receiving adult formulations were male for periods 2010/11, 2011/12 and 2012/13, respectively.

Table 12: Relationship between sex and ARVs formulation

	Adult formulation	**Paediatric formulation**	**P value**
2010/11			
Male	1626 (55.4)	328(47.6)	0.00*
Female	1307 (44.6)	361 (52.4)	
2011/12			
Male	1,462 (59.8)	532 (50.0)	0.00*
Female	981 (40.2)	531 (50.0)	
2012/13			
Male	1,285(58.8)	505(47.8)	0.00*
Female	901(41.2)	551 (52.2)	

**=significant at p<0.05*

4.2.3.3 Relationship between age category and weight

In forecasting for antiretroviral drugs for children in Kenya, it has been assumed that children below age of 15 years weigh 25 Kg and below. However, plot of mean weight over age for the study participants revealed that children are likely to attain 25 Kg from the age of 8 years. This is demonstrated in the mean profile plot of weight over age in Figure 9.

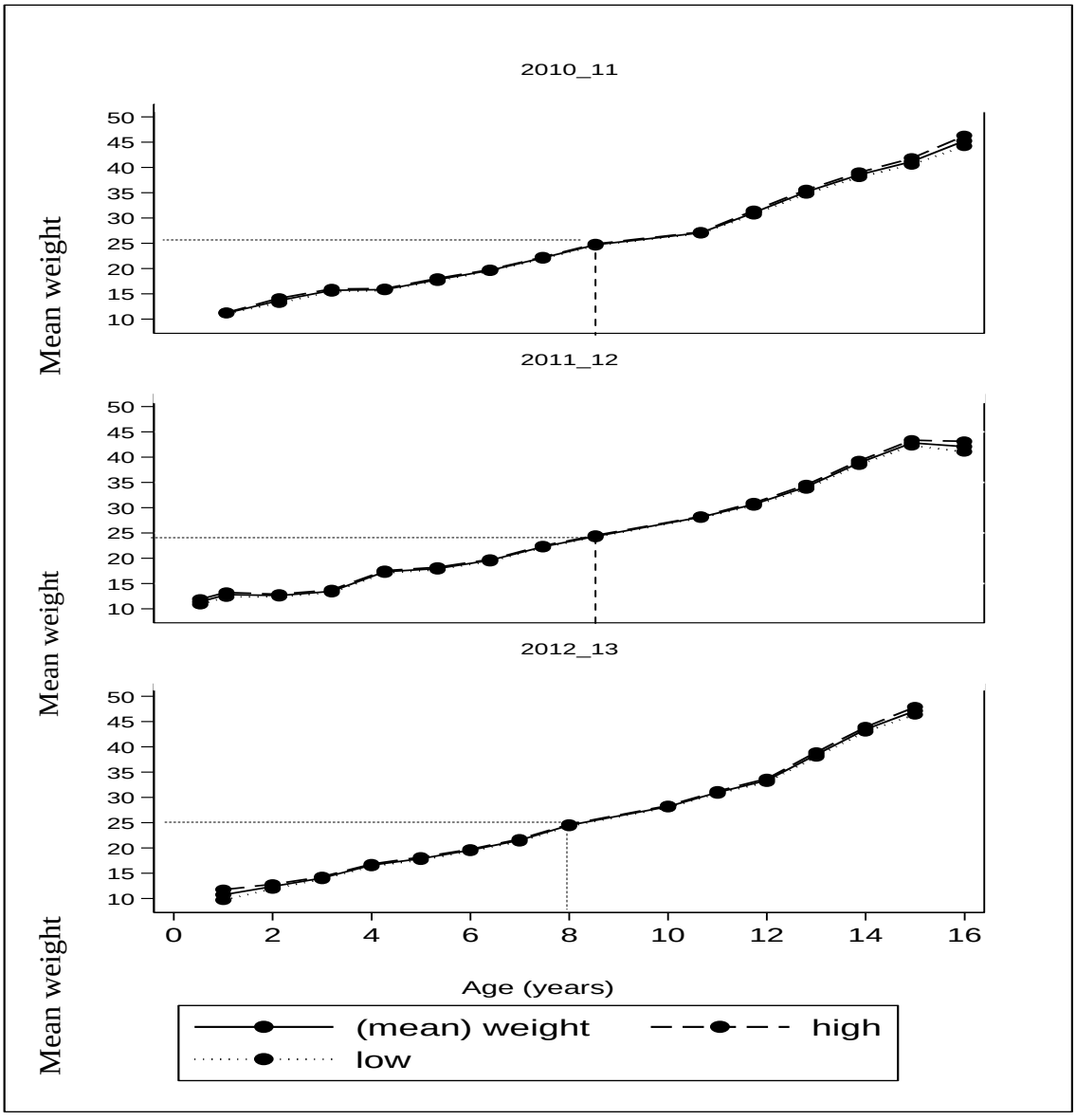

Figure 9: Profile for mean weight over age for 2010/11, 2011/12 and 2012/13

4.2.4 Within-subject effects and between-subject effects for children on antiretroviral drugs

Repeated measures logistic regression was used to carry out exploratory analysis. Within-subject and between-subject effects were observed for age, regimen, ARV dispensed, ARV formulation, weight, weight categories and weight bands across three periods; 2010/11, 2011/12 and 2012/13. For sex, no within-subject effects were observed as this is a time invariant variable. The overall mean and standard deviations for within and between-subject are presented in Table 13.

Table 13: Summary statistics for within-children and between-children effects

	Overall mean	**Overall Standard deviation**	**Within-children Standard deviation**	**Between-children Standard deviation**
2010_11				
Age (years)	9.70	3.22	3.19	0.38
Sex (n)	0.46	0.5	0.0	0.5
Regimen(n)	7.82	4.44	4.35	0.89
ARV dispensed (n)	9.90	4.93	4.73	1.37
ARV Formulation (n)	0.19	0.39	0.1	0.38
Weight (Kg)	28.07	10.33	10.20	1.67
Weight category (n)	0.59	0.49	0.15	0.47
Weight band (Kg)	6.04	1.64	1.61	0.34
2011_12				
Age(years)	9.90	3.30	3.33	0.31
Sex(n)	0.43	0.5	0.0	0.5
Regimen(n)	6.22	4.79	4.36	1.99
ARV dispensed (n)	8.48	6.02	5.52	2.31
ARV Formulation (n)	0.30	0.45	0.18	0.43
Weight(Kg)	28.78	10.44	10.29	2.16
Weight category(n)	0.65	0.48	0.15	0.45
Weight band(Kg)	6.22	1.66	1.64	0.39
2011_12				
Age(Years)	10.36	3.25	3.30	0.28
Sex(n)	0.45	0.5	0.0	0.5
Regimen(n)	4.98	4.66	4.50	1.10
ARV dispensed (n)	7.45	6.42	6.15	1.58
ARV Formulation(n)	0.32	0.47	0.12	0.46
Weight(Kg)	30.06	10.94	10.84	1.66
Weight Category(n)	0.68	0.46	0.11	0.46
Weight band(Kg)	6.40	1.68	1.68	0.32

n=number

Analysis for within- subject effects of weight and age on ARV formulation dispensed to a child revealed that weight category had statistically significant (p=0.00) within-subject effects for both the fixed-effects and random effects logistic regression models. However, Hausman test was found to be statistically significant (p=0.00) and therefore null hypothesis that random-effects model was preferred was not accepted. Further within-subject effects analysis was therefore carried out using fixed-effects logistic regression model.

Within-subject effects of weight category on ARV formulation were observed in 17(5.5%), 49(16.0%) and 26(9.1%) children for the periods 2010/11, 2011/12 and 2012/13, respectively. In this proportion of children, there were changes in ARV formulation dispensed to them due to change in weight category. The ARV formulation dispensed remained constant in 294 (94.5%), 257 (84.0%) and 259 (90.9%) children for periods 2010/11, 2011/12 and 2012/13, respectively.

Analysis of population average response for effect of weight category change on ARV formulation dispensed to a child revealed statistically significant (p=0.00) effects across the three periods. It was observed that odds ratio of being dispensed a paediatric ARV formulation when the weight is ≥ 25 Kg was 0.37, 0.03 and 0.07 for periods 2010/11, 2011/12 and 2012/13, respectively. This meant that on average, 63%, 97.0% and 93.0% of children were likely to receive adult formulations when they changed from <25 Kg to ≥25Kg weight category for periods 2010/11, 2011/12 and 2012/13, respectively.

Table 14: Odds ratio for population average response for effects of weight category change on ARV formulations

Year	Odds ratio (CI)	p-value
2010/11	0.37 (0.31, 0.45)	0.00*
2011/12	0.034 (0.023,0.049)	0.00*
2012/13	0.072 (0.052,0.1)	0.00*

*=Significant at p<0.05

4.3. Factors influencing choice of formulation dispensed to a child from dispensing staff perspective

There were fourteen dispensing personnel in Mbagathi District hospital, 13 pharmacists and one pharmaceutical technologist. At the time of the study there were 2 interns. 12 interviews were carried out where 11 pharmacists and one intern attached to the pharmacy dispensing antiretroviral drugs were interviewed.

Four thematic codes were identified as factors influencing choice of antiretroviral formulation dispensed to the paediatric patient. The thematic codes 1 to 4 represented weight, age, availability of paediatric ARV drugs and preference of the dispensing staff to dispense paediatric antiretroviral drugs to children below 15 years regardless of the weight, respectively. Thematic codes per interviewee are as displayed in Appendix 12

It was observed that all the four thematic codes were generated by the 3rd interview. Data saturation was achieved by the 8th interview. At this point, each of the thematic codes had been repeated at least three times and no new theme was generated afterwards. Weight as a factor influencing choice of antiretroviral formulation dispensed to the paediatric patient was generated from all the interviews. Age and availability of paediatric ARV drugs were identified in 58% of the interviews while preference of dispensing staff to dispense paediatric ARV formulations was identified in 42% of the interviews (Table 15). There were 71% of interviewees had 75% of the thematic codes, i.e. 3 out of the 4 codes

Table 15: Prevalence for thematic codes generated for In-depth interviews

Code number	Theme	No. of interviews with theme	Thematic prevalence
Code1	Weight	12	100%
Code2	Age	7	58%
Code3	Drug availability	7	58%
Code4	Staff preference to dispense paediatric formulations	5	42%

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CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 DISCUSSION

5.1.1 Forecast accuracy for paediatric antiretroviral drugs

Forecasts with Mean Absolute percentage Error (MAPE) of 0-10% have been categorized as highly accurate, 11-20% as good, 21-50% as reasonable and 51% and above as inaccurate (Lawrence *et.al*, 2009). All products were observed to have inaccurate forecast with the exception of nevirapine 10mg/ml. Nevirapine 10mg/ml is consumed by children on antiretroviral therapy and those HIV exposed for prevention of mother-to-child transmission. This could have attributed to the observed reasonable forecast.

In Kenya, forecasting for antiretroviral drugs heavily relies on assumption making due to lack of required data. In addition, there is no support of some of the assumption with study findings. There could also be challenges on the skills and competencies of the people involved in forecasting. In the Kenyan set-up, no attempts have been done to compare forecast outputs from different models. As such factors that may be attributed to observed forecast inaccuracies in this study include inadequacies in data used for forecasting, high reliance on assumption that have no research or survey findings support, skills and competency of the staff involved in forecasting process and probably the model used. These factors have been reported in other studies. Laila *et.al* (2011) reported that forecast accuracy for antiretroviral drugs was due to delays or failure to implement policy changes, prescribing practices not changing as anticipated, poor or inadequate data for use in forecasting and difficulties in forecasting for pediatric ARVs.

On forecast model used, Raja and Mohammad (2005) reported that forecast accuracy can be affected by the forecasting techniques and approaches. Bass (1987) reported that there are two possible explanations for forecast errors; model misclassification and inherent randomness in the model. According to him, omission of variables was probably one of

the most important types of misspecifications. Gunasekaran et.al (2004) reported that type of forecasting technique used was also important to forecast accuracy. Use at two different forecasting methods is important to improving forecast accuracy since it allows comparison of forecast output (Raja and Mohammad, 2005).

On skills and competencies, Armstrong (2001) reported that where domain knowledge existed, judgmental forecast were shown to have lower MAPE than statistical forecasts. According to Braekkan (2010), judgmental forecasting is characterized by biases inherent in human decision making and people's inability to process information in large quantities. Laila *et.al* (2011) reported that having well trained and motivated staff is fundamental to forecast accuracy.

5.1.2 Randomness of forecast errors for paediatric antiretroviral drugs

Forecasts errors for all the paediatric antiretroviral drugs namely abacavir/lamivudine 60/30mg; zidovudine/lamivudine 60/30mg; zidovudine/lamivudine/nevirapine 60/30/50mg; efavirenz 200mg; Lopinavir/ritonavir 80/20mg; nevirapine 10mg/ml and zidovudine 10mg/ml were non-random. A good forecasting model is one which only exhibits random variation.

In this study, it was found that forecast errors for all products were non-random. This meant that forecast errors were heteroscedasticity, had significant trends and patterns, and data points meandered across the centerline in a non-random manner. The non-randomness of the errors could have been due to inadequacies in data used. As noted, weight and age were wrongly applied in terms of proportions allocated to different categories. In addition, lack of data contributed to use of assumptions that were mainly judgmental and not informed. Where patterns exist in data, it means a better model used for forecasting can be developed to help predict the pattern. According to Stevenson (2009), good forecast should only have inherent variation, that is, variation that remains in the data after all cause of variation has been accounted for.

Lawrence *et.al* (2009) reported that where significant trends are observed in forecast errors, they should be removed; where forecast errors have heteroscedasticity, transforming the data using logarithmic or causal forecasting techniques would help. Where data points meandered across the centerline in a non-random manner, they suggested that one of the smoothing techniques would be useful.

5.1.3 Determinants of forecast accuracy for Paediatric Antiretroviral drugs

In forecasting for paediatric antiviral drugs, factors considered included formulation, weight, regimen and drug combinations. In addition to these factors, the study explored whether age and sex would be important factors for consideration in forecasting process. For the periods 2010/11, 2011/12 and 2012/13, forecast assumed that all children less than 15 years of age would weigh <25kg and would use paediatric antiretroviral drugs. To calculate the dosage, 8, 12 and 20 Kg for children on first line and 15 and 25Kg for children on second line were assumed to assist in calculation of dosages and quantities required. It was also assumed that there would be no children on stavudine based regimen from year 2010 (NASCOP, 2010; NASCOP, 2011 and NASCOP, 2012). These assumptions were found to differ with study findings for the study population. Where standard treatment guidelines are not adhered to, forecast errors are observed (Laila et.al (2011). In the Kenyan, set-up children were to be phased-out of stavudine in year 2010. However, a good proportion of children (58.9%, 38.9% and 22.8% in 2010/11, 2011/12 and 2012/13, respectively) were on d4T/3TC/NVP. It is therefore important that the rates to which guidelines are adhered to be reviewed and be considered during forecasting.

According to Laila *et.al* (2011), high errors for pediatric antiretroviral drugs may be attributed to difficulties in predicting formulations and dosages prescribed for different age groups and weight bands. This information they cited, was difficult to collect with some logistics management information systems (LMIS) therefore posing a challenge during forecasting. However, where data on weights of pediatric patients was collected in the LMIS reports and used to review assumptions made in forecast as well as

consumption patterns, forecast accuracy would improve with subsequent pediatric ARV forecasts.

In Kenya, data on weight and specific ARV formulations children are on is not part of the routine program data. This gap in data may have contributed the observed inaccuracies in paediatric ARV formulations. One important finding reported in this study was that majority of children were unlikely to change the formulation they were on for the 12 months forecast period. This therefore is a fundamental finding because assumptions made that a child would be on a particular ARV formulation for a period of 12 month (forecast period) supports forecast accuracy on this aspect. The forecast inaccuracies observed in this study can therefore attributed to data inadequacies on what weight categories to use to represent the children on ART and what proportion of children are on various ARV formulations.

5.1.4 Factors influencing choice of formulation dispensed to a child from dispensing staff perspective

The guidelines for antiretroviral therapy provide antiretroviral drugs dosing chart for application among children (NASCOP, 2011). With use of morbidity based forecasting method, it is expected that the treatment guidelines will be adhered to in terms of prescribing and dispensing as well as client compliance. The ARV supply chain has been lacking ARV formulations that are friendly to children in terms of reduced pill burden, and palatability. Some adult ARV formulations can conveniently be split into required dose requirements for children and therefore are preferred due to reduced pill burden. As such both paediatric and adult ARV formulations are available for dispensing to children and it is left to the discretion of the dispensing staff to choose the formulation to dispense. Forecast for paediatric ARV drugs assume that all children age less than 15 years will weigh less than 25 Kg and will use paediatric ARV formulations (NASCOP 2010; NASCOP 2011 and NASCOP 2012). However, in-depth interview of the dispensing staff revealed that even among the children aged less than 15 years, there were

weight and age considerations. As such not all children aged less than 15 years received paediatric ARV formulations. In addition, the dispensing staff reported that availability of paediatric ARV drugs was considered during ARV drugs dispensing to children. This could mean that the study sites experiences occasional shortages or stock-outs of some paediatric ARV formulations. Some staff reported that they preferred dispensing paediatric ARV drugs to children below 15 years regardless of the weight were reported as factors that influenced choice of regimen. From prior discussion, weight and age were shown to be important factors from analysis of dispensing data.

5.2 CONCLUSION

This study found that forecasts for abacavir/lamivudine 60/30mg; zidovudine/lamivudine 60/30mg; zidovudine/lamivudine/nevirapine 60/30/50mg; efavirenz 200mg; Lopinavir/ritonavir 80/20mg and zidovudine 10mg/ml were inaccurate and only nevirapine 10mg/ml had accurate forecast for the period 2010/11, 2011/12 and 2012/13. The forecast errors were found to be non-random meaning that models used for forecasting were inadequate. As such, there existed trends and patterns that could be predicted by developing a better model.

The assumptions that all children aged less than 5 years weighed less than 25Kg were found to be inaccurate. Children were likely to attain 25Kg at the age of 8years. More than 50% of children aged less than 15 years weight more than 25 Kg and majorly used adult formulations while among those weighing less than 25Kg, a small proportion used adult formulations.

Adherence to treatment guidelines is one of the assumptions made in forecasting for using the morbidity based forecasting method. In Kenya, the use of stavudine based regimen was to be phased-out in year 2010. However, it was noted that 58.9%, 38.9% and 22.8% of children were on stavudine based regimen in 2010/11, 2011/12 and 2012/13, respectively. It is therefore concluded that, standard treatment guidelines were not adhered to as envisaged and contributed to the observed forecast inaccuracies. .

This study also concludes that dispensing staff consider age and weight when choosing the ARV to dispense to children. On this, the dispensing staff adheres to the treatment guidelines. However, from analysis done on the dispensing data, a good majority of children are dispensed adult formulations. Drug availability is an important factor to consider when forecasting. The purpose of forecasting is to plan for the future and ensure uninterrupted supply of ARV drugs. As such the supply chain needs to be evaluated to determine whether health facilities receive their supplies on time. Only 48% of the dispensing staff reported to prefer to dispense paediatric formulations to children.

5.3 RECOMMENDATIONS

This study recommends that forecast accuracy for antiretroviral drugs should be monitored quarterly or biannually in order to make necessarily adjustments in good time. Annual evaluations for forecast accuracy should also be done to guide the annual forecasting. The reasons as to why the forecast for NVP 10mg/ml was accurate should be explored and lessons be learnt from this. There is need to identify all variables required for forecasting and carry out intensive data review including studies review where applicable prior to forecasting. Specifically, data on weight, age, formulations, regimen and drug combinations children are on should be collected and reviewed periodically. Forecast output can be compared using two or more forecast methods to assess closeness levels. There is also need to evaluate to what extent guidelines and policies are adhered as well as to what extent strategies for guideline and policy implementation are met.

Using this study's findings as baseline, a bigger study would be more representative need to be carried out for generalizability purposes. Human resource capacity to carry out quality forecasting and supply planning needs to be assessed and where applicable capacity building done to be equip staff with knowledge and skills to support uninterrupted supply chain bot at national and county governments.

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5.4 DISSEMINATION PLAN

National AIDS/STI Control Program (NASCOP) holds monthly commodity security meeting where all relevant stakeholders in products for HIV infection, care and treatment participate. During this meeting, reports and updates on supply chain in terms of stock status, procurement requirements, delivery status of ordered products is discussed. In addition, any challenges are discussed. NASCOP also hold annual HIV care and treatment scientific conferences annually. This avenue will be explored to disseminate the study findings. A policy brief paper will also be written to inform the management on the findings and need to change the forecast approach as well as need to train staff on forecasting. The findings of this study will also be published in a local or international review journal. Opportunities for oral presentation of the findings will also be explored locally and internationally.

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APPENDICES

Appendix 1: Antiretroviral drugs dosing chart for children

ANTIRETROVIRAL DRUGS DOSING CHART FOR CHILDREN

Weight	ABC 60mg + 3TC 30mg	AZT 60mg + 3TC 30mg	AZT 60mg + 3TC 30mg + NVP 50mg	ABC 300mg	3TC 150 mg	AZT 10mg/ml	AZT 300 mg	EFV 200g and 600mg	NVP 10mg/ml	NVP 200 mg	NVP 10mg/ml	NVP 200 mg	LPV/r 80/20mg/ml	LPV/r 200/50 mg
	Twice Daily	Twice Daily	Twice Daily	Twice Daily	Twice Daily	Twice Daily	Twice Daily	Once Daily	Induction Dose: once daily		nce Dose: Twice Daily		Twice Daily	
3-3.9	1 tab	1 tab	1 tab	-	-	6ml	-	Not recommended	5ml	-	5ml	-	1ml	-
4-4.9	1 tab	1 tab	1 tab	-	-	6ml	-	Not recommended	5ml	-	5ml	-	1.5ml	-

5-5.9	1 tab	1 tab	1 tab	-	-	6ml	-	Not recommended	5ml	-	5ml	-	1.5ml	-
6-6.9	1.5 tab	1.5 tab	1.5 tab	-	-	9ml	-	Not recommended	8ml	-	8ml	-	1.5ml	-
7-7.9	1.5 tab	1.5 tab	1.5 tab	-	-	9ml	-	Not recommended	8ml	-	8ml	-	1.5ml	-
8-8.9	1.5 tab	1.5 tab	1.5 tab	-	-	9ml	-	Not recommended	8ml	-	8ml	-	1.5ml	-
9-9.9	1.5 tab	1.5 tab	1.5 tab	-	-	9ml	-	Not recommended	8ml	0.5 tab	8ml	0.5 tab	1.5ml	-
10-10.9	2 tab	2 tab	2 tab	-	-	12ml	-	200mg tab	10ml	0.5 tab	10ml	0.5 tab	2ml	-
11-11.9	2 tab	2 tab	2 tab	0.5 tab	-	12ml	-	200mg tab	10ml	0.5 tab	10ml	0.5 tab	2ml	-
12-13.9	2 tab	2 tab	2 tab	0.5 tab	0.5 tab	12ml	-	200mg tab	10ml	0.5 tab	10ml	0.5 tab	2ml	1 tab
14-16.9	2.5 tab	2.5 tab	2.5 tab	0.5 tab	0.5 tab	-	0.5 tab	1.5 tab of 200mg	15ml	-	-	1 tab am, 0.5 tab pm	2.5ml	1 tab

17-19.9	2.5 tab	2.5 tab	2.5 tab	0.5 tab	0.5 tab	-	0.5 tab	1.5 tab of 200mg	15ml	-	-	1 tab am, 0.5 tab pm	2.5ml	1 tab
20-24.9	3 tab	3 tab	3 tab	1 tab am, 0.5 tab pm	1 tab am, 0.5 tab pm	-	1 tab am, 0.5 tab pm	1.5 tab of 200mg	15ml	-	-	1 tab am, 0.5 tab pm	3ml	1 tab
25-29.9	Treat as adult	Treat as adult	Treat as adult	1 tab	1 tab	-	1 tab	2 tab of 200mg	-	1 tab	-	1 tab	3.5ml	2 tab am, 1 tab pm
30-34.9	Treat as adult	Treat as adult	Treat as adult	2 tab	2 tab	-	1 tab	2 tab of 200mg	-	1 tab	-	1 tab	4ml	2 tab am, 1 tab pm
35-39.9	Treat as adult	Treat as adult	Treat as adult	3 tab	3 tab	-	1 tab	2 tab of 200mg	-	1 tab	-	1 tab	5ml	2 tab am, 1 tab pm

Appendix 2: Runs Test Table

Runs Test Table

This Table gives upper and lower critical values of r. Reject the Null hypothesis of Randomness at the 5% level if r, the number of runs is less than or equal to the first value in Table 4 or Greater than or equal to the second value in Table 4. For example if $n_1 = 10$, $n_2 = 11$ and $r = 8$, we find the numbers 6 and 17 on the Table. Since 8 is between these two numbers, we do not reject the hypothesis of randomness.

n_2

n_1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
2											2	2	2	2	2	2	2	2	2
											-	-	-	-	-	-	-	-	-
3					2	2	2	2	2	2	2	2	2	3	3	3	3	3	3
					-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4				2	2	2	3	3	3	3	3	3	3	3	4	4	4	4	4
				9	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5		2	2	2	3	3	3	3	3	4	4	4	4	4	4	4	5	5	5
		-	9	10	10	11	11	-	-	-	-	-	-	-	-	-	-	-	-
6		2	2	3	3	3	3	4	4	4	4	5	5	5	5	5	5	6	6
		-	9	10	11	12	12	13	13	13	13	-	-	-	-	-	-	-	-
7		2	2	3	3	3	4	4	5	5	5	5	5	6	6	6	6	6	6
		-	-	11	12	13	13	14	14	14	14	15	15	15	-	-	-	-	-
8		2	3	3	3	4	4	5	5	5	6	6	6	6	6	7	7	7	7
		-	-	11	12	13	14	14	15	15	16	16	16	16	17	17	17	17	17
9		2	3	3	4	4	5	5	5	6	6	6	7	7	7	7	8	8	8
		-	-	-	13	14	14	15	16	16	16	17	17	18	18	18	18	18	18
10		2	3	3	4	5	5	5	6	6	7	7	7	7	8	8	8	8	9
		-	-	-	13	14	15	16	16	17	17	18	18	18	19	19	19	20	20
11		2	3	4	4	5	5	6	6	7	7	7	8	8	8	9	9	9	9
		-	-	-	13	14	15	16	17	17	18	19	19	19	20	20	20	21	21
12	2	2	3	4	4	5	6	6	7	7	7	8	8	8	9	9	9	10	10
	-	-	-	-	13	14	16	16	17	18	19	19	20	20	21	21	21	22	22
13	2	2	3	4	5	5	6	6	7	7	8	8	9	9	9	10	10	10	10
	-	-	-	-	-	15	16	17	18	19	19	20	20	21	21	22	22	23	23
14	2	2	3	4	5	5	6	7	7	8	8	9	9	9	10	10	10	11	11
	-	-	-	-	-	15	16	17	18	19	20	20	21	22	22	23	23	23	24
15	2	3	3	4	5	6	6	7	7	8	8	9	9	10	10	11	11	11	12
	-	-	-	-	-	15	16	18	18	19	20	21	22	22	23	23	24	24	25
16	2	3	4	4	5	6	6	7	8	8	9	9	10	10	11	11	11	12	12
	-	-	-	-	-	-	17	18	19	20	21	21	22	23	23	24	25	25	25
17	2	3	4	4	5	6	7	7	8	9	9	10	10	11	11	11	12	12	13
	-	-	-	-	-	-	17	18	19	20	21	22	23	23	24	25	25	26	26
18	2	3	4	5	5	6	7	8	8	9	9	10	2	11	11	12	12	13	13
	-	-	-	-	-	-	17	18	19	20	21	22	23	24	25	25	26	26	27
19	2	3	4	5	6	6	7	8	8	9	10	10	11	11	12	12	13	13	13
	-	-	-	-	-	-	17	18	20	21	22	23	23	24	25	26	26	27	27
20	2	3	4	5	2	6	7	8	9	9	10	10	11	12	12	13	13	13	14
	-	-	-	-	-	-	17	18	20	21	22	23	24	25	25	26	27	27	28

Appendix 3: Ethical approval letter

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/112 Link:www.uonbi.ac.ke/activities/KNHUoN 16th April 2014

Dr. Njogo Susan M.G.
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Dr. Njogo

RESEARCH PROPOSAL: DETERMINATION OF FORECAST ACCURACY FOR PAEDIATRIC ANTIRETROVIRAL DRUGS IN KENYA (P41/01/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 16th April 2014 to 15th April 2015.

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 severe 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-Ethics & Research Committee 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 **www.uonbi.ac.ke/activities/KNHUoN.**

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Chairperson, KNH/UoN-ERC
The Deputy Director CS, KNH
The Dean, School of Pharmacy, UoN
The Chairman, Dept. of Pharmacology and Pharmacognosy, UoN
The Assistant Director, Health Information, KNH
Supervisors: Dr. G.O.Osanjo, Dr.E.M. Guantai

Protect to Discover

Appendix 4: Data collection forms

1. **Forecast accuracy Table**

FORECAST ACCURACY TABLE

Year……

Period	**Actual (A)**	**Forecast (F)**	**Error (A-F)**	**Error**	**(Error/Actual) x 100**
July					
August					
September					
October					
November					
December					
January					
February					
March					
April					
May					
June					

2. Antiretroviral drug dispensing records to children

ANTIRETROVIRAL DRUG DISPENSING RECORDS FOR CHILDREN

Part I: Patient's details at ART initiation

1. Study ID: …….
2. Date of ART initiation: ……
3. Weight (Kg) at ART initiation: ……
4. Age (years) at ART initiation: …….
5. Patient's regimen at ART initiation: …….
6. Antiretroviral drugs dispensed at ART initiation:

	ARV drug	Formulation
1		
2		
3		
4		

7. Sex: Male ☐ Female ☐
8. Did the patient discontinue antiretroviral therapy during the study period?

   Yes ☐ No ☐
9. If Yes, what was the reason for discontinuation

Deceased ☐ Stopped ☐ Transfer-out ☐

Lost-to-follow-up ☐ Reason not indicated ☐

Part II: Patient's details on repeated measurements.

Study period: July 2010 to June 2013

				Drug dispensing details				
Date of ARVs dispensing	Age (years)	Weight (Kg)	Regimen	ARV drugs dispensed (use codes provided)	Formulation (1-solid; 2-liquid)	Dose	No. of Tablets per dose	Dispensed formulation. 1-Solids only; 2-liquids only; 3-both solids and liquids

ANTIRETROVIRAL DRUGS CODES

Drug	code
AZT/3TC 60/30mg	1
AZT/3TC/NVP 60/30/50mg	2
AZT/3TC 300/150mg	3
AZT/3TC/NVP 300/150/200mg	4
AZT 10mg/ml	5
AZT 300mg	6
ABC/3TC 60/30mg	7
ABC 300mg	8
ABC 20mg/ml	9
d4T/3TC 12/60mg	10
d4T/3TC/NVP 12/60/100mg	11
d4T/3TC 30/150mg	12
d4T/3TC/NVP 30/150/200mg	13
3TC 150mg	14
3TC 10mg/ml	15
NVP 50mg	16
NVP 200mg	17
NVP 10mg/ml	18
EFV 30mg/ml	19
EFV 50mg	20
EFV 200mg	21
EFV 600mg	22
LPV/r 80/20mg/ml	23
LPV/r 250mg	24
LPV/r 125mg	25

3. In-depth interview guide

IN-DEPTH INTERVIEW GUIDE

Introduction

My name is ……. I am a student at the University of Nairobi (UON) pursuing a master's degree in Pharmacoepidemiology and Pharmacovigilance. My colleague is ……He/she is my study assistant. This study is on "Determinants of forecast accuracy for paediatric antiretroviral drugs in Kenya". As we all know, uninterrupted supply of antiretroviral medicines is key to HIV infection prevention and treatment. The aim of this interview is to get insight on factors that influence your choice of antiretroviral medicine formulations you dispensed to paediatric patients.

The interview involves open discussion on your knowledge and experience regarding the study. The interview will take 30 to 45 minutes. Your responses will be recorded in notebooks and not tape recorded as explained in the informed consent forms.

It is my hope that your responses will help toimprove the forecast accuracy for paediatric antiretroviral medicines. Please note that whatever information you provide will be held in confidence.

Thank you. We may now start

1. What regimen are majority of the children on?
    - What factors influences/determine choice of regimen a child is put on when starting therapy?
    - What factors influences/determine choice of regimen a child is put on when changing therapy?
    - Who determines the regimen to put a child on?

2. What antiretroviral drugs do you have for dispensing to children on antiretroviral therapy?
    - Specify whether they are liquid or solid formulations
        - How are paediatric antiretroviral drugs packed? e.g. is it according to
            - monthly dosage requirements
            - regimen combinations
            - any other reason
    - Do you stock paediatric antiretroviral drugs that are fixed dose combinations (FDC)?
        - What antiretroviral drugs do you have as FDCs?
        - When did you start stocking and dispensing FDCs?
        - Are FDCs always available
    - For ARVs that are not FDCs, do you combine only paediatric formulations or you also combine with adult formulations?
    - Do you dispense adult formulations to children?
        - What are the major adult formulations mainly dispensed to children?
        - Why are adult formulations dispensed to children?
        - Is use of adult formulation among children intermittent or constant for those on the formulations?
        - What formulations are majority of the children on? Adult or paediatric formulations?

3. Do you experience any challenges dispensing to the paediatric patients? If yes..
    - What challenges do you experience dispensing to the paediatric patients?

4. What factors do you consider when choosing the formulation to dispense to children on ART?

- age, weight, availability, others
- What influence does the caregiver have on choice of formulation?
- What influence do the personnel dispensing antiretroviral drugs to children have on choice of formulation?

Closing remarks

As we come to a close, is there any other additional information you think relevant for the study?

As I had mentioned, no information given here will be linked back to you.

Thank you for your time and for the information you have shared with us.

4. Informed Consent Form

INFORMED CONSENT FORM

Informed Consent for INTERVIEW PARTICIPATION "Determinants of forecast accuracy for paediatric antiretroviral drugs in Kenya"

The principle investigator for this study is:

Dr. Susan Njogo

Master's Student, School of Pharmacy, University of Nairobi.

The study is being carried out with approval from Kenyatta National Hospital/University of Nairobi Ethics and Research committee (KNH/UoN-ERC).

This Informed Consent Form is in **two parts**:

1. Information Sheet (to share information about the study with you)

2. Certificate of Consent (for signatures if you choose to participate)

You will be given a copy of the full Informed Consent Form.

Part 1: Information Sheet

This study is on "Determinants of forecast accuracy for paediatric antiretroviral drugs in Kenya". Information is being provided to you about the study, and you are invited to willingly participate. Before making the decision to participate you are free to ask all the questions you deem relevant to your understanding of the study.

This study aims to establish the forecast accuracy for paediatric antiretroviral medicines in Kenya and determine the factors that affect this accuracy. As we all know availability and accessibility of antiretroviral medicines is key to HIV infection management. As such antiretroviral medicines should have a robust supply chain that should be supported by good forecast for future demand to support existing patients and any future scale-up.

You are being requested to participate in this study as I believe that that your experience in providing information will help answer the study question. This is an in-depth interview where probing questions will be used and your response will be recorded down in notebooks. The interview will not be taped. Whatever is discussed will be held in confidence. The interview will take about 30 to 45 minutes.

You participation in this assessment is entirely voluntary. Your response will have no bearing on your job or any work-related evaluations or reports. You will not be ask personal questions, and you do not have to share any information that you are not comforTable sharing.

There is a risk that you may share some personal or confidential information by chance, or that you may feel uncomforTable talking about some of the topics. However, we do not wish for this to happen. You do not have to answer any question or take part in the discussion if you are uncomforTable.

Your participation in this study will not necessarily provide a direct benefit to you, but your participation will help strengthen the forecast accuracy for paediatric antiretroviral medicines.

Data collected from this discussion will be combined with data collected from multiple other interviews and records, and upon analysis a report will be written. This information will be shared with your health facility, and key stakeholders in antiretroviral medicines in Kenya. There will be no information included which can be linked back to you in any way.

Part 2: Certificate of Consent

I have read the foregoing information. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

PRINTED NAME OF PARTICIPANT:
_____

SIGNATURE OF PARTICIPANT: _____

DATE: _____

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that:

1. He/she will take part in an interview

2. The discussion will be recorded on notebooks and later analyzed.

I confirm that the participant was given an opportunity to ask questions about the study, and all questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant

PRINTED NAME OF RESEARCHER/PERSON TAKING CONSENT:

_____

SIGNATURE OF RESEARCHER/PERSON TAKING CONSENT:

_____

DATE: _____

Appendix 5: Sample data for actual and forecast consumption used for computation of Mean Absolute Percentage Errors (MAPE)

ABC/3TC 60/30mg			*AZT/3TC/NVP 60/30/50mg*			*LPV/r 80/20mg/ml*			*AZT 10mg/ml*		
	Consumption			**Consumption**			**Consumption**			**Consumption**	
Month	**Actual**	**Forecast**	**Month**	**Actual**	**Forecast**	**Month**	**Actual**	**Forecast**	**Month**	**Actual**	**Forecast**
Jul-10	4,619	12648	Jul-10	12,055	29152	Jul-10	1,626	176	Jul-10	9,190	8639
Aug-10	5,174	13004	Aug-10	12,517	29591	Aug-10	1,108	351	Aug-10	8,075	8836
Sep-10	6,622	13361	Sep-10	10,963	30031	Sep-10	1,187	527	Sep-10	7,851	9033
Oct-10	9,265	13717	Oct-10	14,656	30470	Oct-10	1,254	703	Oct-10	8,413	9230
Nov-10	7,969	14074	Nov-10	17,664	30909	Nov-10	1,354	878	Nov-10	7,981	9428
Dec-10	7,312	14430	Dec-10	18,688	31348	Dec-10	1,175	1,054	Dec-10	10,792	9625
Jan-11	12,503	14787	Jan-11	24,928	31787	Jan-11	1,422	1,230	Jan-11	7,458	9822
Feb-11	16,565	15143	Feb-11	22,392	32227	Feb-11	2,059	1,405	Feb-11	4,218	10019
Mar-11	18,082	15500	Mar-11	25,968	32666	Mar-11	1,775	1,581	Mar-11	9,279	10216
Apr-11	7,647	15856	Apr-11	15,834	33105	Apr-11	1,398	1,757	Apr-11	4,938	10413
May-11	7,561	16213	May-11	18,036	33544	May-11	1,971	1,932	May-11	14,368	10610
Jun-11	10,723	16569	Jun-11	17,157	33983	Jun-11	1,681	2,108	Jun-11	6,062	10807

Appendix 6: Regimen proportion for children at baseline

		N(%)		
		July 2010	July 2011	July 2012
1	d4t/3TC/NVP	189(60.8)	153(50.0)	70(24.6)
2	AZT/3TC/NVP	77(24.8)	87(28.4)	131(46.0)
3	ABC/3TC/NVP	21(6.8)	36(11.8)	46(16.1)
4	ABC/3TC/LPV/r	8(2.6)	1(0.3)	5(1.8)
5	ABC/DDI/LPV/r	7(2.3)	11(0.3)	6(2.1)
6	d4t/3TC/EFV	4(1.30	1(1.6)	1(0.4)
7	AZT/3TC/EFV	3(1.0)	5(1.6)	7(2.5)
8	d4t/3TC/LPV/r	1(0.3)	0(0.0)	0(0.0)
9	TDF/3TC/NVP	1(0.3)	3(1.0)	2(0.7)
10	AZT/3TC/LPV/r	0(0.0)	2(0.7)	4(1.4)
11	AZT/DDI/LPV/r	0(0.0)	0(0.0)	0(0.0)
12	ABC/3TC/EFV	0(0.0)	4(1.3)	6(2.1)
13	TDF/3TC/EFV	0(0.0)	3(1.0)	4(1.4)
14	TDF/3TC/LPV/r	0(0.0)	0(0.0)	3(1.1)

Appendix 7: Proportion for antiretroviral drug combination in July 2010

ARV drug	**N**	**%**
d4T/3TC/NVP 30/150/200mg	189	60.8%
AZT/3TC/NVP 300/150/200mg	32	10.3%
AZT/3TC/NVP 60/30/50mg	25	8.0%
ABC/3TC 60/30mg + NVP 200mg	10	3.2%
ABC 300mg + DDI 250mg + LPV/r 250mg	9	2.9%
ABC 300mg + 3TC 150mg + NVP 200mg	8	2.6%
AZT 10mg/ml + 3TC 150mg + NVP 200mg	8	2.6%
AZT 300mg + 3TC 150mg + NVP 200mg	4	1.3%
ABC 300mg + DDI 250mg + LPV/r 125mg	3	1.0%
AZT 10mg/ml + 3TC 10mg/ml + NVP 10mg/ml	3	1.0%
AZT 10mg/ml + 3TC 150mg + NVP 10mg/ml	2	0.6%
d4T/3TC 30/150mg + EFV 200mg	2	0.6%
d4T/3TC 30/150mg + EFV 200mg + EFV 50mg	2	0.6%
ABC 20mg/ml + 3TC 10mg/ml + NVP 10mg/ml	1	0.3%
ABC 20mg/ml + 3TC 10mg/ml + NVP 200mg	1	0.3%
ABC 20mg/ml + 3TC 150mg + NVP 10mg/ml	1	0.3%
ABC 20mg/ml + DDI 25mg + LPV/r 125mg	1	0.3%
ABC 300mg + 3TC 150mg + LPV/r 250mg	1	0.3%
ABC/3TC 60/30mg + LPV/r 125mg	1	0.3%
AZT 10mg/ml + 3TC 10mg/ml + NVP 200mg	1	0.3%
AZT 300mg + 3TC 150mg + EFV 200mg + EFV 50mg	1	0.3%
AZT 300mg + 3TC 150mg + NVP 10mg/ml	1	0.3%
AZT/3TC 300/150mg + EFV 200mg	1	0.3%
AZT/3TC 300/150mg + EFV 600mg	1	0.3%
AZT/3TC 300/150mg + NVP 200mg	1	0.3%
d4T/3TC 30/150mg + LPV/r 250mg	1	0.3%
TDF/3TC + NVP 200mg	1	0.3%
ABC 300mg + 3TC 150mg +EFV 600mg	311	100.0%

Appendix 8: Proportion for antiretroviral drug combination in July 2011

ARV drug	**N**	**%**
d4T/3TC/NVP 30/150/200mg	147	48.0%
AZT/3TC/NVP 60/30/50mg	47	15.4%
AZT/3TC/NVP 300/150/200mg	39	12.7%
ABC/3TC 60/30mg + NVP 200mg	18	5.9%
ABC 300mg + 3TC 150mg + NVP 200mg	14	4.6%
ABC 300mg + DDI 250mg + LPV/r 250mg	6	2.0%
d4T/3TC/NVP 12/60/100mg	6	2.0%
ABC 300mg + 3TC 150mg + LPV/r 250mg	4	1.3%
ABC 20mg/ml + 3TC 10mg/ml + NVP 10mg/ml	3	1.0%
ABC/3TC 60/30mg + EFV 200mg + 50mg	3	1.0%
TDF/3TC + NVP 200mg	3	1.0%
TDF/3TC/EFV	3	1.0%
AZT/3TC 300/150mg + EFV 600mg	2	0.7%
AZT/3TC 300/150mg + LPV/r 250mg	2	0.7%
AZT/3TC 60/30mg+EFV 200mg + 50mg	2	0.7%
ABC 300mg + DDI25mg+ LPV 250mg	1	0.3%
ABC/3TC 60/30mg + EFV 200mg	1	0.3%
ABC/3TC 60/30mg + LPV/r 250mg	1	0.3%
ABC/3TC 60/30mg + NVP 10mg/ml	1	0.3%
AZT 10mg/ml + 3TC 10mg/ml + NVP 10mg/ml	1	0.3%
AZT/3TC 300/150mg + EFV 200mg	1	0.3%
d4T/3TC 30/150mg + EFV 200mg	1	0.3%
	306	100.0%

Appendix 9: Proportion for antiretroviral drug combination in July 2012

ARV drug	N	%
d4T/3TC/NVP 30/150/200mg	70	24.6%
AZT/3TC/NVP 300/150/200mg	68	23.9%
AZT/3TC/NVP 60/30/50mg	62	21.8%
ABC/3TC 60/30mg + NVP 200mg	24	8.4%
ABC 300mg + 3TC 150mg + NVP 200mg	21	7.4%
ABC 300mg + 3TC 150mg + LPV/r 250mg	6	2.1%
ABC/3TC 60/30mg + EFV 200mg	4	1.4%
ABC/3TC 60/30mg + LPV/r 250mg	4	1.4%
AZT/3TC 60/30mg+EFV 200mg	3	1.1%
AZT/3TC 60/30mg+LPV/r 250mg	3	1.1%
TDF/3TC + LPV/r 250mg	3	1.1%
TDF/3TC/EFV	3	1.1%
ABC/3TC 60/30mg +LPV/r 80/20mg/ml	2	0.7%
AZT/3TC 300/150mg + EFV 200mg	2	0.7%
AZT/3TC 300/150mg + EFV 600mg	2	0.7%
TDF/3TC + NVP 200mg	2	0.7%
ABC 300mg + 3TC 150mg +EFV 600mg	1	0.4%
ABC 300mg + 3TC 150mg+EFV 200mg	1	0.4%
AZT/3TC 300/150mg + LPV/r 250mg	1	0.4%
AZT/3TC 60/30mg+NVP 200mg	1	0.4%
d4T/3TC 30/150mg + EFV 200mg	1	0.4%
TDF/3TC+EFV 200mg	1	0.4%
Total	**285**	**100.0%**

Appendix 10: Proportion of children dispensed antiretroviral drugs for 12 months

	N(%)		
Dispensing months	2010/11	2011/12	2012/13
12	289(92.9)	275(89.9)	251(88.1)
11	3(1.0)	3(1.0))	4(1.4)
10	3(1.0)	1(0.3)	2(0.7)
9	4(1.3)	2(0.7)	6(2.1)
8	2(0.6)	6(0.2)	3(1.1)
7	1(0.3)	6(0.2)	3(1.1)
6	1(0.3)	3(1.0)	4(1.4)
5	2(0.6)	3(1.0)	4(1.4)
4	1(0.3)	3(1.0)	3(1.1)
3	3(1.0)	2(0.1)	3(1.1)
2	1(0.3)	2(0.1)	0(0.0)
1	1(0.3)	0(0.0)	2(0.7)
Total	**311(100.0)**	**306(100.0)**	**285(100.0)**

Appendix 11: Average proportion of children on various ARV drug combination per period

ARV drug combination	2010/11	2011/12	2012/13
d4T/3TC/NVP 30/150/200mg	58.90%	36.91%	22.76%
AZT/3TC/NVP 300/150/200mg	11.43%	20.08%	28.01%
AZT/3TC/NVP 60/30/50mg	11.76%	18.25%	19.62%
ABC/3TC 60/30mg + NVP 200mg	4.10%	6.39%	7.62%
ABC 300mg + 3TC 150mg + NVP 200mg	2.62%	4.99%	7.43%
d4T/3TC/NVP 12/60/100mg		2.00%	
ABC 300mg + 3TC 150mg + LPV/r 250mg	0.61%	1.97%	2.22%
TDF/3TC/EFV	0.03%	1.65%	1.57%
ABC 300mg + DDI 250mg + LPV/r 250mg	3.31%	1.20%	
TDF/3TC + NVP 200mg	0.91%	1.03%	0.99%
ABC/3TC 60/30mg + EFV 200mg		0.86%	1.20%
ABC/3TC 60/30mg + LPV/r 250mg		0.80%	1.23%
AZT/3TC 300/150mg + LPV/r 250mg	0.11%	0.57%	0.40%
AZT/3TC 60/30mg+EFV 200mg + 50mg	0.22%	0.54%	0.15%
AZT/3TC 300/150mg + EFV 600mg	0.20%	0.48%	0.74%
ABC/3TC 60/30mg + EFV 200mg + 50mg		0.46%	
AZT/3TC 60/30mg+EFV 200mg		0.43%	0.89%
ABC 20mg/ml + 3TC 10mg/ml + NVP 10mg/ml	0.03%	0.23%	
ABC 300mg + DDI25mg+ LPV 250mg		0.23%	
TDF/3TC + LPV/r 250mg	0.20%	0.23%	1.11%
AZT/3TC 300/150mg + EFV 200mg	0.33%	0.20%	0.74%
ABC/3TC 60/30mg + NVP 10mg/ml	0.06%	0.14%	
d4T/3TC 30/150mg + EFV 200mg	0.52%	0.14%	0.25%
AZT/3TC 60/30mg+LPV/r 80/20mg/ml		0.09%	
AZT 10mg/ml + 3TC 10mg/ml + NVP 10mg/ml	0.28%	0.06%	
TDF/3TC + EFV 200mg		0.06%	
AZT/3TC 60/30mg+LPV/r 250mg		0.03%	1.05%
ABC 20mg/ml + 3TC 10mg/ml + NVP 200mg	0.06%		
ABC 20mg/ml + 3TC 150mg + NVP 10mg/ml	0.03%		
ABC 20mg/ml + DDI 25mg + LPV/r 125mg	0.33%		
ABC 300mg + 3TC 150mg +EFV 600mg			0.37%
ABC 300mg + 3TC 150mg+EFV 200mg			0.37%
ABC 300mg + DDI 250mg + LPV/r 125mg	0.58%		
ABC/3TC 60/30mg + LPV/r 125mg	0.33%		
ABC/3TC 60/30mg +LPV/r 80/20mg/ml			0.74%

AZT 10mg/ml + 3TC 10mg/ml + NVP 200mg	0.06%		
AZT 10mg/ml + 3TC 150mg + NVP 10mg/ml	0.20%		
AZT 10mg/ml + 3TC 150mg + NVP 200mg	1.55%		
AZT 300mg + 3TC 150mg + EFV 200mg + EFV 50mg	0.25%		
AZT 300mg + 3TC 150mg + NVP 10mg/ml	0.06%		
AZT 300mg + 3TC 150mg + NVP 200mg	0.36%		
AZT/3TC 300/150mg + EFV 200+50mg	0.03%		
AZT/3TC 300/150mg + LPV/r 125mg	0.20%		
AZT/3TC 300/150mg + LPV/r 80/20mg/ml			0.03%
AZT/3TC 300/150mg + NVP 200mg	0.11%		0.06%
AZT/3TC 60/30mg+EFV 600mg			0.03%
AZT/3TC 60/30mg+NVP 200mg			0.03%
d4T/3TC 30/150mg + EFV 200mg + EFV 50mg	0.20%		
d4T/3TC 30/150mg + LPV/r 250mg	0.06%		
TDF/3TC+EFV 200mg			0.37%

Appendix 12: Summary of thematic codes generated per interviewee

	Thematic code 1	**Thematic code 2**	**Thematic code 3**	**Thematic code 4**
Interviewee number	**(Weight)**	**(Age)**	**(Availability of paediatric ARV drugs)**	**(Dispensing staff)**
1	√			
2	√	√	√	
3	√	√	√	√
4	√	√		
5	√			
6	√		√	√
7	√	√	√	
8	√	√		√
9	√		√	
10	√	√		√
11	√	√	√	√
12	√		√	
Response rate per thematic code	**100%**	**58%**	**58%**	**42%**