The Cost of Implementing HIV Drug Resistance Testing in Kenya: A Case Study of a Service Delivery Site at Kenyatta National Hospital

By

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Declaration

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

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Date

This Paper has been submitted for examination with my approval as University of Nairobi supervisor

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DR. Daniel Mwai

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Date

Abstract

World health organization (WHO) recommends the inclusion of HIV drug resistance (HIVDR) testing in management of Human Immunodeficiency Virus (HIV) patients on treatment to mitigate the rising cases of HIVDR. However, despite this recommendation, there is paucity of information related to the cost of HIVDR testing in Kenya. This study aimed at estimating the unit cost of HIVDR testing, identifying the cost drivers for the HIVDR test, exploring opportunities for cost saving and documenting challenges and lessons learnt in implementation of HIVDR testing. To achieve these objectives, the cost analysis was performed at Molecular and Infectious Diseases Research (MIDR) Laboratory, a KNH/UON-CoEHM project initiative situated at the University of Nairobi Tropical and Infectious Diseases Institute (UNITID). The study utilized a mixed costing approach in quantification and valuation of the cost categories from the provider's perspective. Data collection involved time and motion study of the laboratory procedures for HIVDR testing and interviewing the Laboratory personnel and the operations manager. As one of the cost saving opportunities adopted by the laboratory, we evaluated the cost of reagent volume reduction at amplification and sequencing processes intervention. Data entry and analysis was done in Microsoft excel and costs converted to US dollar (2019). The estimated unit cost for a HIVDR test was $271.78 per test. The main cost drivers for the HIVDR test included capital cost ($102.42, 37.68%) and reagent cost (101.50, 37.35%). The other costs included, personnel ($46.81, 17.22%), utilities ($14.69, 5.41%), maintenance cost of equipments ($2.37, 0.87%) and quality assurance program ($4, 1.47%). Costs in relation to laboratory processes were, sample collection ($2.41, 0.89%), RNA extraction ($22.79, 8.38%), amplification ($56.14, 20.66%), gel electrophoresis ($10.34, 3.80%), sequencing ($160.94, 59.22%) and sequence analysis ($19.16, 7.05%). Halving reagents volume at amplification and sequencing processes reduced the cost for HIVDR test to $247.30. All the test performance characteristics for the modified assay were within acceptable ranges. The challenges experienced included, high staff turnover, insufficiencies in the supply chain and lack of a functional laboratory network for sample-referral mechanisms leading to sub-optimal utilization of the facility. Furthermore, uncertainty in donor funding raises concerns on the sustainability of such capital intensive endeavors.

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Abbreviations

AIDS	Acquired immunodeficiency Syndrome
ART	Antiretroviral Therapy
DBS	Dried blood spot
FDA	Food and drug Authority
COEHM	Center of excellence in HIV Medicine
CRISSP	Central Province Response Integration, Strengthening and Sustainability Project
CRFs	Circulating Recombinants Forms
GDP	Gross Domestic Product
HIV	Human Immunodificiency Virus
HIVDR	HIV drug resistance
KNH	Kenyatta National Hospital
MID	Molecular and Infectious Diseases
MOH	Ministry of Health
NNRTI	Non-Nucleoside Reverse Integrase Inhibitors
NRTI	Nucleoside Reverse Integrase Inhibitor
PDR	Pretreatment Drug resistance
PI	Protease Inhibitors
TDR	Transmitted Drug Resistance
UON	University of Nairobi
UNAIDs	United Nations Programme for HIV and AIDS
WHO	World Health Organization

Chapter One: Introduction

1.1Background to the study

The scaling up of anti-retroviral therapy (ART) has been one of the greatest mile stones in the fight of the HIV epidemic. Improved access to ART treatment has led to improved quality of life and longer life years. The global estimate of people on ART as at December 2016 was 19.6 million, in Kenya this number was estimated to be about 1 million which represents 64% of the population eligible for ART (World Health Organization (WHO), 2017). Globally, there has been a decline in deaths from AIDs-related causes by 48% from the year 2010 to 2016 ((United Nations Programme for HIV and AIDS) UNAIDS, 2017) This reduction was steepest in eastern and southern Africa at 62% from the year 2004 to 2016. Annually, the number of new Human Immunodificiency Virus (HIV) infections has been reducing at a rate of 16% as a result of HIV prevention and treatment programmes (UNAIDS, 2017). Regionally, Eastern and Southern Africa region has achieved a 29% decline in the annual number of new HIV infections between the year 2010 and 2016. Kenya has also achieved a notable decline in the number of new infections from 79000 to 62000 yearly, which is approximately 27%.

This milestone in HIV management is under threat due to the emerging issue of ART drug resistance. HIV drug resistance(HIVDR) is defined as a change in the HIV genome that reduces the effectiveness of the antiretroviral drugs (WHO, 2017). The WHO reports a 68% global prevalence of one or more drug resistance mutation in patients with unsuppressed viral load. Resistance to Non-Nucleoside Reverse Integrase Inhibitors (NNRTI) had an observed rate of 61%, with Nucleoside Reverse Integrase Inhibitor (NRTI) and Protease Inhibitors (PI) recording a rate of 55% and 6% respectively. WHO resistance reports 29% yearly increment in NNRTI transmitted drug resistance in Eastern Africa, 23% in South Africa, 15% in Latin America and 11% in Asia countries. A recent surveillance study done in Kenya found an overall transmitted drug resistance prevalence of 9.2 % with an observed rate of NNRTI transmitted drug resistance of 6.9% (Onywera et al., 2017). Resistance to ART drugs downplays the overall health outcomes both at individual and population level (WHO, 2017). In 2014 , UNAIDS set the 90-90-90 targets where by the year 2020, 90% of HIV infected individuals will know their status, start 90% of the known HIV status on ART and achieve 90% viral suppression. To achieve the 90-90-

90 targets, especially the third 90(achieving the viral load suppression) the problem of the HIV drug resistance needs to be re-evaluated (UNAIDS, 2014).

Antiretroviral therapy is delivered through the public health approach in most low and middle income countries where standardized drug regimen with simplified laboratory monitoring such as HIV viral load and CD4 count assays (Lessells et al., 2013). The genotype test is widely used in the developed world for clinical management of people living with HIV and for surveillance purposes. Kenya national ART guidelines recommend a genotypic resistance testing for adults when virological failure occurs on the second line ART and children with virological failure on PI-based regimen(Ministry of Health, 2018). Several studies have also recommended the inclusion of HIV drug resistance testing in management of patients living with HIV to mitigate the rising cases of HIV drug resistance yet a little is known of the cost of HIV drug resistance intervention in Kenya (Onywera et al., 2017; Lessells et al., 2013; Lihana et al., 2009).

HIV drug resistance can be determined phenotypically through cell culture-based assays and genotypically by sequencing the protease and reverse transcriptase coding regions. The main role of genotyping is to identify mutations associated with the reduced susceptibility of antiretroviral treatment. The use of genotypic testing has been limited in resource limited settings as a result of lack of laboratory capacity, the cost and the complexity of the HIV genotype test (WHO, 2010).

The World Health Organization recommends population based surveillance and monitoring of HIV drug resistance in resource limited settings where the pattern and rates of transmitted and acquired drug resistant is used to inform regional and global recommendations on the line regimens. The main population sequence-based genotyping methods are ViroSeq, TRUGENE and in house assays (Zhou et al., 2011). These assays are affordable and they are very informative in clinical practice. The two FDA approved genotyping assays are TRUGENE (Siemens, Germany) and Viroseq systems (Abbott Molecular, Abbott Park, IL) which are designed for HIV-1 group M subtype B which are predominant in resource rich settings. The two assays are not sensitive to non-B subtypes which present a challenge in resource limited settings where we have non B sub types and circulating recombinants forms (CRFs) as the predominant strains (Zhou et al., 2011). In house assay has been validated to be used with non-B subtypes and CRFs. In addition, the assay is considerably cheaper compared to the two FDA approved assays (Inzaule et al., 2013; Zhou et al., 2011; Chaturbhuj., 2014).

HIV financing in Sub-saharan countries is majorly by the development partners where they accounts for 87% of all AIDs spending with exception to Botswana, Namibia and South Africa (Resch et al., 2015). In Kenya, the national government expenditure on AIDS programmes is approximately 20% of total national AIDs spending. According to the 2012-2013 National Health Accounts, the total health HIV/AIDS expenditure was Ksh 43.7 billion in 2012/2013 which accounted for 1.3% of GDP and 19 % of the total health expenditure. Donors were the most significant source of financing revenue at 73 % in 2012/2013; the national government contribution was at 18% with the household's contribution at 6%. Other contributors are private employers at 1.8% and parastatals at 0.6% (Ministry of Health, 2015).

1.2 Problem statement

There are ten centralized laboratories across the country offering the HIV viral load testing. Of the ten only four are performing HIV drug resistance testing. Two of the four are at the initial start up period. The main barriers to the implementation of genotypic resistance testing in resource limited countries are associated with the cost, laboratory capacity and the issues with specimen transport to the centralized laboratory (WHO, 2010). This has lead to omission of HIV drug resistance testing in clinical management of people living with HIV in resource limited set up. In Kenya, little is known of the cost of implementing the HIV drug resistance testing to facilitate the management of people living with HIV. As the country gears towards the attainment of the Universal health coverage as part of the "big four agenda", costing information on HIV drug resistance testing is essential in the mobilization of the resources required to achieve the universal health coverage. The three policy dimensions of universal coverage are extending services to uncovered population, including services that are not covered and reducing cost sharing and fees. To achieve the three policy dimensions it requires resources mobilization and reallocation. The HIV drug resistance testing cost information is a good guide in the process of reallocation of resources among competing priorities in financing of HIV services thus increasing the variety of services offered to the people living with HIV.

As indicated in the 2012/2013 Kenya National Health Accounts, HIV care and treatment is majorly funded by the development partners. This funding has been decreasing over the last few years as illustrated by the 23.5% donor contribution of the total health expenditure for the year 2015/2016 down from 34.5 % in the year 2009/2010. This requires the country to seek

opportunities to increase the efficiency in offering the HIV services. In order to ensure efficiency and cost saving, cost information for HIV services such as HIV drug resistance testing must be available. Lack of such cost information on HIV services offered, hinders such opportunities for efficiency evaluations and cost saving.

There is also a knowledge gap in resource needed to deliver HIV drug resistance testing to the population in need; this makes it difficult to scale up the service to the rest of the country. Without costing information, laboratories that wish to implement HIV drug resistance testing are not able to perform cost projections and budgeting for future. The costing study focused on establishing the cost of implementing drug resistance testing in Kenya, one of the barriers to the implementation of genotypic testing in resource limited countries

1.3 Research questions

1. What is the unit cost of HIV drug resistance test?
2. What are the cost drivers for HIV drug resistance test?
3. Is there an opportunity to increase efficiency in HIV drug resistance testing
4. What are the challenges and lessons learnt in setting up in HIV drug resistance testing laboratory

1.4 Main objective

To evaluate the cost of providing HIV Drug resistance testing services.

1.5 Specific objective

1. To establish the unit cost of HIV drug resistance testing
2. To establish the cost driver for HIV drug resistance testing
3. To explore the opportunity for cost-saving for HIV drug resistance testing.
4. To document challenges and lesson learnt in setting up in HIV drug resistance testing laboratory.

1.6 Justification

The study findings illustrate the cost implications and sustainability of HIV drug resistance testing. The high cost of drug resistance testing has been one of the limiting factors in low income settings (WHO, 2010). This has lead to omission of HIV drug resistance in care and treatment of Patients living with HIV (Ministry of Health, 2016). The cost analysis gives an

insight on the affordability of the inclusion of HIV drug resistance testing in the standard package care of HIV. The cost information is also useful to other HIV service delivery center in the Kenya that wishes to implement HIV drug resistance testing.

The costing information is beneficial in performing economic evaluation on the HIV drug resistance testing to inform ART regimen switches verses the status quo. The economic evaluations are very important in establishing the efficiency of a program to identify the potential areas for saving. HIV takes a big chunk of total health expenditure as demonstrated in 2012/2013 National health accounts, performing an economic evaluation on HIV interventions would help in reallocating resources to the most cost-effective interventions.

The study findings could also be utilized by HIV care and treatment providers to lobby for more funds from the government and development partners. The HIV financing in Kenya is majorly by the development partners(Ministry of Health, 2015), the costing information aids in justifying funding requests by organizations when writing grant proposal to donors to fund HIV care and treatment programs.

The Laboratories offering HIV drug resistance testing could use the costing information to perform cost projections, planning, budgeting and pricing of HIV drug resistance tests. This helps the Laboratory to indentify the gap between the budget and the expenditure and take the necessary action.

Chapter Two: Literature Review

2.1 Introduction

This is organized in three sections, a review of the theoretical and empirical literature and an overview of the literature citing the gaps in the literature that guide the research problem.

2.2 Theoretical Literature

2.2.1 Costing

Cost is defined as the monetary value of resources utilized to produce something such as a specific health services or a set of services as in the health programme (Muthuri, 2009; Creese and Parker, 1994). Economists make a distinction between financial costs and economic costs whereby; financial cost is the market price of a good is or a service and it is mostly found on invoices or book-keeping records; whereas economic cost is the value of the benefits of the opportunities' forgone (Muthuri, 2009).

Costs can be categorized as direct costs, indirect cost and intangible costs (Muthuri, 2009). The direct cost of all input that can be directly associated with health activity or programme such as personnel, money paid by patients in accessing the services, non-pharmaceuticals supplies and pharmaceuticals (Muthuri, 2009). Direct costs can either be fixed or variable costs. Variable costs are recurrent costs, that is, costs incurred annually and they vary with output produced. Examples of recurrent costs are, personnel time, short term training, utilities like water and electricity, non pharmaceutical supplies out of pocket expenses etc. Fixed costs are costs incurred at the beginning of a project and do not vary with the quantity of output produced. Their useful life goes beyond one year and they can be shared among different interventions. This calls for a need to apportion the value of such an input through step-down or direct allocation methods. Examples of fixed costs are equipment, vehicles, and building and long term training (Muthuri, 2009).

Cost information is very important for the decision makers in various ways. One of the ways is to ensure accountability in government and nongovernmental organizations, employees are accountable to their employer for the resources they use (Creese and Parker, 1994) . To meet this obligation, the employee need to know how they have spent the finances available to them and if the money they have in their control has been spent as planned. This is a mechanism government

and non-governmental organization use to protect their resources from misuse and waste. The costing information is used to make the budget which gives guidelines on the resources to be spent on various activities. In an ideal situation the expenditure should balance the budget. The expenditure that exceeds the budget requires lobbying for additional resources, which is time consuming and difficult. An expenditure that is less than the budgeted amount leads to a reduction in future resource allocation. For these reasons, organizations require a well prepared budget that reflects an adequate understanding of resources required to achieve the organization's goal. This gives a clear picture when evaluating whether the program is poorly implemented or resources are being squandered (Creese and Parker, 1994).

Costing is an essential aspect in assessing the efficiency of a program; a good example is using cost information to identify cost categories to conduct further efficiency studies (Creese and Parker, 1994) . The category with the highest cost receives the greatest attention in efficiency studies to examine the potential for savings. Cost profiles are also used to compare efficiency in different units, for example, to compare spending on drug for different districts. Efficiency studies do not stop at the cost profile, they involve a step further to evaluate the outcome or the units delivered by a particular cost.

Costing information is also a fundamental aspect in assessing equity in terms of health resources allocation (Creese and Parker., 1994). This assessment is done by comparing the people served by different facilities or in different geographical location. Cost data is also very useful in making future cost projections; this is made possible through establishing the past association between capital costs and the recurrent costs. A health program may also use cost information to plan for the cost recovery through introduction of the user fee as one finance source. Cost information is also used by countries or programs to assess the priorities. The level of priority is determined by the amount of resources spent on a particular program (Creese and Parker, 1994).

2.2.2 Costing Methodologies

There are three main costing methodologies used to measure healthcare costs namely; gross costing, micro costing and mixed approach.

In gross costing the cost of various cost centers is estimated from the total cost of the intervention or the program. An example of gross costing is if a certain percentage of hospital's population receives antiretroviral therapy, say 20 %, 20% of total hospital costs will be assigned

to the provision of antiretroviral therapy. Gross costing does not require a lot of resources as compared to the micro-costing but in return provides a limited level of cost details (Hendriks et al., 2014). The costs are usually obtained retrospectively from the administrative databases.

Micro-costing studies involve direct itemization and costing out every input utilized in an intervention (Frick, 2009).Micro costing ensures reproducibility in cost estimation that reflects the actual resource utilization and the economic cost by collecting detailed data on the input and their unit costs. Research has demonstrated micro costing method to be the best method in costing for diagnostic and treatment programmes where costs are absent or still evolving (Xu et al., 2014) It is very useful in estimating cost for new interventions where there is no established estimate for their total cost making the gross costing impossible.

Mixed approach studies combine the top down and bottom approaches which depend on the availability of data and the feasibility of estimating the costs (Creese and Parker, 1994)

2.2.3 Steps for costing

Costing involves eight sequential steps, that is, identification of the problem or questions that need answering ,specification of the costing perspective, description of the intervention to cost, identification of the inputs needed in the intervention, quantification of the cost of items, valuation of the inputs, adjusting costs for differential timing and sensitivity analysis (Muthuri, 2009; Hendriks et al., 2014;Drummond et al., 2005).

The first step in a costing study is problem identification. This is the objective that the policy makers or the program experts seek to achieve should guide the cost analyst on type of costing study to conduct (Muthuri, 2009) . A cost analyst would perform a financial costing if the cost information is needed for planning, budgeting or assessing the financial feasibility of a health activity. If the purpose is to conduct an economic evaluation, an economic costing would be more relevant.

The second step is deciding on the perspective of the costing. The problem statement determines the viewpoint of the study, this is very important in deciding on the cost to be considered in the cost analysis (Hendriks et al., 2014). In costing there are several perspectives that could be considered. One of these perspectives is societal perspective. It is the broadest of all because it considers all the cost borne by all the stakeholders. Societal perspective is often not feasible in

resource limited countries due to the unavailability of data and lack of the resource to perform it (Hendriks et al., 2014). It is the best perspective as it guards against shifting of financial burdens to the patients and their families (Muthuri, 2009). The other perspective is hospital perspective, this is the cost borne by the health facility attending to the patient. It excludes costs by other health providers, patient and the ministry of health (Muthuri, 2009). Patient's perspective considers only the cost borne by the patients and their families or friends excluding all other cost incurred by the health facilities of the ministry of health. The third party payer perspectives include costs incurred by the state or insurance (Hendriks et al., 2014).

The third step is description of the intervention, this involves determination of the unit of analysis which is also dependent on the problem statement (Hendriks et al., 2014). For this to be achieved Drummond et al. (2005) recommends that information on who does what to whom, where and how often should be available.

The fourth step is the identification of the inputs needed for the interventions. This involves the listing of all ingredients used to produce a health care activity. Such inputs include; staff, equipment, productivity loss, drugs and consumables (Muthuri, 2009; Drummond et al., 2005). The study perspective in use determines the input to be include, Muthuri (2009) gives an example of how to conduct a study done from the perspectives of the ministry of health and the patients. In this case the analyst will consider the cost incurred in providing services such as variable and fixed costs and the out of pocket expenses incurred by the patients receiving the intervention. Indirect costs such as the loss of patient productivity should only be considered when conducting economic not a financial costing study (Muthuri, 2009) .

The fifth and sixth steps in costing involve quantification and valuation of the costs items. Once a list of the inputs that are likely to be consumed has been drawn up, the quantities of these inputs are determined in terms of physical/natural units. After the quantification the quantities of inputs are valued in local currency based on the prevailing market prices (Muthuri, 2009). Different cost types are quantified and valued differently, for example, the personnel, consumables, utilities, maintenance and capitals.

The seventh step is adjusting for differential timing of costs. This is the process of converting future costs to their present value. This is important for health programmes because effects of a

health intervention do not happen at the same time and they can last for more than one year (Muthuri, 2009).Some health interventions require life time resource commitment. Naturally, individuals have a positive rate of time preference, that is, they prefer to gain benefits today and incur the costs later. The positive preference rate of time preference is as a result of individual having a short term view of life, future uncertainty and the positive economic growth (Drummond et al., 2005). To convert the future costs to their present value is done by multiplying the value of the cost by the discounting factor. The discounting rate is the social rate of time preference. It is defined as the measure of society's to forgo gratification today in order to have a greater consumption in future (Drummond et al., 2005). This social rate of time preference is represented by the interest rate on a risk free investment such as long term government bonds (Drummond et al., 2005).

The eighth step is sensitivity analysis. This is done to test for the robustness of the study's conclusion. This process involves varying the assumption made during the analysis such as the discount rate. The analyst could decrease or increase the discount rate to check if there is any variation in the study findings (Drummond et al., 2005; Hendriks et al., 2014).

2.2.4 HIV drug resistance testing

HIV drug resistance genotyping is the process of identifying the mutations on the HIV genome that are associated with the reduced effectiveness of the antiretroviral therapy. Routinely this is done by sequencing the whole protease region and most of the reverse transcriptase region (WHO, 2010).

HIV drug resistance testing involves 5 major processes namely, sample collection and preparation, Nucleic acids extraction, Nucleic acid amplification, genotyping and sequence analysis (WHO, 2010)

Specimen collection and preparation involves collection of whole blood from the patient into blood collection tubes that contain Ethylenediaminetetraacetic (EDTA) anticoagulant or a Dried blood spot on a filter paper. Once the blood is collected into the blood collection tubes, the specimen is prepared for storage by spinning, pipetting and aliquoting in to the storage vials. The second step in HIV genotype testing is the nucleic extraction from the plasma. In this step HIV

ribonucleic acid (RNA) is isolated from plasma using manual or automated procedures. If a dried blood spot sample was taken total nucleic acids are extracted. There are many commercially available standard nucleic acid procedures that can be used in this step. Once extracted and purified the nucleic acid is amplified by polymerase chain reaction (PCR) and genotyped. Genotyping involves amplicon purification, sequencing, amplicon purification, sequence detection and visualization (Inzaule et al., 2013). There are two FDA approved genotyping kits, Viroseq HIV-1 and Trugene HIV-1. The other genotyping assay is in house assay developed by experienced genotyping laboratories. The last step in HIV drug resistance testing is sequence analysis which involves sequence data validation, sequence assembly, interpretation and quality analysis (WHO, 2010).

2.3 Empirical Literature

In a study to develop, validate and perform clinical evaluation of a low cost in house HIV-1 drug resistance genotying assay for indian patients, the authors performed a comparative cost analysis between the in house HIV assay and Viroseq genotyping assay (Acharya et al., 2014). In addition to the comparative cost analysis the authors compared the hands on time spent in different laboratory process in performing the two assays. Of note is that the costs analysis did not comprise the costs of establishing the laboratory and major cost categories such as personnel and the logistics. All the costs were presented in US dollars. The total cost for running an in house HIV assay was $85.0, looking at the costs break down for the different process in production of the in house HIV assay test; the genotyping process incurred the largest cost of $ 55.0, with Amplification ranking the second at $ 20.0. Nucleic extraction, Gel documentation and sample preparation costs for in house assay were $ 7.0, $2.0 and 1.0 respectively. The cost analysis established that the cost of producing HIV drug resistance testing using the Viroseq HIV-1 assay was at $303.0. A breakdown of costs according to the processes involved shows that the largest cost was incurred at nucleic acid extraction; the cost at this process was $250. The genotyping, gel documentation and sample preparation costs were $40, $2 and $1 respectively. The hands-on time spent on Viroseq HIV assay and In house HIV assay was 18h 45 minutes and 17h 15minutes respectively (Acharya et al., 2014).

Zhou et al., (2011) in an optimization of a low cost and broadly sensitive genotyping assay for HIV-1 drug resistance surveillance and monitoring in resource limited settings study, estimates

the reagents costs per test for the three assays, that is, optimized in house, TRUGENE and Viroseq to be $40, $213 and $172.86 respectively. The genotype testing was performed in CDC Atlanta, GA, USA. The study used 2011 U.S market values in dollars for all the reagents used in every HIV drug resistance testing. The cost analysis did not include fixed costs such as personnel, cost of purchasing the equipments, logistics and cost of running the controls and repeats (Zhou et al., 2011).

In a study to evaluate the performance of an In house Immunodeficiency Virus type 1 genotyping system for Assessment of drug resistance in Cuba, the cost for performing the In house assay was estimated by considering the cost of reagents and consumables. The estimated cost for performing the procedure was estimated to be $ 78.5 per genotype test and $ 98.1 after the initial amplification failure. Other cost related to genotype test such as personnel, equipment, utilities, were excluded for the calculation (Alemán et al., 2015).

Chaturbhuj et al., (2014) in a study to evaluate a cost effective in house method assay, the authors report unit cost incurred for the in-house method was (US 112$) and (US300$) for viroseq assay. The sequencing was done at National AIDS Research Institute, Pune India. Both assays utilized same manpower and had equal turnaround time. The cost incurred in the in-house method was half the cost incurred viroseq assay.

In a study to assess the cost-effectiveness of genotype testing for primary resistance in Brazil the costs used to run the simulation model were estimated from the public health system perspective where only direct medical costs were considered (Luz et al., 2015). HIV drug resistance testing in Brazil is paid by the Brazillian federal government free of charge, similarly to the drugs for HIV treatment, CD4 and viral load tests to all patients in 24 treatment centers throughout the country. The author considered all costs as paid for by the government. The cost for the genotype test was estimated at $230. On comparing the whether to have genotype or not to have genotype, the arm with genotype testing yielded an increased life expectancy of 18.47 from 18.45 with reduced lifetime cost from $45,000 to $44,770. This illustrated that genotype testing was cost saving (Luz et al., 2015).

In a study done in Botswana to evaluate the long range HIV genotying Using viral RNA and Proviral DNA analysis of HIV Drug Resistance and HIV clustering, the estimated cost for

performing amplification and sanger sequencing for proviral DNA and viral RNA is $137.5 and $139.5 respectively. The cost calculation includes the reagents and consumables. It omits the personnel, training, capital and indirect cost (Novitsky et al., 2015)

In a study done in Zimbabwe to evaluate the cost-effectiveness of HIV drug resistance testing to inform switching to second line antiretroviral therapy in low income settings, the estimated potential future cost for HIV drug resistance testing is to be $30. The costs calculations include all the costs incurred by the health system including the personnel and other overhead costs. The study found that the use of genotype test at the time for first time failure was not cost-effective even with a low cost genotype test (Phillips et al., 2014).

In a study to evaluate the net cost of incorporating resistance testing into HIV/AIDS treatment in South Africa: a markov model with primary data, the author uses an estimated resistance test cost of $ 242 to run the model. The study found that resistance testing in HIV care and treatment in South Africa would be cost saving and could unmask other reasons for failure leading to conserving the treatment options as well as generating information on resistance patterns (Rosen et al., 2011).

Levison et al., (2013) uses a genotype unit cost of $300 to evaluate the clinical and economic impact of genotype testing at first-line for HIV infected patients in South Africa. The study found that doing a genotype had a projected life of 108.3 while not doing a genotype had a life expectancy of 106.1 months. The lifetime per person discounted lifetime costs for genotype arm was $16540, while no genotype arm had lifetime of 16360. This was an illustration that the doing a genotype testing at first-line ART is a cost saving intervention in South Africa, though this was dependent on the prevalence of Wild Type virus and the turnaround time for the genotype results.

Inzaule et al., (2013) in a study to evaluate broadly sensitive HIV-1 in house Genotyping assay for use with both plasma and dried blood spot specimens in a resource limited country, the authors performs a comparative cost analysis between in house assay and Viroseq HIV assay on plasma and DBS specimen. The cost analysis was performed at KEMRI/CDC HIV laboratory situated in Kisumu, Kenya. The analysis is inclusive of the reagents, consumables and the major equipment maintenance costs. All the costs were based on the 2011 U.S dollars. Of note is the

omission of the fixed costs, such as initial cost of buying the equipment, human resource, sample transportation and storage and cost associated with the quality assurance program in the laboratory. The cost of perfoming the in house HIV assay using DBS and plasma specimen was $110.05 and 113.33 respectively. The cost of running the viroseq HIV assay using plasma specimen was $278.31. The cost driver for the in house HIV-1 assay was the genotyping step which gave a total cost of $59.88 for both the plasma and DBS specimens. The step with the highest cost in the viroseq HIV-1 assay was the nucleic acid extraction at $150. The hand on time spent on in house HIV-1 assay for plasma and DBS specimens and viroseq HIV-1 assay on plasma specimen was 16 h 30min, 24h 20 min and 17h 10 min respectively. The longest time experienced in the in house HIV-1 assay was as a result of manual extraction procedure (Inzaule et al., 2013)

2.4 Overview of the literature review

Of note from the reviewed literature is that most of the studies do not include all the cost categories involved in genotype testing to calculate the unit cost (Acharya et al., 2014; Inzaule et al., 2013; Zhou et al., 2011; Novitsky et al., 2015). Some of the essential costs when performing a costing analysis are equipment costs, personnel costs and the utilities cost. Most of these studies have included only the reagent costs and consumable cost in their calculations, hence posing a challenge in comparison of the costs of HIV drug resistance testing from different studies. Omission of some of the key costs categories makes it difficult to evaluate the cost drivers in HIV drug resistance testing. This warranty a complete costing analysis taking into consideration all the cost categories involved in the HIV drug resistance testing. The complete costing analysis will give an insight on the actual cost incurred all the way from the establishment of the laboratory and provision of the HIV drug resistance testing services, which has been grossly omitted from the previous studies.

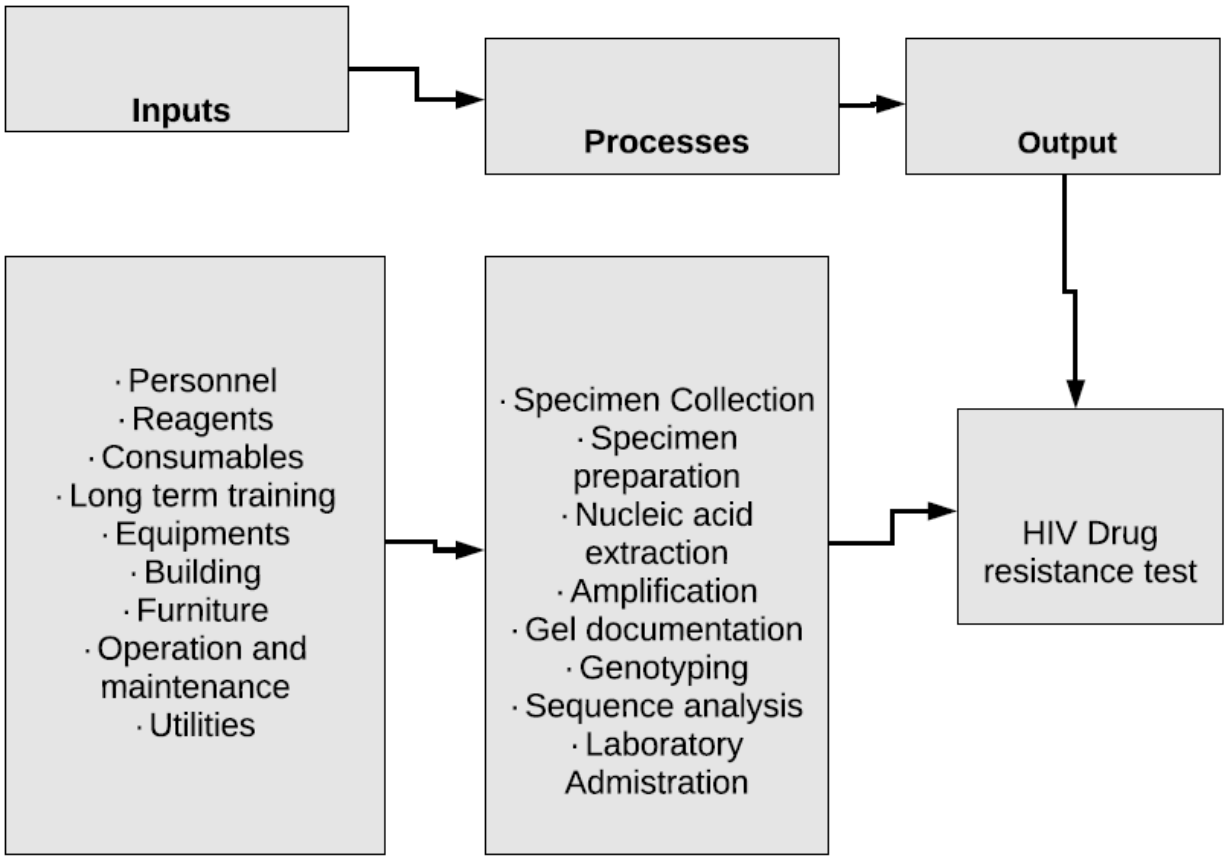
Chapter Three: Methodology

3.1 Introduction

This section is organized into six sections namely; conceptual framework, theoretical framework and field methodology.

3.2 Conceptual Framework

Figure 1: Conceptual framework



Source: Researcher's based on the literature reviewed.

3.3 Analytical Framework

3.3.1 Costing Methodology

The study utilized both micro and gross costing in quantification and valuation of the cost categories. The cost analysis was done from the provider's perspective and only costs specific to the HIV drug resistance testing sections were considered.

3.3.2 Input identification

Costs were collected for the various processes in HIV drug resistance testing that is, Laboratory administration, sample collection and preparation, RNA extraction, RNA/DNA amplification, gel electrophoresis and sequencing. At the time of data collection the laboratory was using the in house HIV assay (Thermofisher, US) to analyze samples for the HIV drug resistance testing

3.3.3 Costs Quantification and valuation

Personnel costs

We quantified the personnel costs by identifying all the staff categories involved in HIV drug resistance testing and the number of staff in each category. Once this was done the gross earning for each category was obtained and multiplied with the time a certain category dedicates to the HIV drug resistance testing. The cost for each cadre was calculated as:

*Cost per cadre = (Number per carde of staff * share of HIV drug resistance *Average (Daily equivalent salary+ annual fringe benefits)* (Muthuri, 2009).

Personnel cost per test = (∑Cost per cadre)/No. test

Cost of consumables and Reagents

This was determined by quantification of consumables and reagents in their appropriate unit of each item that was used up in production of one HIV drug resistance test. This was obtained from the laboratory staff. Prices were extracted from the invoices, price lists and catalogues and local purchase order. The total costs were inclusive of the purchase cost, transport, Value added tax and insurance. The cost for each item was calculated as:

*Cost of consumables = (Quantity of the item * Price per item * HIV drug resistance testing Share)*

Consumables cost per test = (∑Cost of consumables)/No. of test

Cost of operation and maintenance

The two methods for estimating the operation and maintenance cost are the itemization approach and maintenance cost as a percentage of replacement cost approach(Muthuri, 2009). The study utilized the itemization approach which involved listing and quantifying all inputs used to maintain and operate an item for example, vehicles, equipments and buildings. For the study data was collected on the cost of service contract for various machines in the laboratory. The maintenance costs were calculated as:

*Cost of input (e.g service contract) = (Quantity of the input * Price per unit * HIV drug resistance testing share)*

Cost of input per test = (∑Cost of inputs)/No. test

Utilities costs

To estimate the utilities cost quantities for each utility used in the course of the year by the HIV drug resistance testing were obtained. The market prices per unit were obtained from the relevant local company that supplies the utility and payment records by the programme. The cost of a specific utility was calculated as;

*Utility cost = (Quantity of the utility * HIV drug resistance share* Price per unit)*

Utility cost per test = (∑Utility cost) / No.test

Capital costs

These are inputs whose useful life is more than one year. Examples of such inputs are vehicles, equipments, long-term training and building space(Muthuri, 2009). For capital costs, there are two types of costs that can be estimated, that is, the annual financial cost and the annual economic cost. The economic cost puts in consideration the opportunity cost of making the investment and the depreciation rate for the capital (Edejer et al., 2003). The study estimated the annual economic cost (AEC), calculated as:

*AEC = [(C*Q)/ A (T,r)]*S*

Where;

C is the current replacement value per unit of each input

T is the useful life of each input taken to be 5 years as the length of project

Q is the quantity of the input

S is the HIV drug resistance testing share

r is the depreciation rate taken to be 10%

[A(T,r)] is the annuity factor given by $[(1+r)^T-1]/[r*(1+r)^T]$

Capital cost per test= (∑AEC)/No. test

3.3.4 Validation of the miniaturization assay

To explore an opportunity for cost saving by halving the reagent volume recommended by the manufacturer, the Laboratory performed a validation process to test the performance characteristics of the new assay. This was performed in accordance with the WHO/HIV ResNet guideline for validation of genotyping assay(WHO, 2018). The validation included assessment of amplification sensitivity, accuracy, precision and reproducibility.

Accuracy

To assess for accuracy, the laboratory genotyped 10 samples using the half reaction volume assay that were already genotyped using the full reaction volume protocol. The accuracy was determined by mean nucleotide and amino acids identity between the two protocols.

Amplification Sensitivity

This was assessed by genotyping 10 samples with viral load between 214 to 86,040 copies per milliliters where the genotyping sensitivity was established as the viral load copy range where greater than 95% of the samples were successfully genotyped.

Precision and reproducibility

Precision was assessed using two samples done with four replicates and reproducibility was done with 10 samples in duplicate. The reproducibility test was done by one laboratory staff in two different days. The reproducibility and precision was determined the degree of similarity in drug resistance mutation and mean nucleotide sequence identity

3.4 Field methodology

3.4.1 Study Area

The costing study was done at Molecular and Infectious Diseases (MID) Research Laboratory situated at the University of Nairobi Tropical and Infectious Diseases Institute. The MID research Laboratory is a Kenyatta National Hospital/University of Nairobi COEHM and CRISS plus projects initiative which are funded by US centre for Disease Control and Prevention to support the implementation of high quality, sustainable and comprehensive HIV prevention, care and treatment in Nairobi and parts of central Kenya. The MID Research Laboratory has 3 sections, namely; Tuberculosis (TB), Routine and HIV drug resistance section.

3.4.2 Sampling Method

The study was carried out in only one study area, thus no sampling was be done since it was a case study.

3.4.3 Data collection

Data collection was done using the data collection tool (see Appendixes). The tool depicted all the steps in HIV drug resistance testing. In addition, other cost data collected depicted other cost categories, that is, personnel, utilities, building office, quality assurance program and maintenance cost. To achieve the objectives, data collection involved time and motion study of the laboratory procedures for HIV drug resistance testing and interviewing of the Laboratory personnel and the program manager. No Research assistant was involved since it was a small scale costing study.

3.4.4 Data analysis

Data entry and analysis was done in excel. All costs were converted to US dollar (2019).

Chapter Four: Results

4.1 Cost breakdown in terms of cost categories

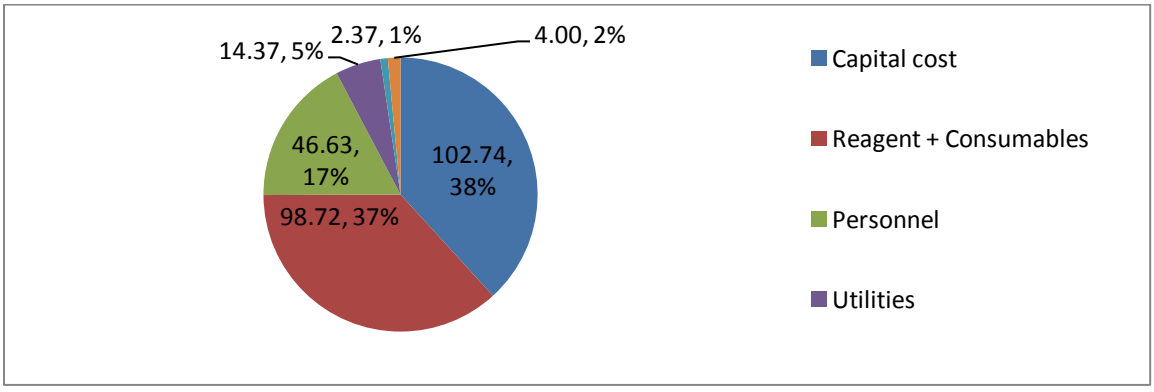
An activity based costing for HIV drug resistance testing was performed at MIDR Laboratory by collecting cost data for each step in drug resistance testing. At the time of the study, sample collection for drug resistance testing was done at Kenyatta National Hospital Comprehensive care center Laboratory (KNHCCC Lab). This is one of the centers that sends sample for HIV drug resistance testing to MIDR Laboratory. Cost Data pertaining sample collection was collected from the KNHCCC Laboratory while cost data for other steps in HIV drug resistance was collected from MIDR Laboratory. The overall cost for performing HIV drug resistance testing was US$ 271.78 per test where Capital Costs took the biggest chunk at $102.42 followed by Reagents and consumable cost at $101.5. Cost for personnel, utilities, maintenance cost of equipment and quality assurance program was $46.81, $14.69, $2.37 and $4 respectively.

Table 1: Cost breakdown for each category

Item	Cost per test in USD	% cost per test
Capital cost	102.42	37.68
Reagent + Consumables	101.5	37.35
Personnel	46.81	17.22
Utilities	14.69	5.41
Maintenance cost of equipments	2.37	0.87
Quality assurance program	4.00	1.47
Total cost	**271.78**	**100.00**

Source: Author's computation

Figure 2: Cost breakdown for each category



Source: Author's computation

Capital costs included equipment cost, laboratory furniture, networking and long term training for drug resistance testing. To determine the cost for the capital item were multiplied item cost with the percentage of the item used for HIV drug resistance testing divided by the expected equipment lifespan. Five year lifespan for all the equipment were assumed as this was the project period and a 10% depreciation rate.

Personnel cost included but not limited to the staffs that are directly involved in the HIV drug resistance testing.

Reagents and consumables cost defined as the supplies utilized during the sample analysis for drug resistance testing. The utilities included in the cost computation were: rent, electricity, water, internet and airtime.

T**he maintenance cost of equipment** included in the cost analysis were the cost of service contract for the machines used in the HIV drug resistance testing times the share divided by the number of tests per year. As one of the essential components in laboratory quality systems, quality assurance program costs were included in the cost analysis. This included registration fee for the external quality assurance program, licensing fee paid to the laboratory regulatory body and accreditation process fee.

At the time of data collection the laboratory was not working to full capacity, the cost analysis utilized **1000 number of test** as this was the target for year one.

4.2 Cost breakdown in terms of Laboratory processes

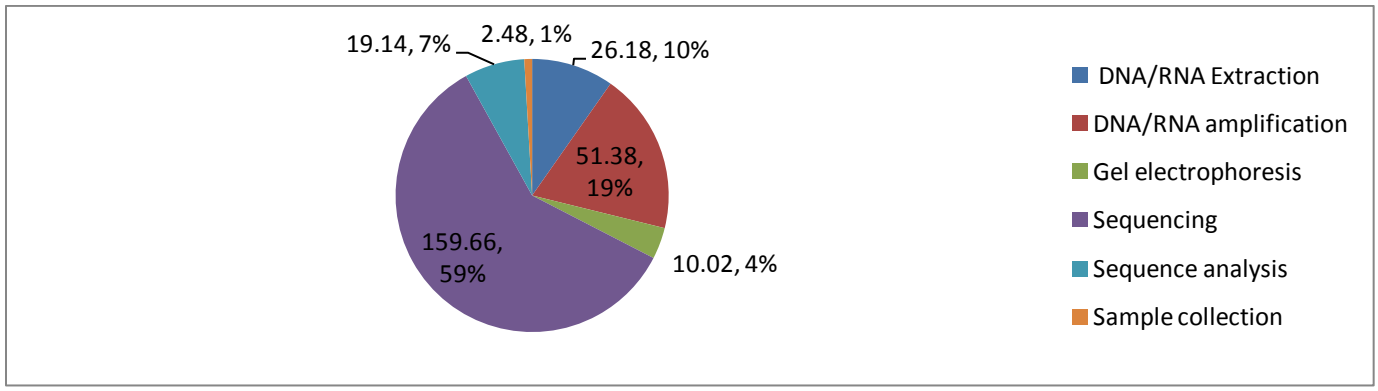
HIV drug resistance testing involves five processes namely; sample collection and preparation, RNA extraction, DNA/RNA amplification, Gel electrophoresis, sequencing and sequence analysis. According to the cost analysis, sequencing step had the largest cost of $160.94 per test which was attributed to large capital and reagent costs. DNA/RNA amplification had the second largest cost of $56.14. DNA/RNA extraction, Gel electrophoresis, sequence analysis and sample collection had a cost of $22.79, $10.34, $19.16 and $2.41 respectively.

Table 2: Cost breakdown in terms of Laboratory Processes

	Item	DNA/RNA Extraction	DNA/RNA amplification	Gel electrophoresis	Sequencing	Sequence analysis	Sample collection	Total cost
1	Capital cost	7.66	4.48	6.55	82.57	1.21	0.10	102.56
2	Reagent + Consumables	5.42	37.30	1.47	55.63	0.00	1.67	101.48
3	Personnel	4.68	9.36	1.87	15.44	15.44	0.47	47.27
4	Utilities	4.39	3.96	0.20	5.20	0.41	0.11	14.28
5	Maintenance cost of equipments	0.24	0.24	0.09	0.78	0.78	0.02	2.15
6	Quality assurance program	0.40	0.80	0.16	1.32	1.32	0.04	4.03
	Total cost in USD	**22.79**	**56.14**	**10.34**	**160.94**	**19.16**	**2.41**	**271.78**
	% Total Cost	**8.38**	**20.66**	**3.80**	**59.22**	**7.05**	**0.89**	**100.00**

Source: Author's computation

Figure 3: Cost breakdown in terms of Laboratory processes



Source: Author's computation

4.3 Validation of a miniature assay to increase efficiency in HIV drug resistance testing

To explore the opportunity for cost-saving for HIV drug resistance testing the MIDR laboratory validated a miniature assay against the recommended assay by the manufacturers. This involved using half the recommended reagents volumes to perform the amplification and sequencing

steps. To validate the assay against existing protocol, accuracy, precision, reproducibility and amplification sensitivity tests were performed.

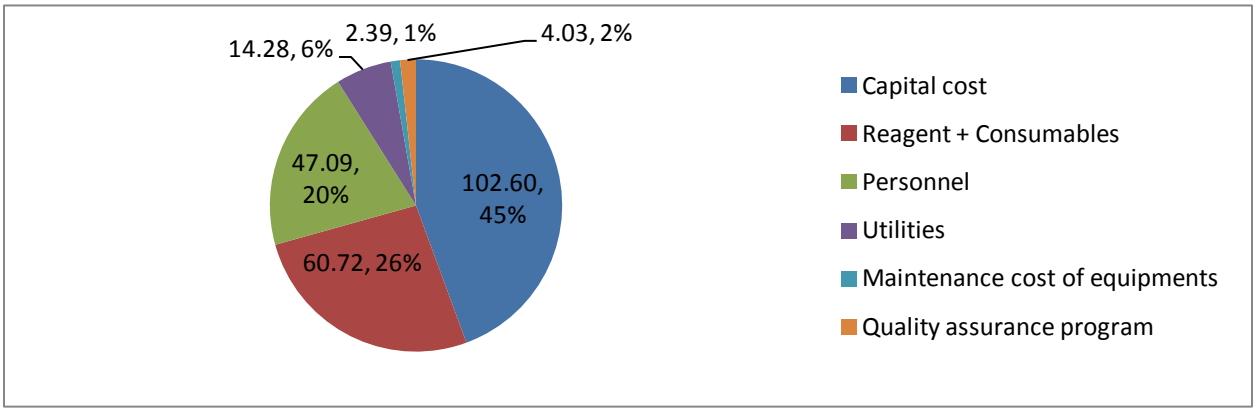
4.3.1 Cost of the miniature assay

The cost for the miniaturization assay was $247.30 a reduction from $271.78 for the recommended assay. There was a notable reduction for the amplification and sequencing costs to $38.38 and $140.70 from $56.14 and $160.94 respectively. There was no change for the other steps in HIV drug resistance testing since there was no halving of the reaction volume.

Table 3: Cost for the Miniaturization assay

	Item	DNA/RNA Extraction	DNA/RNA amplification	Gel electrophoresis	Sequencing	Sequence analysis	Sample collection	Total cost
1	Capital cost	7.65	4.48	6.55	82.57	1.24	0.10	**102.60**
2	Reagent + Consumables	18.92	19.30	1.47	35.38	0.00	1.67	**76.74**
3	Personnel	4.68	9.36	1.87	15.34	15.44	0.47	**47.27**
4	Utilities	4.39	3.96	0.20	5.20	0.41	0.11	**14.28**
5	Maintenance cost of equipments	0.24	0.47	0.09	0.78	0.78	0.02	**2.39**
6	Quality assurance program	0.40	0.80	0.16	1.32	1.32	0.04	**4.03**
	Total cost in USD	**36.28**	**38.38**	**10.34**	**140.70**	**19.20**	**2.41**	**247.30**
	% Total Cost	**14.67**	**15.52**	**4.18**	**56.89**	**7.76**	**0.98**	**100**

Figure 4: Cost of the miniaturization assay



Source: Author's computation

4.3.2 Performance characteristics

The performance characteristics for the miniaturization assay were in agreement with the manufacturer's recommended assay.

Amplification sensitivity

Seven samples with viral load ranges 214 to 86,040 copies/ml were tested for the amplification sensitivity. Of the seven samples only six were successfully genotyped by both assays yielding an amplification sensitivity of 100% for samples with viral load above 1000 copies per milliliter.

Accuracy

To optimize for the trueness of the assay 10 panel samples were genotyped using the full reaction protocol as well as the half reaction protocol. The mean nucleotide and amino acid identity between the two protocols were 96 +/-3% and respectively. A total of 67 drug resistance mutations were detected by the half reaction assay compared to 61 detected using the full reaction protocol. This generated analytical accuracy of 83.33%.

Precision and reproducibility

To test for the precision, two samples were tested in four replicates. All the four replicates from both samples were amplified and sequenced successfully. The mean nucleotide identity for

precision was 96.5 +/- 1.2%. To test for reproducibility 10 samples were analyzed in duplicate; the mean nucleotide identity was 94.6 +/- 1.5%.

Table 4: Performance Characteristics

Performance Characteristics	Results
Amplification Sensitivity	100 % for viral load >1000 copies/ml
Accuracy	96%(mean nucleotide identity)
Precision	96.5%(mean nucleotide identity)
Reproducibility	94.6%(mean nucleotide identity)

4.4 Cost for HIVDR Test using FDA approved reagents (Viroseq HIV genotyping)

Cost for HIVDR test using Viroseq HIV genotyping reagents and consumables (Abbott, US) was estimated at $379.46. It is one of the FDA approved HIV drug resistance testing available in the market and is used alternatively to In-house reagents and consumables manufactured by Thermofisher. Reagents and consumables accounted for 55 % ($209.18) of the unit cost for HIV drug resistance testing.

Table 5: Cost of HIVDR using Viroseq HIV genotyping system

Item	Cost per test in USD	% cost per test
Capital cost	102.42	26.99
Reagent + Consumables	209.18	55.13
Personnel	46.81	12.34
Utilities	14.69	3.87
Maintenance cost of equipments	2.37	0.62
Quality assurance program	4.00	1.05
Total cost	379.46	100.00

4.5 Challenges and Lessons Learnt

As a startup laboratory challenges and lessons learnt experienced in the processes of establishing such a high capital intensive undertaking in a resource limited settings were documented.

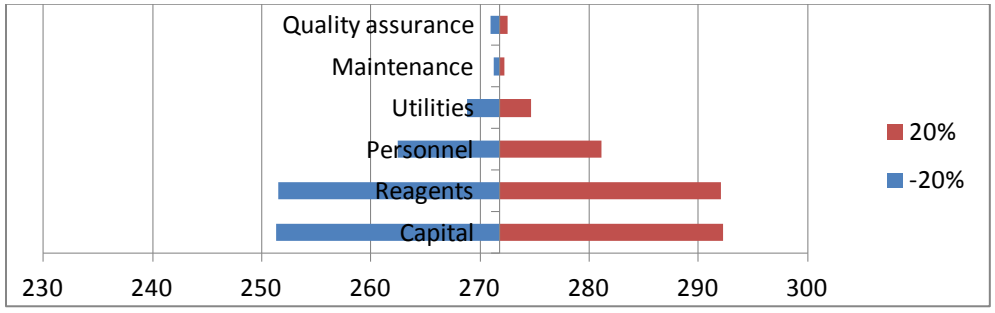
Table 6: Challenges and Lessons Learnt

Challenges	Lesson Learnt
1. High staff turnover 2. Insufficiencies in the supply chain management. 3. Lack of functional laboratory network for sample flow, hence sub-optimal utilization of the facility. 4. Financial sustainability due to decreased funding	1. Building capacity through training grant application. 2. Strategic memorandum of understanding with the suppliers. 3. Instruments suboptimal utilized can be leveraged to be used for other services 4. Engagement of key stakeholders. 5. Need to build relationship with other laboratories.

4.6 Sensitivity Analysis

The costs presented assumes that the laboratory runs 1000 HIVDR tests per year with no machine break down or waste of supplies. Considering that variation in input costs would have an impact on the input costs, a one-way sensitivity analysis for 20% variations to cost categories was performed. Variations to Capital, reagents and personnel inputs had a major impact to the Unit cost, whereas variations to utilities, maintenance and quality assurance results have no significant impact on the unit cost. A 20 percent variation to capital and reagents results in up to 7.5% changes in units cost, approximately $20 difference. Figure 5 shows a tornado graph of one-way sensitivity analysis.

Figure 5: Tornado graph for one-way sensitivity analysis, costs in USD



Source: Author's computation

Chapter Five: Discussion, Strengths, Limitations and Conclusion

5.1 Discussion

The aim of this study was to establish a detailed cost profile for HIV drug resistance testing from a provider's perspective and determine the cost drivers as well as identifying an opportunity for cost saving in performing the HIV drug resistance testing. The study also explored the challenges encountered during the implementation of HIV drug resistance testing.

Through the costing exercise it was possible to establish the cost of performing an in house HIV resistance testing at $271.78 per test. This cost estimate was a representation of all the inputs to HIV drug resistance testing, that is, capital, personnel, reagents, consumables, quality assurance program and service contracts for the machines. A proper cost comparison was not possible as previous studies done did not include all the cost categories involved in producing HIV drug resistance testing(Acharya et al., 2014; Inzaule et al., 2013; Novitsky et al., 2015; Alemán et al., 2015). However, a study done at Kemri Kisumu CDC , Kenya performed a cost analysis on the in house assay HIV drug resistance testing and established the cost to be $113.33 (Inzaule et al., 2013). The cost analysis included reagents, disposable and cost of maintaining the major equipments omitting capital, personnel and external quality assurance programme costs. Considering the reagents, disposable and maintenance cost there was a correlation in the cost results for these items as our study estimated the cost to be $101.50. The difference could be attributed to time difference in performing the cost analysis. Studies performed in other parts of the world found a considerably lower reagent plus consumable costs than those estimated by this study (Acharya et al., 2014; Novitsky et al., 2015; Alemán et al., 2015) . This could be associated to the geographical differences which has an impact on the cost of commodities.

To answer the question on the cost drivers for HIV drug resistance testing, the study categorized the costs on the basis of major cost categories and the processes that are involved in HIV drug resistance testing. In terms of cost categories, capital cost took the biggest share of pie at $102.42(37.68%) followed by reagents plus consumables costs at $101.50(37.35%). High capital costs were attributed to a suboptimal utilization of the sequencing platform. The cost analysis utilized 1000 tests per year which is way below the maximum capacity. If the laboratory would

operate maximally, that is, ~6720 test per year the capital cost would reduce in ~6.7 folds. The reagents costs were considerably high as result of acquiring the sequencing machine at no upfront cost. This bound the laboratory to only procure reagents and consumables from the machine provider. This commitment denies the laboratory an opportunity to practice strategic purchasing which would be a key factor in lowering the cost of reagents. This is not unique to HIV drug resistance testing, a study done in Kenya to estimate cost of HIV viral load and early infant diagnosis(EID) reported high reagents cost as results of machine acquisition on placement basis(Cintron et al., 2017). A comparison with other studies was impossible as most of the cost categories were grossly omitted (Acharya et al., 2014; Inzaule et al., 2013; Novitsky et al., 2015; Alemán et al., 2015). In terms of cost per process, the sequencing step which involves purification of polymerase chain reaction (PCR) products, cycle sequencing, purification of sequencing products and sequence detection was the most costly step in HIV drug resistance testing at $160.94 (59.22%). This is in keeping with other studies evaluating the cost of HIV drug resistance testing; regardless of exclusion of major cost categories. Inzaule et al., (2013) and (Acharya et al., 2014) report $59.88 (52.92%) and $50(58.82%) as the cost for the sequencing step respectively. One way sensitivity analysis performed illustrates a cost saving opportunities through negotiating for lower reagent costs and maximizing utilization of the sequencing platform therefore ensuring sustainable use of health financing resources.

Comparing the cost for HIVDR test to HIV viral load test used in monitoring and management of people living with HIV, HIVDR test is quite expensive. Cintron et al., (2017) estimates HIV viral load test at $ 24.63 for non point of care viral load testing and $29.74 for point of care HIV viral load test. This is attributed to additional processes in HIVDR test, that is, nested PCR and cycle sequencing processes. These increases the amount of cost inputs used in HIVDR testing, especially staff hands on time.

The study sought to find the effects of reducing the reagents volume on the cost and performance characteristics of the HIV drug resistance testing in view of reagents being one of the cost drivers for HIVDR testing. On the cost of the HIV drug resistance testing, there was a significant reduction of the cost from$ 271.78 to$ 247.30, ~9.04% reduction in the cost per test. This assay modification led to a ~24.39% reduction in reagents costs. Of note is the concordance of the two assays in their performance characteristics which increases the confidence in adoption of this

cost saving undertaking by the laboratories that would like to increase their efficiency in offering the HIV drug resistance testing service. The new assay performance characteristics met the WHO HIV drug resistance validation criteria(WHO, 2018). Cost computation using Viroseq reagents, FDA approved and an alternative to in-house reagents (Thermofisher, US) gave a cost of $379.46 per test with reagents cost taking the biggest share at 55.13% ($209.18). This illustrates a lower cost in producing HIV drug resistance testing using in-house reagents by $107.68. These findings are in keeping with other studies (Zhou et al., 2011; Inzaule et al., 2013; Acharya et al., 2014) where cost of HIVDR per test was lower when using in-house system compared to Viroseq system. Zhou et al., (2011) reports $ 132.86 difference in the two systems while (Inzaule et al., 2013) and(Acharya et al., 2014) reports $165.01 and $218 difference respectively.

One of the challenges encountered during the implementation of HIV drug resistance testing was high staff turnover. This is attributed to advanced molecular skills required in sample analysis for HIV drug resistance testing. There are a few laboratory specialists equipped with these skills making them highly sought in the job market. This is a challenge in a low resource set up as training personnel on this area is quite expensive(WHO, 2010). To counteract this challenge one of the staff won a training grant to learn HIV drug resistance testing from a laboratory that was already establish. The sequencing machine provider is also bound by the contract to train the laboratory staff to the highest level possible and provide machine service when due. Maintaining a good working relationship with other laboratories performing the test helps in exchange of new ideas and also it facilitates an inter-laboratory proficiency testing program.

Unlike HIV viral load and EID, HIV drug resistance testing is not included in Global Access Program which has helped in scaling up of HIV viral load and EID in Kenya at a relatively low cost(WHO, 2014). This raises sustainability concern owing to the reduced donor funding, however HIVDR testing can ride on already established sample referral network, human resources, some of the laboratory equipment and database for HIV viral load. The polyvalence of the sequencing platform also provides an opportunity to tests other diseases which reduces the overall upfront cost. Sensitization of key stakeholders involved in management of people living with HIV through regular stakeholders meetings has been instrumental in uptake of HIVDR test.

5.2 Strengths of the study

This was a complete cost analysis study, unlike other previous studies that omitted major cost category in their cost calculation. The study was done in the early stages of implementation of HIV drug resistance testing hence giving a good picture of how the process is like and a good source of planning and budgeting information for better resource management thereafter. The inclusion of the cost-saving assay evaluation makes the study one of the kind as it provides an evidence of cost reduction and comparable performance characteristics for both assays.

5.3 Study limitations

The study estimated costs from the provider's perspective thus limiting the inclusion of cost incurred at patient's level. The study design also excluded transport cost incurred for the samples drawn at peripheral facilities. Cost analysis was carried out in only one facility hence hindering the comparison across facilities offering HIV drug resistance testing. This was a partial economic evaluation; a complete economic evaluation would give a clearer picture on the cost-effectiveness of HIV drug resistance testing versus the status quo. At time of the study the laboratory was not operating at full capacity which increases the Unit cost of HIV drug resistance testing.

5.4 Conclusion

Amidst a few challenges in the beginning, Molecular and infectious disease Laboratory (MIDRLab) has implemented an efficient HIV drug resistance testing system for patients failing ART at cost of $271.78 per test. The major cost driver is the capital cost which is bound to reduce as the laboratory maximizes the utilization of the sequencing platform. Cost saving in offering HIVDR testing service is possible through reagent volume reduction without compromising on the quality of test results.

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Appendices:

Appendix 1

Laboratory Questionnaire

Step1: Sample collection

1. What is the time spent to bleed a patient for one drug resistance test……
……..
2. What are the consumables used to collect blood from patient for Drug resistance testing?

No.	Consumables	Quantity	Model	Cost	Share to HIVDR

Step 2: Specimen Preparation and Storage

1. What are the consumables and equipments used to prepare and store the specimen

Item	Quantity	Model	Cost	Lifespan(for equipments)	Share of HIVDR Cost
Equipments					

Consumables					

2. What is time is spent on preparing a specimen for storage……
……
……
……

Step 3: Nucleic Acid Extraction

1. How much time is spent on the nucleic acid extraction? ……..
2. What are the equipment, reagents, controls and consumables used during this step?

Item	**Quantity**	**model**	**cost**	**Life span (**for equipments)	**Share to HIVDR**
Equipments					

Consumables					
Reagents					

Step 4 Amplification of the Nucleic Acid

1. What is the time spent on Amplification of the Nucleic Acid……
……
……..
2. What are the consumables, reagents and equipments used during the amplification step?

Item	**Quantity**	**Model**	**Cost**	**Life span(**for equipments)	**Share to HIVDR**
Equipments+ Laboratory Furniture					

Consumables					
Reagents					

Step 5 Sequencing

1. What is the time spent on sequencing……
2. What are the equipment, reagents and consumables used during sequencing

Item	**Quantity**	**Model**	**Cost**	**Life span(**for equipments**)**	**HIVDR Share**
Equipments+ Laboratory Furniture					
Reagents					

Consumables					

Step 6 Data management:

Item	**Quantity**	**Model**	**costs**	**Lifespan**	**Share to HIVDR**
Equipments					
Networking Accessories					

Personnel Questionnaire

Type of staff	Number of staff in each category	Job group	Average Annual cost	Total annual cost	Time spent on HIV drug resistance

Longtime trainings

1. What are the estimated HIV drug resistance tests in a year? ……
2. Trainings attended and the duration of each training……..

Maintenance cost of equipments/service contracts

Item	Number of Items	Replacement value(*equipment cost)*	Percentage for maintenance	HIV drug resistance testing share

External Quality Assurance Program

Item	Frequency	Cost	Share to HIVDR

Building cost

Building space for each section(in Sq/m2)	Replacement value of a building	Proportion of the space used by HIV drug resistance testing	Total number of life years
Sample collection			
Sample Preparation and storage			
Nucleic acid extraction			
Amplification			
Sequencing			
Office			

Utility costs

Item	Quantity	Cost	HIV drug resistance testing share
Electricity			
Water			
Internet			

Office costs

Item	Quantity	Model	Lifespan for equipment + furniture	Costs	HIV drug resistance testing share
Equipments					
Stationery					

Office furniture					

What are some of the challenges experienced in Implementation of HIV drug resistance testing?

1. .....
2. .....
3. .....
4. .....
5. .....
6. .....
7. .....
8. .....
9. .....
10. .....

What are some of the lessons learnt in Implementation of HIV drug resistance testing?

1. .....
2. .....
3. .....
4. .....
5. .....
6. .....
7. .....

8. .....
9. .....