HIV DRUG RESISTANCE IN TANZANIA:
A literature review of socio-cultural, economic and health systems determinants

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HIV drug resistance in Tanzania: A literature review of the socio-cultural, economic and health systems determinants.

A thesis submitted in partial fulfillment of the requirement for the degree of Master of Public Health

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency syndrome
AMO	Assistant Medical Officer
ART	Anti Retroviral Therapy
ARV	Anti Retroviral
CHWs	Community Health Workers
CO	Clinical officer
CSO	Civil Society Organisation
CTCs	Care and Treatment Centre
DACC	District AIDS Control Coordinator
DMO	District Medical Officer
DRC	Democratic Republic of Congo
EWIs	Early Warning Indicators
FBO	Faith Based Organisation
GDP	Gross Domestic Product
HBC	Home Based Care
HCWs	Health Care Workers
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
MDG	Millennium Development Goals
MO	Medical Officer
MoHSW	Ministry of Health and Social Welfare
MSD	Medical Stores Department
NACOPHA	National Council of People Living with HIV

NACP	National AIDS Control Program
NBS	National Bureau of Statistics
NGOs	Non Governmental Organisations
NMSF	National Multisectoral strategic Framework
OCGS	Office Of Chief Government Statistician
OOP	Out of Pocket
PEPFAR	President's Emergency Plan for AIDS Relief
PLHIV	People Living with HIV
PMO-RALG	Prime Minister's Office – Regional Administration and Local Government
PMTCT	Prevention of Mother to Child Transmission
RACC	Regional AIDS Control Coordinator
SSA	Sub Saharan Africa
STIs	Sexually Transmitted Infections
TACAIDS	Tanzania Commission for AIDS
TB	Tuberculosis
THMIS	Tanzania HIV/AIDS and Malaria Indicator Survey
UNAIDS	United Nations Program on HIV/AIDS
URT	United Republic of Tanzania
USAID	United States Agency for International Development
WB	World Bank
WHO	World Health Organization
ZAC	Zanzibar AIDS Commission

GLOSSARY

HIV drug resistance: Is the ability of the human immunodeficiency virus to change its genetic structure(mutation) and replicate in the presence of antiretroviral drugs leading to failure of the drugs to suppress the virus and hence development of treatment failure (1).

ART adherence: ART adherence is the ability of a person to correspond to agreed recommendations from health care provider when taking medication, following a diet or executing lifestyle changes in order to achieve maximum viral suppression and decrease the risk of developing ARV resistance (2).

Task shifting: Redistribution of tasks among health care workers from highly qualified cadres to less specialised cadre (2).

Lost to follow up: Missing three scheduled appointment or drug refill for more than 90 days by PLHIV (3).

HIV related stigma: Is a condition in which a person is devaluated because of being HIV infected. Self stigma or internalised stigma is a condition whereby a person who is HIV infected feels a sense of shame, guilty and blame (4).

ABSTRACT

Background and Problem: Occurrence of HIV drug resistance (HIVDR) in Tanzania has been demonstrated in both antiretroviral therapy (ART) naive and patients on ART. Standardized ART regimens known to be effective at population level are used for treatment. HIVDR will reduce the effectiveness of ART therefore increasing HIV related morbidity and mortality.

Objectives and Methodology: This study analysed socio-cultural, economic and health systems determinants of HIVDR, review interventions addressing HIVDR in SSA in order to make specific recommendations to minimize occurrence of HIVDR. Literature review was conducted and adapted framework from Roura was used to analyse the determining factors.

Results: Presence of misinformation and false beliefs about HIV and ART and high indirect cost were identified as individual determinants for HIVDR. These were influenced by the existing traditional beliefs, some religious beliefs and practices and stigma. Health system weaknesses such as poor client retention mechanism, client overload at clinics, inadequate providers' skills, shortage of health workers, poor access to services and frequent stock-out of antiretroviral drugs (ARVs) were also identified as determinants for occurrence of HIVDR.

Conclusion and Recommendations: Occurrence of HIVDR in Tanzania is determined by factors occurring at community and health system level. Minimizing HIVDR needs interventions which focus on reducing healthcare worker workload through formulating policy on task shifting, reducing unnecessary clinic visits, ensuring continuous supply of ARVs, bringing services close to the community and analysing early warning indicators for HIVDR quarterly for prompt action.

Keywords: HIV, drug resistance, determinants, socio-cultural, health system.

Word count: 12,826

INTRODUCTION

Worldwide, 35 million people were estimated to be living with HIV by 2013, In Sub Saharan Africa (SSA) alone 24.7 million people are said to be living with HIV and these account for 71% of the total global HIV infection. Tanzania is among 10 countries which contribute to 81% of HIV infection in SSA (5,6).

More than ten years have passed since provision of HIV treatment began in Tanzania. Since then efforts to respond to HIV epidemic have gradually intensified mainly through prevention programs and provision of care, treatment and support for people living with HIV (7). In 2013, an approximated 1.4 million people were said to be living with HIV in Tanzania (8) and 850,274 were put on antiretroviral therapy (ART) (7).

More emphasis has been put on universal access to HIV services all over the country and as a result more HIV infected people have enrolled in care and treatment services. With increasing number of people being continuously enrolling into HIV services, ensuring provision of quality services for people living with HIV (PLHIV) is mandatory. HIV is a chronic illness which requires lifelong treatment without interruptions and good patient monitoring system for better outcome, contrary to that the outcome is poor and leads to increased morbidity and mortality.

As a medical doctor, I have worked as a clinician at HIV clinic and also worked as a program officer for HIV program in Tanzania. There are a lot of challenges with regards to provision of HIV care in Tanzania and of particular interest to me has been HIV drug resistance which leads to poor treatment outcome therefore increasing morbidity and mortality associated with HIV. Occurrence of HIV drug resistance also means switching HIV clients to second line ART and therefore decreasing future treatment options for patients.

Due to scale up of ART services in Tanzania, it is important to look at the determinants of HIV drug resistance and to design appropriate interventions for prevention. The aim of this study is to analyse socio-cultural, economic and health systems determinants of HIV drug resistance in Tanzania and make recommendations to the National AIDS Control Program (NACP) to improve provision of HIV care and treatment services thereby reducing occurrence of HIV drug resistance.

CHAPTER 1: BACKGROUND INFORMATION

1.1 Country profile

Located in Eastern part of Africa, the United Republic of Tanzania (URT), commonly known as Tanzania occupies 945,087 square kilometres of land. It is bordered by 8 countries namely Kenya, Uganda, Burundi, Rwanda Democratic Republic of Congo, Zambia, Mozambique and Malawi and is divided into 30 administrative regions as shown in annex 1.The regions are further divided into districts, wards and villages, currently there are 169 districts in the country (9,10). Total population of Tanzania is estimated to be 45 million according to the population and housing census conducted in 2012, 51% of the population are females while 49% are males. Children up to 14 years make 44% of the total population, the estimated total fertility rate is 5.2 children per woman while the annual population growth rate is said to be 2.7%. Life expectancy at birth as estimated in 2012 is 61 years, majority of the population 70% live in the rural areas (10).

1.2 Socio−cultural and economic situation

Culture of the Tanzanian is mostly influenced by the norms and traditions of their ethnic groups and their religion, there are currently more than 120 tribes in the country and religions found in the country are Christianity, Islam and indigenous beliefs. Being a patriarchal society, women in Tanzania are more disadvantaged compared to men due to the existing gender imbalance (9,10). With regards to the socio-economic status, World Bank (WB) estimates in 2012 showed that 28% of people were living below poverty line in Tanzania (11).

1.3 State of HIV epidemic in the country

Tanzania faces a generalized type of HIV epidemic, according to Tanzania HIV and malaria indicator survey (THMIS) conducted in 2011/2012 prevalence of HIV is 5.1% among adults (15 to 49 years). Women are more affected than men prevalence being high in females (6.2%) as compared to males (3.8%). There has been a decline in HIV prevalence from 5.7% in 2008/2009 to 5.1% in 2011/2012 surveys, a statistically significant decline in HIV was seen in men but not in women (12). Of the estimated 1.4 million people that are currently living with HIV in Tanzania mainland, 28% are children below 15 years (7). In 2012, HIV was the ninth leading cause of

morbidity in the country but it was also the second leading cause of mortality after malaria (13).

1.4 HIV Policy and Financing
HIV policy of 2001 aimed at HIV prevention, control and impact mitigation and is currently guided by the third national multisectoral strategic framework for HIV/AIDS (9,14). Healthcare financing still depend on donor funding for the most parts. Government expenditure on health was 10.4% of the total budget for the year 2012 (15), which is lower than the proposed 15% of the Abuja declaration. Funding for HIV responses is almost entirely dependent on external funds, in 2011/2012 for example 95% of the funds for HIV response were from international donors (9).

1.5 Human Resources for Health
Tanzania is facing shortage of human resources for health, in 2014 it was estimated that there was a shortage of 56% of health care workers. Production of health care workers of all cadres and recruitment after completion of the training is also low. Poor working environment and lack of motivation are among the factors contributing to low retention of health care workers (16). There is also unequal distribution of the available health workers whereby the rural areas are affected more compared to urban areas shortage. A study that was conducted in rural Tanzania showed only 14% of required nurses and 20% of required clinical staff were employed (16,17).

1.6 Organization of health care services in Tanzania
The health care system in Tanzania is organized into primary, secondary and tertiary levels for both public and private facilities as shown in figure 1 below. At primary level of health care there are community or village health posts, dispensaries and health centres (15,18–20). Village health posts provide preventive services and are run by two people who undergo a special training (15,20). A dispensary serves a population of up to 10,000 and provides basic preventive and curative health services. Health centre which can serve up to 50,000 people provide more comprehensive care than the dispensary. At secondary level there are district hospitals which provide comprehensive care and are responsible for supervising dispensaries and health centres. At tertiary level, there are regional hospitals, specialized hospitals and national hospital which provide specialized care as well as basic primary care (18–20).

Figure 1: Tanzanian health system referral pyramid.
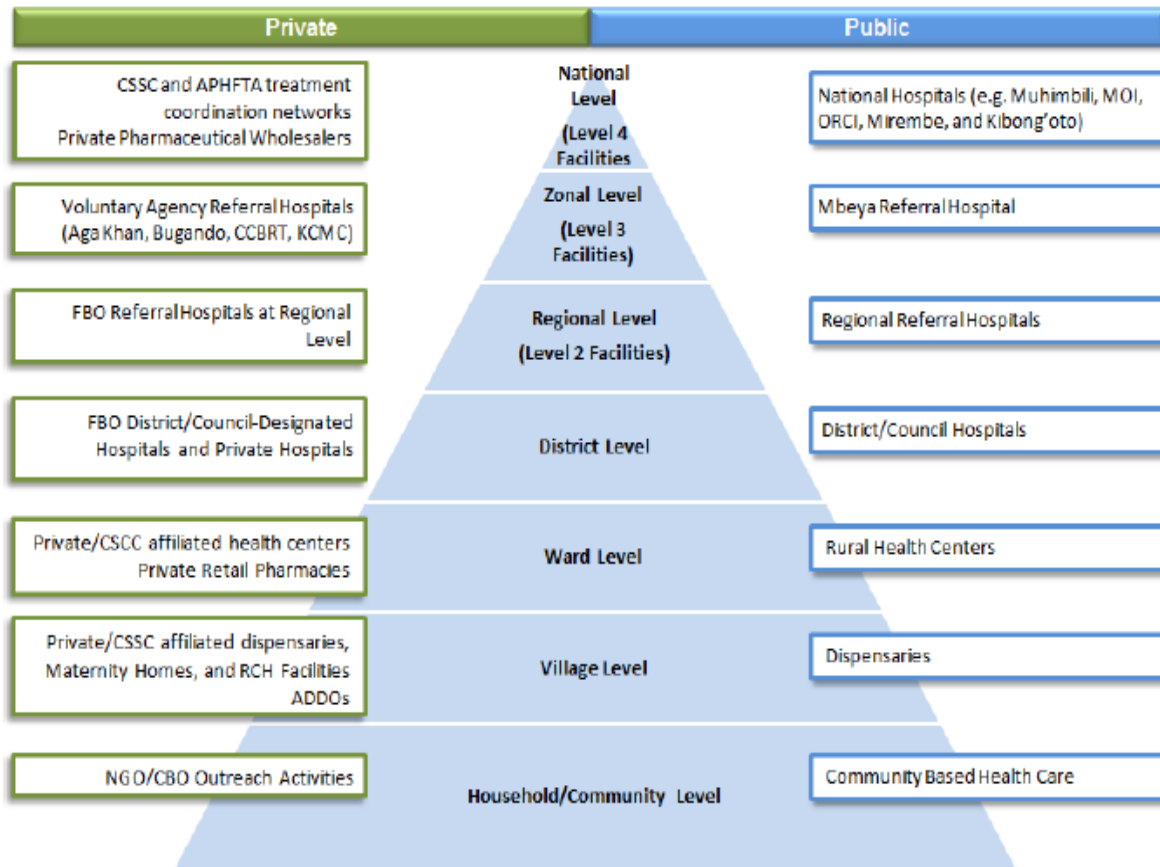
Source: Tanzania private health sector assessment (21)

CHAPTER 2: STUDY OVERVIEW

2.1 Problem statement

HIV drug resistance (HIVDR) is defined by WHO as the ability of the human immunodeficiency virus to change its genetic structure(mutation) and replicate in the presence of antiretroviral drugs leading to failure of the drugs to suppress the virus and hence development of treatment failure. Drug resistance is often caused by presence of suboptimal antiretroviral (ARV) drug levels in blood however to some extent drug resistance can occur even in the presence of optimal drug levels due to HIV ability to rapidly replicate and develop mutations. HIVDR occurs in two forms, acquired HIVDR which occurs in patients receiving ART as a result of emergence of resistance mutations, this is also known as secondary drug resistance. The second form is transmitted HIVDR which occurs when an individual is infected with a drug resistant virus also known as primary resistance (1).

In Tanzania, studies conducted have shown both acquired and transmitted forms of HIVDR occur. In a study conducted among HIV pregnant women naïve to antiretroviral therapy attending antenatal clinic in an urban town in mainland Tanzania revealed prevalence of HIVDR to be 11.9% (22). In another study conducted among ART naïve youth aged 13- 25 years in Dar es Salaam revealed 9% prevalence of HIVDR (23). In Mwanza region, a similar study conducted among HIV patients who had not started ART and had not been previously exposed to ART revealed HIVDR prevalence of 14.8% (24). These studies show occurrence of transmitted HIVDR (primary drug resistance) in different population groups in Tanzania.

Studies conducted in some eastern and southern Africa cities to assess prevalence of transmitted drug resistance have shown lower prevalence compared to Tanzania. Transmitted HIVDR prevalence was found to be 8% in Kigali-Rwanda, 4% in Kilifi- Kenya, and 3% in Lusaka-Zambia. On the other hand in Entebbe-Uganda and Cape Town-South Africa prevalence of transmitted HIVDR was higher than that found in Tanzania, 19% and 20% respectively (25).

Prevalence of acquired HIVDR (secondary HIVDR) appears to be higher compared to that of transmitted HIVDR (primary HIVDR) in Tanzania and it occurs across all ages. In a study conducted in Northern Tanzania among infants born to HIV positive mothers and who were previously exposed to Nevirapine as prophylaxis for prevention of mother to child transmission (PMTCT) of HIV, prevalence of HIVDR was as high as 28% (26).

Another study conducted in rural Tanzania among adult patients on ART revealed prevalence of HIVDR tend to increase with increase in number of years on ART, prevalence was 3.9%, 8.4%, 16.7% and 12.5% among clients after 1, 2, 3 and 4 years on ART respectively (27). Data from WHO surveys of acquired drug resistance conducted in 12 low and middle income countries of which Tanzania was not a part has shown prevalence to be rising from 4.8% in 2007 to 6.8% in 2010 (1). Prevalence of HIVDR in the WHO surveys is lower compared to prevalence from studies conducted in Tanzania.

HIVDR in Tanzania occurs against all available first line regimens, studies conducted have shown presence of resistance mutations against the following drugs Zidovudine, Lamivudine, Nevirapine, Efavirenz, Kaletra, and Abacavir (24). These drugs form the basis for first line as well as second line ART regimen in Tanzania. HIVDR occur when HIV is exposed to sub optimal drug levels following extended periods of treatment interruption or inadequate drug intake although some degree of HIVDR can also occur spontaneously. The factors which may cause treatment interruption or inadequate drug intake and hence influence development of HIVDR include poor adherence, frequent stock out of ARVs, improper prescription practices, non retention into HIV care and poor access to services.

Development of HIV drug resistance will lead to increased HIV related morbidity due to development of treatment failure. This will cause emergence of opportunistic infections and increase the cost of care to the patients. For the patients it will necessitate use of second line and third line ART and due to lack of fixed dose combination poor adherence may occur leading to further resistance to second line and third line ART as well (28). HIVDR will add more burdens to health facilities currently operating on shortage of financial and human resources. For HIV programming it will increase demand on more expensive second and third line ART. HIVDR will also have effects on PMTCT programs and contribute to increased mother to

child transmission of HIV infection. It will also mean that people will be infected with resistant virus which will not respond to the standard first line regimens. HIVDR will sustain HIV epidemic due to limited effectiveness of antiretroviral therapy.

2.2 Justification

Initiation of ART to eligible HIV clients in Tanzania uses a public health approach whereby treatment options are selected and standardized for all individuals (29). The choice of ART for initiating patients therefore depends on their efficacy at population level (28). Due to high burden of HIV infection in Tanzania, this approach is feasible for initiating ART to large number of eligible clients rather than individualizing the regimens.

In order to prevent occurrence and spread of HIVDR and ensure population level efficacy of ART WHO has issued a set of recommendations for countries that use public health approach in providing anti retroviral drugs. These recommendations include monitoring HIVDR early warning indicators (EWIs), surveillance of HIVDR in population initiating ART, surveillance of transmitted drug resistance in populations recently infected with HIV and surveillance of HIVDR in children below 18 months (30). In Tanzania uptake of the mentioned recommendations is at slow rate, only one HIVDR EWIs monitoring study has been conducted so far (31).

Occurrence of HIVDR in Tanzania can be minimized if the underlying causes are addressed. To date there is limited information about determinants which explain the overall occurrence of HIVDR in Tanzania. Understanding the determinants of HIVDR is important for designing appropriate interventions for minimizing the problem.

2.3 Objectives

2.3.1 Overall objective
The overall objective of this study is to analyze socio-cultural, economic and health system determinants of HIVDR, review interventions that address HIVDR in SSA in order to make specific recommendations to minimize occurrence of HIVDR in Tanzania.

2.3.2 Specific objectives
- To analyze socio-cultural and economic determinants that lead to occurrence of HIV drug resistance in Tanzania.
- To analyze health system determinants that lead to occurrence of HIV drug resistance in Tanzania.
- To review current interventions that addresses the determinants of HIV drug resistance in sub Saharan Africa.
- To provide recommendations on HIV/AIDS care and treatment services provision in order to minimize occurrence of HIV drug resistance in Tanzania.

2.4 Methods
The methodology used in this study is literature review whereby peer reviewed articles and grey literature were reviewed and analysed for evidence. The peer reviewed articles and grey literature were based in Tanzania and Sub Saharan Africa context depending on the objectives. Inclusion criteria for the literature search were publications in English language, timeframe from 2001 to 2015, publications from sub Saharan Africa. Articles and publications in other language other than English, outside SSA and those published before 2001 were excluded. Key words were used singly or in combination in order to narrow down the search. The search strategy used per each objective and key words used are summarized in table 1 below.

Table 1: Summary of the search strategy for each objective

OBJECTIVE	SOURCE	TYPE OF LITERATURE OBTAINED	KEY WORDS USED SINGLY AND IN COMBINATION
Objective 1 To analyze socio-cultural and economic determinants that lead to occurrence of HIV drug resistance in Tanzania.	Pub med and Google scholar	Peer reviewed articles	Determinant, HIV, ARVs, ART, drug resistance, treatment, failure, socio-cultural, economic, sub-Saharan Africa, Tanzania
	Google	NGOs, government and institution reports	Report, strategy, plan, health, HIV, Tanzania, sub Saharan Africa
	Government, NGOs and Institutional websites	NGOs, government and institutional reports	Report, strategy, plan, health, HIV, report, Tanzania, sub Saharan Africa
	Reference list of the articles	Peer reviewed articles	-
Objective 2 To analyze health system determinants that lead to occurrence of HIV drug resistance in Tanzania	Pub med and Google scholar	Peer reviewed articles	Health system, determinants, HIV, ART, ARVs, drug resistance, access, retention, treatment, Tanzania, sub Saharan Africa.
	Google	NGOs reports, government reports, guidelines, reviews, Institutional reports.	Strategy, Policy, Plan, health system, report, HIV, ARVs, ART, procurement, supply, Tanzania, sub- Saharan Africa
	Government, NGOs and Institutional websites	NGOs reports, government reports, guidelines, reviews, Institutional reports.	Strategy, Policy, Plan, health system, report, HIV, ART, ARVs, Tanzania, sub- Saharan Africa
	Reference list of the articles	Peer reviewed articles	-
Objective 3 To review current interventions that addresses the determinants of HIV drug resistance in sub Saharan Africa	Pub med and Google scholar	Peer reviewed articles	HIV, Interventions, Sub Saharan Africa, ART, ARVs, supply chain, drug resistance, Procurement.
	Google	-	
	Reference list of the articles	Peer reviewed articles	

2.4.1 Conceptual framework

After a thorough review of a number of conceptual frameworks, no conceptual framework was found to be perfectly fitting for the analysis of the socio-cultural, economic and health system related factors that determine occurrence of HIVDR, modification was required for the frameworks to fit this study. Two conceptual frameworks were found to be relevant for the study.

The first conceptual framework that was reviewed was "Information Motivation Behaviour Skills Model (IMB) for ART adherence" by Wekesa (32), this framework was used to analyze factors for ART adherence in resource poor setting. The topic relates to this study and the model would have been adapted but this model considered the individual level factors. Other factors such as socio-cultural and other structural factors such as those related to the health system which could also determine adherence behaviour were not taken into consideration.

The second conceptual framework which was reviewed was "social-ecological framework to the exploration of barriers and facilitators to sustained treatment adherence experienced by ART patients" by Roura (33). The framework takes into consideration the social, individual, programmatic and structural factors that influence adherence to treatment and how these factors influence each other (33). This conceptual framework was also adapted by Musheke (34) in a study conducted to assess individual and contextual factors affecting patient attrition in Lusaka. The "social-ecological framework to the exploration of barriers and facilitators to sustained treatment adherence experienced by ART patients" by Roura (33) was found to be suitable for this study and was adapted to align with the objectives of the study.

Conceptual framework for analysing determinants of HIVDR in Tanzania

The social- ecological framework has been adapted to guide the analysis of determinants of HIV drug resistance in Tanzania. Sustained attendance to ART clinic has replaced with HIVDR which is the outcome of this study and in the structural factors poverty was removed and placed under individual factors. The health system factors include human resources for health,

health information system, ARV procurement and supply, health finance and governance. Programmatic factors have been replaced with health service delivery factors which include provider's skills, client retention, client load and access to health services. In Roura (33) framework, access was linking individual factors and individual factors.

The individual factors in Roura (33) framework which were perceived benefits and perceived constraints were more specified and gave rise to adherence, information and treatment beliefs, side effects, perceived illness and wellness, economic factors, self stigma and disclosure. The socio-cultural factors were specified into traditional and religious beliefs and practices, stigma and gender. The interlinking factors were integrated in the socio-cultural factors and individual factors. Figure 2 below shows the adapted conceptual framework which will be used in this study.

Figure 2: Conceptual framework for analyzing determinants of HIVDR in Tanzania adapted from Roura (33).
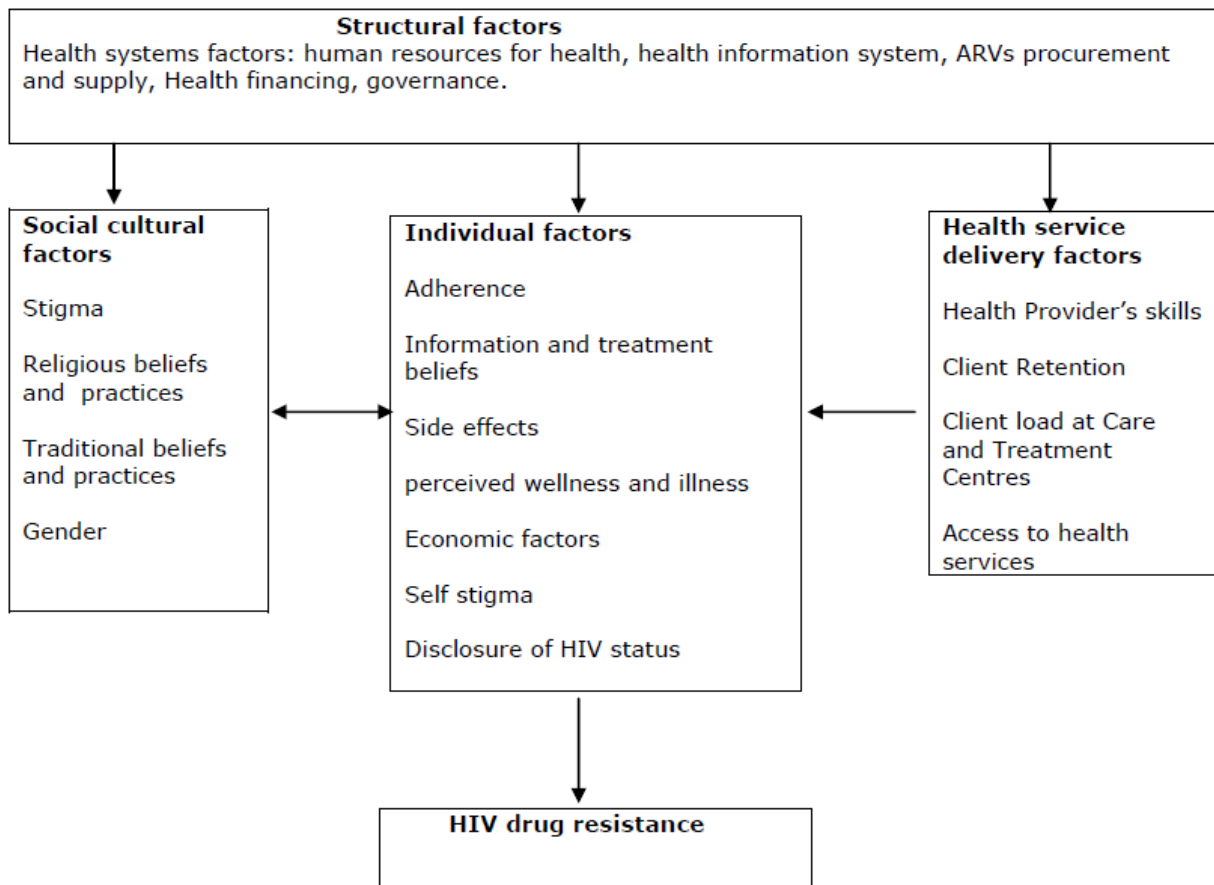
CHAPTER 3: ANALYSIS OF SOCIO CULTURAL, ECONOMIC AND HEALTH SYSTEMS DETERMINANTS OF HIV DRUG RESISTANCE

In this chapter the adapted conceptual framework will be used to analyse the socio cultural, economic and health system determinants of HIV drug resistance in Tanzania. The factors that will be discussed include individual factors, social cultural factors, service delivery factors and structural factors.

3.1 Individual factors

3.1.1 Adherence

Management of HIV infection requires continuous treatment without interruptions for treatment to be successful and minimize occurrence of HIV drug resistance. According to WHO, patients who are on first line ART medication require to have good adherence levels of 95% and above for viral suppression to be achieved and hence less likelihood of developing drug resistance (35). Drug adherence is defined as a person's ability to correspond to agreed recommendations when taking medications (2)

Denison (36) in the study conducted among adult patients in Tanzania, Uganda and Zambia showed 40% of patients took less than 90% of their required ART in a period of 6 months using a medication possession ratio method. This indicates low adherence levels than the recommended minimum level which may predispose patients to develop HIVDR. In the same study however adherence was reported to be high using self reported adherence method whereby nearly 97% patients reported to have good adherence. Measuring adherence levels using self reported method may be subjected to social desirability bias which may underestimate the problem of poor adherence.

Among children and adolescents ART adherence level was found to be 84% in a study conducted by Nyogea (37) in rural Tanzania. Although the study defined optimal adherence to be 80%, this is lower than the minimum required levels of adherence of 95% which is required to prevent risk of developing HIVDR.

3.1.2 Information and Treatment beliefs

Different studies have described reasons for interruption or stopping treatment among PLHIV. Lack of clear information about ART were identified

as factors that led to discontinuation of treatment in a study done by Tomori(38), this qualitative study however was a community based study in which only 12% of the participants were HIV positive. The study largely gave the views of the non HIV infected community members.

In line with the above findings, studies have shown certain beliefs about HIV and ART medication were reasons for PLHIV to interrupt use of ARVs. These included the belief that they only increase the severity of the disease and therefore leading to death (33,38). Other beliefs like ARVs can't be taken when one drinks alcohol or smokes or having sex is prohibited when using ARVs have led to preferences of not to using ART medications. In some societies it is also believed that HIV can be cured through faith healing as it is considered to be caused by witchcraft (33,38,39).

3.1.3 Side effects

Side effects that are associated with the use of anti retro viral drugs are also known to be the reasons as to why patients discontinue using ART or skipping doses of ART medications. This was shown in a study conducted by Nsimba (40) in which patients reported not taking their ART medication as required due to experiencing side effects. Similar findings were shown in the TUNAJALI (41) project report in which 14% of PLHIV who were lost to follow up and were traced back to care revealed that they had stopped treatment due to side effects. Different findings were shown in Lyimo (39) study whereby drug side effects did not result in patients stopping their medication. The above findings in Lyimo study may be due to differences in counselling and information provided to the patients on ART use as the studies were conducted in different settings.

3.1.4 Perceived wellness and illness

Feeling well after use of ART has also been documented to be one of the reasons that lead to treatment interruption and discontinuation of ART medication among PLHIV in Roura (33) and Lyimo (39) studies. It has also been shown that being well as a result of being on treatment for longer periods of 4 years or more is associated with missing clinic visits leading to treatment interruption. This was shown in Muya (42) in a prospective cohort study where patients who were longer on treatment that is 4 years or longer were more likely to miss clinic visits than those who were on ART for less than 4 years. The findings above indicate that there is still a gap in

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knowledge about ART medication and HIV itself as it shows that participants of the study perceived that they were cured and hence stopped treatment.

In addition Roura (33) also shows that failure to experience recovery among patients also leads to loss of hope and hence discontinuation of use of ARVs and loss of follow up into HIV care. Denison (36) also shows similar findings in which patients who experience more HIV related symptoms were more likely not to adhere well to treatment. Patient on ART medication requires continuous counselling and reassurance when such incidences of drug side effects occur. The above results may be due to inadequate adherence counselling and lack continuous health education to patients regarding the use of ART.

But on the other hand improved wellbeing after use of ART has been shown to a motivating factor for improving adherence and staying on treatment. This has been shown in Nyogea (37) study conducted to assess determinants of adherence among children and adolescents in rural Tanzania. In this study overall improvement in health was a determinant for treatment adherence. Similar findings were also described in studies conducted among adults whereby improved health after ART initiation was found to be a motivating factor to continue with treatment (38,39).

3.1.5 Economical factors
Although Tanzania demographic and health survey of 2012 has shown that HIV prevalence is high among those with high socio-economic status as compared to low socio-economic status (12), several studies have shown that high cost associated with HIV care and treatment services to be among the reasons for stopping treatment and loss of patients in the HIV program.

Studies have shown that most patients fail to attend HIV clinics and hence interrupt their treatment due to high indirect costs they incur. High transport costs to the health facilities were found to hinder adherence to clinic schedules among PLHIV, thus PLHIV attended clinics only when they had money to cover for transport costs (33,40,41). This leads to interruption of treatment for those on ART and may lead to development of HIV drug resistance.

Apart from transportation costs, patient also usually incur other cost for laboratory tests and other investigations like chest radiography and buying opportunistic infections drugs which may not be available freely for them. Most patients who cannot afford to pay for these expenses as out of pocket expenditure refrain from attending care and treatment centres (CTCs) (38,41). High out of pocket expenditures result from the fact that majority of people are not covered by health insurance. According to 2012 national census approximated 6% of people were under national health insurance scheme and community health fund (10). Inability to afford to pay for the services causes non retention into HIV care and hence development of drug resistance due to treatment interruptions.

Several studies have identified PLHIVs concern over food availability as they cannot take medication without having their meals and they therefore skip taking medications (39,40). Others have expressed concern about ARVs increasing their appetite thus requiring more food intake which they cannot afford to buy, however in this study further analysis revealed that food was not significantly associated with poor adherence (40). Tomori (38) study also shows due to poverty PLHIV cannot afford to buy food that they are usually advised to eat and still be able to afford transportation and other hospital costs. Similar findings are seen in the TUNAJALI project report where lack of money to buy food and transport fare was a reason for stopping treatment for 12% of PLHIV who were on ART (41)

Log waiting hours are associated with loss of earnings as a result of time spent waiting to see a health provider at HIV clinics due to high client load. This has been identified in the TUNAJALI project report as one of the reasons for discontinuing follow up at HIV clinics (41).

3.1.6 Self stigma
Self stigma is another reason that has been identified to cause PLHIV not to take their drugs as required. Denison (36) study found out that self stigma was associated with incomplete adherence among patients on ART in a study conducted in Tanzania, Uganda and Zambia. Due to self stigma, some patients avoid attending nearby clinics for fear of being identified as HIV infected by the community and health care workers whom they know. In his study, Lyimo (39) showed 23% of patients avoided attending nearby clinics. Attending long distanced clinics is associated with high cost of transportation

which may make patients not to adhere well to their clinic schedules therefore interrupt their treatment.

3.1.7 Disclosure of HIV status

Due to surrounding stigma around HIV infection, disclosure of HIV status has been a difficult task among PLHIV. It has been described that disclosing one's HIV status is associated with increased psychosocial support especially from family members therefore motivating PLHIV to stay on treatment (33,39,40). Low levels of social support are known to be associated with incomplete adherence as demonstrated by Denison (36) study. In this study Denison (36) showed that low levels of social support for PLHIV was associated with incomplete adherence to ART medication. Meanwhile Nyogea (37) study conducted among children and adolescents on ART revealed that poor adherence was not significantly associated with disclosure of HIV status. The different results in Dennison (36) and Nyogea (37) studies seem to be due to the difference in their study groups whereby Nyogea study the target was adolescent and children whose HIV status is usually known to parents or caretakers therefore have family support.

Non disclosure of HIV status has also been shown to result in poor follow up of clinic visits and interruption of treatment. Non disclosure of HIV status by PLHIV is due to the stigma surrounding HIV infection at family, community, workplace and even health facility level which leads to discrimination and lack of social support (40). Although 94% of PLHIV on ARVs had disclosed their HIV status in Nsimba (40) study, some report to have faced problems like losing their jobs, being regarded as promiscuous in the society and banned from attending social events.

While family members maybe a source of support and encouragement to the patients, Roura (33) study also shows opposing results whereby disclosing HIV status to family members can also be a cause for treatment interruption when family members make choices about alternative treatment for the patient. This finding shows that there is low knowledge about HIV treatment among families of PLHIV which then influence patient's use or non-use of ART medication.

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3.2 Socio-cultural factors

3.2.1 Stigma

Community involvement in provision of psychosocial support to individuals on ART is important for ART programs to be successful. Support from the community ensures PLHIV adhere well to their treatment thus reducing the chance of developing drug resistance (43). Presence of stigma for PLHIV in the community has described in both Nsimba (40) and Tomori (38). Nsimba (40) study goes further to highlight that the level of stigma in the community is even higher compared to that at family level.

Stigma and discrimination in the community are identified as barriers to seeking medical care, remaining in care and adhering well to ART medication (38). Due to fear of stigma it is difficult for PLHIV to attend CTCs so as to avoid being recognized by other community members as PLHIV. Lyimo (39) study shows that 23% of patients involved in the study attended CTCs that were not close to where they lived due to fear of stigma. Meanwhile Muya (42) study findings revealed no significant association between stigma and failure to attend CTCs as scheduled among PLHIV. While Lyimo (39) and Tomori (38) studies were qualitative in design and did not involve many clients, Muya et al study was a large prospective cohort study whose results may be more reliable. However the findings in Lyimo and Tomori studies cannot be ignored because they provide an in-depth understanding of the reasons for discontinuation of treatment among PLHIV.

3.2.2 Traditional beliefs and practices

Beliefs surrounding HIV infection and its treatment may lead to occurrence of HIV drug resistance. In some societies there are beliefs that HIV is a result of witchcraft and that it can be cured through spiritual healing by traditional healers and through religious healing (33). It has been shown by Nsimba (40) that PLHIV identifies traditional healers and religious leaders as having alternative treatment for HIV. While Stanifer (44) revealed high use of traditional medicine by 55.7% of the respondents, Kayombo (45) study showed that HIV/AIDS was among the leading condition to be treated by traditional health practitioners, second only to mental illnesses. In Tomori (38) study it has been shown that PLHIV stop using ART medication and go for traditional medicines. The use of traditional medicine occurs when there is no improvement and symptoms persist.

The findings above about use of traditional medicine may be due to traditional healers announcing to have cure for HIV. The national multisectoral strategic plan for HIV identifies the problem of unregulated advertisement by traditional healers who claim to have cure for HIV to be growing (9).

3.2.3 Religious beliefs and practices

Faith based organisation play an important role in provision of health care services in Tanzania (46,47). Private facilities make up approximately 40% of health facilities in the country and these largely include faith based hospitals (46). Provision of HIV care, treatment and support services also occurs at faith based hospitals and institutions (9). Religious denominations involved in the provision of HIV services include Roman Catholics, Lutherans, Evangelical churches, Seventh Day Adventists and Muslims (21).

Despite the involvement of faith based organisations in provision of HIV services, it has been identified that some of the religious leaders in some denominations are involved in provision of alternative treatment and cure for HIV thus contributing to increase for occurrence of HIV drug resistance. Roura (48) in her study conducted to assess the attitudes of Faith leaders towards HIV treatment options found out that most considered ART to be a temporary treatment and that healing can occur through prayer. This study involved religious leaders from mainstream churches like Roman Catholic, Lutheran-Anglican, SDA, African inland church, as well as revivalist churches and Muslim religious leaders. Similar findings were also shown in Tomori (38) and Lyimo (39) study in which some church leaders insisted that HIV could be cured by faith alone. In these studies however some religious leaders were positive about ART as it prolongs the lives of PLHIV and they encouraged people to seek for treatment (38,48).

Some religious leaders have also been shown to have high influence on the health seeking behaviour of people in their communities and therefore affecting their decision to use or not use ART medication (38,39,42). For example in 2010, a religious leader claimed to have cure for HIV and other chronic conditions drew thousands of PLHIV to take his miracle cure and abandon ART (38,49).

It was also shown in a report by TUNAJALI report that religious beliefs to be among factors that contributed to PLHIV stopping treatment and loss from HIV care. In this report 10% of patients who were loss to follow up and on ART had stopped taking their medication because they thought they had been healed spiritually (41). Another study conducted by Zou (50) among parishioners concluded that people's decision to use or not use ART was linked to knowledge they have about ARVs rather than their religious beliefs.

3.2.4 Gender

The existing gender inequalities in the society have an influence in the uptake of HIV care and treatment services in Tanzania. Due to gender imbalance some women are predisposed to financial dependence on men. A proportion of women are unable to make decisions concerning their health therefore have to ask for permission and financial assistance from their male partners in order to attend clinic (9,51).In NMSF III it is indicated that 40% of women are not final decision makers with regards to their health and children's health as well as in household expenditures (9) .Women also fear of being labelled as promiscuous and abandonment by partners, as a result they don't disclose their HIV status to their partners, family and community. This affects how women adhere to clinic schedules and their adherence to treatment as often they have to hide in order to take ARVs (51).

It has also been shown that men being head of the families and breadwinners also fear to disclose their HIV status because they don't want to be seen as weak and have to maintain their jobs (52). As a result of this they tend to avoid visiting HIV clinics and share the drugs of their women partners who attend HIV clinics. This leads to inadequate intake of treatment which may predispose both partners to develop drug resistance.

3.3 Health service delivery factors

3.3.1 Health Providers' skills

Provision of HIV care and treatment services in Tanzania involves nurses, doctors, clinical officers and assistant medical officers. As HIV services are increasingly being provided at primary level of health care that is health centres and dispensaries, health care providers mostly involved in provision of HIV services are nurses, clinical officers and assistant medical officers. The national guideline for the management of HIV requires health care

providers to undergo a specific training for HIV management before being involved in provision if HIV services (29).

Correct prescription of ART regimen is important for attaining maximum viral suppression. The early warning indicator survey conducted by Juma (31) showed that only 54% of PLHIV who were on ART for one year were given correct ART regimen. This finding indicates incorrect prescribing practices which affected 56% of patients involved in the survey predisposing them to the risk of developing HIVDR. Incorrect prescribing practices may be due to lack of training of HCWs for HIV management. Mbilinyi (53) in his study has shown that health care workers who are directly involved in the provision of care for PLHIV don't receive adequate training but rather it is the senior medical officials who usually go for trainings. According to this study lower cadre providers(CO, assistant nurses) who are largely involved in provision of HIV care lack adequate skills as the higher cadre providers (Medical officers, AMO, nurse officers) are the ones who frequently undergo trainings.

Furthermore there is evidence of inadequate counselling skills among HCWs. This has been demonstrated by presence of incorrect information which PLHIV had received from health care providers. Studies have shown that PLHIV were given instructions not to take alcohol, smoke or engage in sexual activities while on ART (33,38,39). Such information may make PLHIV choose to stop or skip ART medication and hence develop HIVDR.

PLHIV don't face stigma and discrimination at family and community level only but also at the level of health care. It has been identified identifies that one of the factors contributing to non retention of PLHIV in care and hence treatment interruption is stigma they face form health care providers (38,4). Similar findings are shown in the TUNAJALI report were reasons for loss to follow up among patients who were brought back to care included perceived negative attitudes of the health care providers (41). These findings show a gap in skills of the health care providers about stigma among health care providers which affects patient retention in care, adherence to treatment and hence determine the occurrence of HIV drug resistance.

3.3.2 Client retention system
Extended drug interruptions are known to cause resistance to antiretroviral drugs and therefore development of virological failure (1).Non retention in HIV care of PLHIV who are already on treatment causes drug interruptions

and hence development of HIV drug resistance. According to the NACP report of 2013 on implementation of HIV CTC services dropout rate of PLHIV on ART one year after treatment initiation increased from 23 per 100 person years for those initiated on ART in 2005 or before to 26.4 per 100 person years for clients initiating treatment in 2010 (54). The increase in dropout rate may be due to increased number of people stopping ART medication, self transfer without referral to other facilities or unreported deaths which are captured as loss to follow up in NACP database.

Community home based care (HBC) providers among other duties are also involved in tracking PLHIV who miss appointments (55). According to NACP each CTC is supposed to have HBC provider although this cadre has not been included in the health plans as one of the healthcare workforce (54), HBC providers currently operate as volunteers receiving incentives from non-governmental organisations (NGOs), faith based organisations (FBOs) and civil society organisations (CSOs).

The national guideline for management of HIV outlines the importance of ensuring close linkages between CTCs and home based care and support system as a strategy for establishing good tracking system for PLHIV. HBC providers work by using facility data to identify PLHIV who miss clinic appointment and who are lost to follow up for tracking (29). PLHIV is defined as a loss to follow up when he/she miss three scheduled appointment or drug refill for more than 90 days (3). There is poor linkage of PLHIV to community HBC services (9) which contribute to non retention in HIV care and treatment program. Inadequate financial resources for HBC services (9) hinder proper functioning of HBC providers.

3.3.3 Client load at Care and Treatment Centres

As the number of PLHIV in HIV care and treatment centres is increasing the healthcare workforce continue to bear the burden of increased workload. A study conducted by Garcia (56) revealed a high health care provider per patient ratio. In this study it was shown that work overload by having too few health care workers or high client volume is a barrier towards provision of quality care by 52% of HCW involved in the study. Short consultations make patients to doubt the quality of care they are given hence may stop attending the clinics compromising their adherence to ART medication (40).

One of the reasons for loss to follow up among patients in the TUNAJALI project supported region was long waiting hours at the clinics (41). The problem of overcrowding at CTCs is also identified in the study conducted by Mbilinyi (53) whereby health care providers spend less time with their clients due to high client volume. Due to this less time is also used in counselling clients for drug adherence and this may lead to occurrence of drug resistance.

3.3.4 Access to health services

HIV care and treatment services are currently being provided at all levels from primary level to tertiary level if the minimum criterion is met in terms of staff availability and infrastructure (29). Most primary level facilities don't meet such criteria due to shortage of staff and poor infrastructure and therefore HIV services are more concentrated at secondary and tertiary levels of care.

Long distance to reach facilities associated with high costs of transportation is another challenge for HIV program in Tanzania and is a barrier towards retention of PLHIV in care. Clients who live far from health facilities providing CTC services for HIV most often miss their appointments and therefore interrupt treatment (38,41). Distance of 5km or less from home to a health facility is considered within reach by walking (57). It is estimated that 96% of urban population and 70% of rural population live within 5 kilometres of a health facility (9). Although the data indicate that majority of people are within reach of the facilities, HIV services are not available at all facilities. Only 22% of the registered health facilities in Tanzania provide HIV services (9). This shows that patient still have to travel far to reach facilities where services are being provided.

Difficulties in obtaining transport in order to get to the clinic is also another factor that interrupts ART treatment among patients therefore putting them at increased risk of developing resistance. Transport problems occur more in rural areas due to poor road infrastructure (33,38,40).

3.4 Structural factors

3.4.1 Human resources for health
Provision of quality standard of care to PLHIV determines their treatment outcome and this requires availability of skilled health care providers in adequate numbers. Tanzania faces shortage of human resources for health of all cadres but the shortage is more severe for doctors, assistant medical officer and clinical officers (16). According to WHO countries with less than 23 health workers (physicians, nurses and doctors) per 10,000 population have shortage of health workforce (58). Graph 1 below shows the available health care workers per 10,000 populations by regions which is below the level recommended by WHO for all cadres.

Graph 1: Health workers per 10,000 populations in the regions in Tanzania mainland
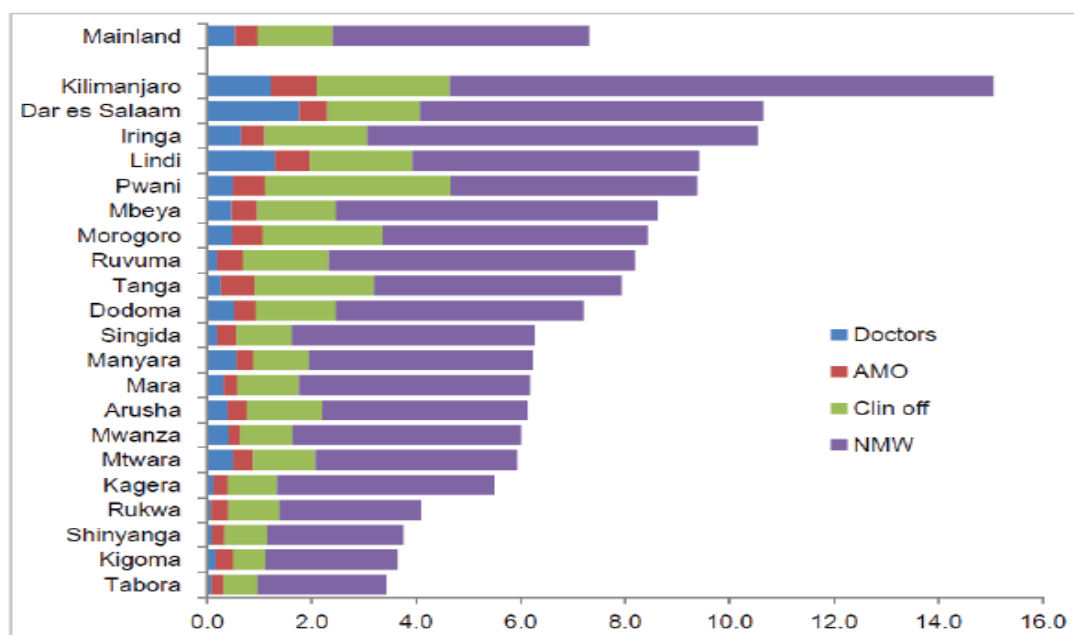
Source: Human resources for health and social welfare strategic plan 2014-2019 (16)

Provision of HIV care and treatment services also faces a serious shortage of health care workers. In a study conducted by Sikika (59) 68% of facilities revealed facing shortage of human resources for provision of HIV care and treatment services. The current strategies which are in place to mitigate

shortage of human resources for health include increasing production of HCWs by collaborating with private institutions, recruitment and retention (16).

Increasing production of health care workforce is a long term process and therefore will not solve the ongoing shortage. Moreover it requires more resources in terms of infrastructure for the teaching institutes and financial resources. This shortage of human resources for health (HRH) is also occurring in health training institutes where it is estimated to be 35% (16). Although another strategy to deal with HRH shortage is to increase recruitment, it has been shown that not all the health care workers that graduate from the training institutions are recruited. For example from 2006 to 2010 35% of medical doctors who finished their internship program were not recruited (60). Moreover of those who are recruited only 63 % report to their duty stations (16). Retention of health workforce is another strategy in place to mitigate HRH shortage. Poor working conditions and lack of incentives have been identified as factors for poor retention (16).

Poor working condition leads to lack of motivation among health care workers. Mbilinyi (53) in his study conducted among CTC workers found out that HCWs were not motivated due to frequent shortage of drugs including drugs for opportunistic infections and laboratory reagents which made them to perform below standard. Moreover health care workers have identified themselves as being the victims as they are blamed for failures of the health system when there is shortage of drugs and other medical supplies when there is shortage (53). HIV services are offered for free in Tanzania, however problems with frequent shortage of drugs leads to loss of motivation and affects how HCW manage their patients. This may lead to occurrence of drug resistance when lack of motivation affects provider patient relationship.

Shortage of HRH results in increased workload therefore compromising the quality of care as shown in Nsimba (40) study. In this study HCWs involved in provision of HIV care acknowledged that increased workload to be affecting the quality of counselling their clients and hence affect PLHIVs adherence to medication (40). In the presence of shortage of HCWs trainings have also been identified to increase workload. Studies have shown that absence from work caused by HCWs attending seminars, meetings, trainings and other administrative duties also contributes to shortage of health care

workers creating even more burden to those who remain behind (17,53). The above problem is due to continuous trainings and administrative seminars or workshops which cause prolonged absence of some HCWs leading increased workload to the few available staff.

Lack of incentives and inadequate supervision has been identified as reasons for lack of motivation (17). Lack of motivation among HCWs may lead to poor patient provider relationship which may make patients stop attending clinic and stop medication. This leads to interruption of treatment and hence risking development of HIV drug resistance. Another study conducted in CTCs in Dar es Salaam showed that health care providers had high levels of motivation despite high client loads in their clinics (61). The results in this study are different from the above findings due to the fact that this study was conducted in CTCs which have strong support system in terms of trainings, supervisions, salary support and also had improved physical infrastructure.

Apart from being a motivating factor support system in terms of supervision is also a form of on job training through which HCWs update their knowledge in managing patients (17). Lack of Supervision and support from senior technical officers is another problem which health care workers involved in provision of HIV services face (53). A study conducted by Manzi (17) also showed lack of effective supervision to health care providers, in this particular study only 13% of the facilities involved in the study received five or more number of supervision visits in a period of six months while 49% of facilities received one or two visits. Health care facilities are supposed to be visited monthly (17). The possible reason for inadequate supervisions may be due to delay in disbursement of funds for the activity.

While supervision is supposed to supportive aiming to improve the quality of care and not to blame this has not always been the case. In a study conducted by Mbilinyi et al health care workers were not satisfied with the quality of supervision received, some received only negative feedback while others did not receive any oral or written feedback (17,53).

Due to shortage of health workers task shifting between health care workers that is, nurses, assistant medical officer (AMO), medical doctor (MD) and clinical officer (CO) is occurring especially in the provision of HIV care and

treatment services although it is not formalised (62). This means that there are no policies or guidelines that oversee the process of task shifting. Despite the ongoing informal task shifting there is still shortage of human resources for provision of HIV services.

3.4.2 Health information system

Health information system is important for the functioning of the HIV program. Monitoring and evaluation as part of the health information system is essential in providing strategic information for planning and decision making (63).The WHO global strategy for prevention and assessment of HIV drug resistance recommends the use of routine health facility data such as inappropriate prescribing practises, treatment interruptions and stock out of ARVs in order to identify early factors which could lead to development of HIV drug resistance. The strategy also proposes population based surveillance of HIV drug resistance to be conducted (28).

Although surveys are component of monitoring and evaluation to date only one early warning indicator survey has been conducted and no single population based surveillance for HIV drug resistance has been conducted in Tanzania (31). The proposed HIV drug resistance surveillance has also not been conducted.

HIV monitoring and evaluation system in Tanzania is facing challenges that hinder the undertaking of the proposed activities that could prevent occurrence of HIV drug resistance. Currently there is shortage of monitoring and evaluation personnel at various levels. For example at regional level and district levels, district AIDS control coordinator (DACC) and regional AIDS control coordinator (RACC) act as monitoring and evaluation focal persons (64). DACC and RACC have other administrative and clinical duties therefore cannot perform well monitoring and evaluation function, they are also not trained for monitoring and evaluation work.

Inadequate monitoring and evaluation supportive supervision is also another challenge which results into poor quality of data at facility level (7). According to WHO the EWIs survey for example uses routine facility level data to identify the determinants of HIV drug resistance. Poor data quality may be misleading and result in delayed action or no action at all with regards to the early warning indicators of HIVDR.

3.4.3 Procurement and Supply of ARVs

In Tanzania the process of procurement and supply for antiretroviral drugs is complex as shown in the medicine supply map of 2007 in annex 2. It involves multilateral donor agencies, bilateral donor agencies private organisation, NGOs and government agent, medical stores department (MSD) (65). From 2009 to 2012 procurement of ARVs and supply chain was under MSD. From the beginning of 2013 procurement of ARVs has been placed under Global Fund (GF) while the role of MSD is storage and distribution (66,67).

Frequent stock out of HIV drugs interrupts treatment for PLHIV thus increasing chances for developing HIV drug resistance (68). HIV care and treatment canters for PLHIV in Tanzania experience stock out of ARVs. Nyogea (69) study which was conducted in a rural district in Tanzania showed 91% of health facilities providing HIV care and treatment services had experienced stock out of ARVs at least once in a year. Urban areas also face shortage of ARVs like rural areas, a study conducted in Dar es Salaam showed 16 out 20 CTCs experienced shortage of drugs in a year which caused 210 patients to be switched to alternative regimens (70).

Coping mechanisms used by facilities to deal with stock out include referring patients to nearby facilities, provision of short term prescriptions and switching patients to alternative treatment if available (70). All these strategies to cope with the stock out create a lot of inconvenience to the patients. For example sending patients to other facilities for drugs may be associated with new cost of transportation. Short term prescriptions increases clinic visits leading to more costs for transportation and loss of earnings due to long time spent at the hospital. Switching patients to alternative treatments may result in patients experiencing new drug side effects.

All the above inconveniences may cause patients to stop visiting the clinics and stop taking ART medication as identified in the TUNAJALI report that one of the causes patients not following up on care was frequent stock out of ARVs (41). Experiencing new side effects may also lead to poor adherence and therefore a risk for development of HIVDR.

The process of procurement of HIV drugs among other things relies on disbursement of funds from the ministry of finance to MoHSW. A midterm review of the health sector strategic plan for pharmaceutical services 2009-2015 revealed delay in disbursement of funds for drug procurement from the Ministry of health and ministry of finance as a factor which delays the process of procurement therefore causing stock out (71). This is caused by lengthy government procedures which delays documents for the grant to be released. Lengthy procedures have also been identified when registration of new drug or re registration of expired drug licence by Tanzania food and drug authority (TFDA). The process of registering a drug may take as long as nine months to register a new drug (67) causing stock out of ARVs.

Prolonged procurement procedures are known to result in stock out of ARVs, MSD midterm strategic plan describes long lead time as one of the causes of stock out of ARVs. This is caused by lengthy legal processes that are associated with shipping and clearing of the drugs at the port of entry (66). This causes further delay in clearing HIV drugs at the port upon arrival from the manufacturer leading to delays in delivering drugs to health facilities.

Changes in HIV management guideline which involves changes in regimens also result in stock out of ARVs. For example the role out of option B+, initiation of ARVs to HIV positive pregnant and breastfeeding women led to the changes in default first line regimen (67). The stock out may have resulted from increased demand for ARVs which was unplanned due to poor communication between NACP and MSD. Moreover the long procedures of registering a new drug to be used as a default first line drug led to stock out of ARVs.

Supply of drugs with short shelf life is another factor which gives rise to stock out of ARVs. Mori and Owenya (70) study revealed that one of the causes of stock out is facilities receiving drugs with short shelf lives and therefore expires early leaving them with no drugs to give their clients. Supply of ARVs with short shelf life may be due to delayed shipping and clearance of drugs at the port of entry. Incomplete supply of the ordered ARVs at facility is also another cause of stock out of medications. Also MSD faces a challenge of not having enough vehicles for distribution of drugs and most times the drugs will be delivered to the DMOs office rather than end facility (66). Delivery of drugs to the end facility then depends on the availability of transport at DMO's office which is also not reliable.

Inaccurate forecasting of demand for ARVs has also been shown to lead to shortage of ARVs at facilities (66). In order to quantify the amount of drugs to order, health care workers have to perform complex paper based calculations which require data from stock ledgers and dispensing registers. Health care providers face difficulties in doing these calculations therefore underestimation of the quantity required leads to stock out of ARVs (66)(70). Correct estimation of the quantity of drugs needed depends on correct documentation in the monitoring and evaluation tools and in the absence of proper documentation there is a chance of incorrect estimation of drugs required.

Secondary and tertiary level facilities send their order of ARVs directly to MSD while health centres and dispensaries place their orders through the office of District Medical Officer (DMO) (70). Delay in placing orders to MSD also determines the occurrence of stock out of antiretroviral drugs due to delayed processing of their order and limited means of transportation of the facilities. Nyogea (69) study describes one of the causes for delay in submitting orders to MSD being lack of responsible person for ordering drugs at facility level, this occurred in 36% of the facilities involved in the study. This study was conducted in rural Tanzania where some of the primary care facilities have shortage of HCWs including pharmaceutical technicians. The absence of such health cadre necessitates appointment of responsible person for filling the order form and sends them to MSD or DMO's office.

3.4.4 Health financing

In 2013, the total government expenditure on health as percentage of GDP was estimated to be 7%. Financing of HIV prevention, care, treatment and supportive services is largely dependent on donor with more than 95% of HIV funding originating from donors. Private health sector contributes to HIV funding by 2% while the national health insurance fund contributes 1%. There are little resources available for HIV responses which results in underfunding of some HIV responses components such as monitoring and evaluation, surveillance and research section which are important for prevention of HIVDR (9). Monitoring and evaluation, surveillance and research are important in prevention of HIVDR.

Health insurance is important in order to prevent catastrophic health expenditure due to out of pocket payment. Out of pocket (OOP) expenditure

has also been shown to be among the factors that cause drop out of patients from HIV care. In Tanzania the number of people covered by the national health insurance or community health fund is almost 6% (10). The low coverage by the national health insurance and community health fund leads to high OOP expenditure for PLHIV when they have to pay additional costs for laboratory tests and buy opportunistic drugs. In 2009/10 overall OOP expenditure as percentage of total health expenditure (THE) was 32%. OOP as percentage of THE for HIV/AIDS services was 17% (72) despite HIV services being offered for free. Inability to pay for additional costs of treatment was identified as one of the causes for drop out in HIV care (38) hence predisposing factor for development of HIVDR for patients on ART.

3.4.5 Governance

Overseeing the HIV responses is the National AIDS Control Program (NACP) which is under the MoHSW. NACP is responsible for coordinating HIV care and treatment services, surveillance of HIV infection and STIs, PMTCT, home based care(HBC), HIV counselling and testing, voluntary medical male circumcision and monitoring and evaluation of the responses (9,64). Tanzania commission for AIDS under prime minister's office coordinates multi-sectoral responses to HIV (64)

The Tanzanian HIV policy of 2001 has stated that importation, manufacture and use of any modern or traditional medicine for HIV shall be approved by the government. Furthermore it has clearly prohibited claims for cure of HIV by faith or traditional healers unless approved by the government (14).

Despite the above policies on HIV medication, claims for HIV cure by some religious and traditional healers still persist. The NMSF III acknowledges that one of the challenges faced is increasing number of alternative treatments for HIV (9). There is a gap in implementation of the policy concerning the presence of alternative treatments. This may be due to ineffective coordination by NACP with various bodies involved in assessing safety, effectiveness and quality of drugs such as national institute for medical research (NIMR) and Tanzania food and drug authority.

CHAPTER 4: REVIEW OF THE INTERVENTIONS THAT ADDRESS DETERMINANTS OF HIV DRUG RESISTANCE IN SUB SAHARAN AFRICA

The outlined determinants of HIVDR in chapter three in Tanzania cut across many similar settings in Sub Saharan Africa. Many sub Saharan countries are struggling with similar challenges in HIV care and treatment service delivery and a variety of interventions have been tested to address these issues. This chapter looks at the interventions that have tried to address determinants of HIV drug resistance. The selection criteria for the interventions based on sustainability, patient outcome, cost effectiveness, workload of HCWs and social acceptability of the intervention.

4.1 Home based approach to ART program in Uganda

Home based ART program is as successful as facility based program in Uganda. This is evidenced by the results of the cluster randomized trial that was set up to compare the two models of delivering HIV care. Participants were randomized into either facility based or home based after ART was initiated at the facility but had hospital visits scheduled every 6 months. Those under home based program were under the care of trained community health workers (CHWs) who apart from delivering drugs to patients at home they also did adherence counselling, check for drug side effects, screen for opportunistic infections and refer sick patients to the clinics for medical care (73,74).

Results of the trial revealed patient outcome in terms of increase in CD4 count and virological suppression was similar in both home based and facility based arms of the trial. Mortality rate and virological failure was not different in the study groups (73,75). Complete ART adherence was reported in 94% of the visits by the home based group while in the facility based group complete adherence was reported in 91% of the visits (75). Home based approach was more effective in reducing the indirect costs that patient incur in terms of transport costs. It was shown in the trial that patient in the facility arm used 15-20% of their monthly earnings for transport to the clinics (73,75)

The main limitation of the home base ART program was withdrawal of some clients from the services due to increased stigma from the community (75).

Another similar intervention in Uganda which was conducted to compare the effectiveness of the community based against facility based ART program

revealed no difference between the two models of care in terms of treatment outcomes of patients. CD4 count increase and mortality was similar in both groups. A difference in outcome was seen whereby the community group patients were more likely to achieve viral suppression compared to facility group (76).

The main limitation of this intervention was increased cost per patient in both community and intervention group which could not be sustained by the primary health care facility (76)

4.2 Community based ART in Democratic Republic of Congo (DRC) and Mozambique

In order to increase ART coverage in Congo where the costs of obtaining the services were too high for patients to afford, ART refill centres were set up in Kinshasa to bring drugs close to patients without additional costs. The centres were managed by trained PLHIV who were able to provide ART refills, adherence support and check on basic health indicators and refer sick patients. Patients attended clinic annually for CD4 count test and medical consultation otherwise they obtained drugs for 3 months period. A system was set in place to trace those who missed appointments. As a result client retention rates in refill centres were almost similar to retention rates when patients were attending health facility. It also resulted in lower costs of treatment per patient and reduced indirect costs for the patient (77).

The limitation of this intervention is that it improved retention in the first year of the program but after the second year there was a reduction in retention by 7.6 %(77).

Another community based ART groups were established in Tete province in Mozambique following a high rate of loss to follow up as a result of high transport costs, long waiting hours and perceived stigma that PLHIV experienced. Community ART groups consisted of PLHIV who were stable clinically for minimum of 6 moths whose CD4 count was above 200. Groups were formulated in such a way that each member had contact with health facility at least once in every six months, the roles of group members included distribution of ART to group members monthly, provide adherence support and treatment outcome monitoring, establishment of social support network. The community ART groups resulted in improved adherence to medication, 92 % of the members had good adherence. It was also reported

that there was a fourfold reduction of workload among health care providers (78).

Limitation was lack of continuous support for the lay workers making sustainability of the intervention difficult (77).

4.3 Six Month Appointment (SMA) systems in Malawi

In efforts to decongest HIV clinics, Malawi set up a six month appointment system was set up in Chiradzulu district. The aim of this appointment system was to reduce the number of times that a patient visits the clinic when they are already doing well on treatment. Therefore adult patients on ART who were clinically stable attended clinic every 6 months instead of one to two months schedules. Drug refills were conducted at the health facilities by trained health surveillance assistants who refer patients to clinicians when they identify a problem. This type of appointment system succeeded in improving retention of PLHIV in care. Retention of clients 36 months after ART initiation was found to be higher in SMA group (94.6%) compared to patients who were not enrolled in SMA (83%) (77).

Limitation of this intervention is that treatment interruptions were common and it was not shown how they affected adherence although retention in care which was reported was high. Also supply chain weaknesses were limiting factors which led to frequent stock outs of ARVs (77).

4.4 Task shifting in Malawi, Kenya, Uganda and DRC

Malawi is one of the countries with severe shortage of human resources for health. In 2007 doctor to population ratio was 1 to 100,000 population while that of all cadres of nurses was 26 nurses per 100,000 population (79). The critical shortage of human resources for health in Malawi necessitated task shifting, that is delegating certain medical responsibilities to a less specialised cadre who undergo special training for the specific duty that will be assigned. For example health surveillance assistants were trained to conduct HIV testing and counselling services and provide ART as refills to HIV clients (77,79).

In other parts of SSA like DRC, Kenya, Uganda and Malawi part of HIV care services have also been shifted to trained community health workers or PLHIV. In DRC for instance PLHIV were trained to provide ART, check for basic health indicators and conduct HIV testing and counselling at established ART refilling centres (77). Similar type of task shifting was done

in Kenya whereby PLHIV were trained as clinical care coordinators for home based ART program where they delivered ART, monitor drug adherence and be able to identify sick clients and refer them for further care (73). In Uganda community health workers were trained to deliver HIV services at home after undergoing training (74).

Limitation of task shifting identified is unsustained remuneration for the lay cadre and lack of continuous supportive supervision (77).

5.5 Adherence clubs in South Africa

Adherence clubs were set up in South Africa to overcome of increased high rates of loss to follow up. The aim of forming these clubs was to reduce overcrowding at HIV clinics and set up adherence support mechanisms for clients who were on ART and were doing well. Adherence clubs were facility based and were led by peer educators who were trained PLHIV, meetings were conducted every two months. During club meetings patients were assessed for general health problems and their weight was checked, they also obtained their drug refills. Those with health problems were referred to the nurse, those with no symptoms see a nurse twice a year for tests and check up. Adherence clubs were effective in reducing loss to follow up by 57% and virological rebound was decreased by 67% reflecting improved adherence to ART. Adherence club model was also more cost effective as compared to facility model, the cost of treating one patient per year was US$ 58 in adherence club model while in the health facility it was US$ 109 (77).

Limitation of the intervention was the requirement for dispensing practices whereby a pharmacist is required which necessitated pre packaging of ART (77).

5.6 Pooled Procurement and Regional Distribution Centres (RDC)

These are mechanisms developed by the supply chain management system (SCMS) a PEPFAR funded project in order to reduce the problem of stock out of ARVs in PEPFAR supported countries. Pooled procurement mechanism (PPM) involves combining procurement of common ARVs across neighbouring countries which reduces shipping time and cost of drugs and shipping. Regional distribution centres have reduced lead time leading to 90% of the orders to be fulfilled on time as compared to 50%-70% order fulfilment without RDC (80).

The main limitation of the interventions is that it focuses on procurement part only and doesn't consider challenges that exist in delivering drugs to the health facilities, the supply side (80). Table 2 below summarizes the interventions.

Table 2: Summary of the interventions that address HIVDR determinants in SSA

Intervention	Source	Outcome	Limitations
Home based ART intervention in Jinja-Uganda	Decroo (73) Amuron (74) Jaffar (75)	Did not result in increased mortality or increased virological failure	Withdrawal of clients form the services due to increased stigma
Community based intervention in Kabarole district-Uganda	Kipp (76)	Reduced indirect cost to the patient	Increased cost to the health facility due home care visits by volunteers
Community based ART Refill Centres in Kinshasa- Democratic republic of Congo (DRC)	Bemelmans (77)	Increased retention in the first year of the program. Lowered indirect to the patient	Retention was high in the first year of the program but after 2 years there was a 7.6% reduction in retention.
Community ART groups in Tete Province- Mozambique	Decroo (78) Bemelmans (77)	Improved adherence Reduced health worker's workload four fold	Lack of sustained support for lay workers
Six month appointment system in Chiradzulu district-Malawi	Bemelmans (77)	Improved retention	Frequent stock out of SRVs leading to treatment interruptions
Task shifting in Malawi, Kenya, Uganda and DRC	Bemelmans (79) Bemelmans (77) Decroo (73) Amuron (74)	Reduced healthcare workload Improved retention	Unsustained remuneration for the lay cadre Lack of continuous supportive supervision.
Adherence clubs in South Africa	Bemelmans (77)	Reduced LTF Reduced viral load Reduced cost of care per patient	Required health care personnel to prescribe ART - Pharmacist
Pooled procurement and Regional distribution centres of ARVs-PEPFAR supported developing countries	Larson (80)	Reduced production and shipping delays Reduced costs of ARVs and cost of shipping ARVs	Does not consider challenges in the supply of ARVs to the health facilities.

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

This chapter discusses the most important findings of the study taking into account the social cultural, economic and health systems determinants of HIV drug resistance in Tanzania and the evidence based interventions that have been identified. From the discussion the conclusion will be drawn and recommendations will be made based on the discussion.

5.1 Discussion

The study findings show that development of HIVDR in Tanzania is determined by the factors that lead to treatment interruption for PLHIV which results from the underlying socio-cultural, economic and health systems factors.

Adherence to ART medication has been shown to determine the occurrence of HIVDR. Good adherence to ART medication is highly linked to correct information and good understanding of the ART medication that patients have. Despite being counselled before starting treatment and the continuous provision of health education at health facilities, misinformation about HIV treatment still exists. Such information about ART treatment has led to dropout of patients from HIV care. Moreover some traditional and religious beliefs and practices tend to provide alternatives for HIV treatment therefore influencing discontinuation of HIV treatment. Poor implementation of the HIV policy with regards to alternative treatments is also factor facilitating continuous claims of existences of HIV cure.

Correct information about HIV, ART and side effects of drugs dispels the surrounding beliefs and misinformation about HIV treatment therefore leading to maintenance of good drug adherence levels. The need for health education among PLHIV is high as identified in TUNAJALI report as a priority issue to be addressed by health facilities (41). Establishment of adherence clubs in South Africa were successful in improving retention and adherence. Establishment of adherence clubs may work well in Tanzania and be used as places where correct information about HIV and ART is passed on. These could also act as ART refill visits however such intervention will require close supervision and provision of incentives to club leaders.

Stigma surrounding HIV has negative effect on PLHIV follow up on HIV services. PLHIV decisions to continue with HIV services depend on how stigma affects them. Stigma as shown in the study findings occurs at various level from community level, health facility level to even family level

necessitating the importance of targeting all these levels with stigma reduction interventions. Interventions that are community based have been shown to be successful if carefully planned. In Uganda the two community based ART interventions both resulted in good clinical outcome for the patients however one resulted in some clients withdrawing from the program due to stigma. In Tanzania, establishment of community based interventions would be effective as it will bring services close to the community. However such intervention would require community involvement from early stages so as to overcome stigma and ensuring effective use of the services by PLHIV.

Provision of quality health services is an important motivating factor that attracts PLHIV to stay on treatment. With the expanding HIV programs the quality of care at HIV clinics is reduced due to high client load affecting efficiency of health care providers. Frequent clinic visits and long waiting hours are associated with high indirect cost to the patient. According to Stanifer (44) PLHIV face challenges which include long waiting time, high cost and perceived poor quality of the care that they receive. Increasing appointment time to six month between visits was used in Malawi and resulted into reduced client load at the clinics and reduced workload for health care workers. Tanzania is also facing a problem of overcrowding at CTCs. Implementation of such intervention will address the high client loads caused by unnecessary visits that PLHIV who are doing well on treatment make to CTCs. This intervention however requires a continuous supply of ARVs, frequent shortage of ARVs was a limitation of this intervention in Malawi. Like Malawi, Tanzania also has challenges with regards to procurement and supply of ARVs leading to frequent stock out.

Maintaining a continuous flow of ARVs without interruptions is a challenging process in Tanzania. As identified in the study results, frequent stock out of ARVs is one of the determinants of development of HIVDR. Currently the role of procuring ARVs is under the global fund while MSD deals with supply of ART to the end facilities. Although the procurement of ARVs uses the pooled procurement mechanism (PPM) there is stock out of ARVs probably due to lengthy government procedures. The pooled procurement mechanism has been shown to work well in Uganda. There is a need to look at the procurement processes on the side of the government so as to minimize unnecessary delays. PPM deals with procurement of ARVs therefore deals with reducing stock out at central level but there is still challenge in

supplying drugs to the facility. This might lead to accumulation of ARVs at central level and stock out at facilities. Adapting this intervention will need development of a supply intervention that will ensure on time delivery of ARVs to zones and facilities.

Shortage of human resources for health has been made severe with expansion of HIV care and treatment services. As the number of people enrolled in care increase the health care workforce is increasingly becoming overburdened. The shortage of all cadres of healthcare workforce is due to low production, low recruitment of graduate health professionals and poor retention. To overcome shortage task shifting has been a practice although it is not officially approved (62). Despite the ongoing task shifting among HCWs there is still shortage. In Uganda, Kenya, Malawi and DRC community health workers and PLHIV were trained to provide HIV services under the supervision of HCWs. Task shifting succeeded in reducing workload and improving client retention. This intervention could be implemented especially with the already existing HBC providers or community health workers. But this requires training and frequent supervision to ensure quality of care and good outcome of patients. Sustained remuneration for the community health workers or home based care providers is also required.

5.1.1 Study limitation
The conceptual framework was useful in analysing the determinants of HIVDR in Tanzania however at some point it was difficult to separate some factors like access and distance therefore they were all considered as access.

The literature search was conducted in English language which led to missing out on some literature published in French language. Also the literature search confined to sub Saharan Africa therefore missing out some useful information which could be obtained from other low-middle income countries. The interventions selected had been evaluated and were successfully implemented however some of them did have cost analysis therefore it was hard to know their cost effectiveness.

5.2 Conclusion
Provision of ART has greatly reduced morbidity and mortality associated with HIV. To date as more efforts are directed towards scale up of ART services, it is also important to ensure that occurrence of HIVDR is minimized for good

outcome of the patients. Since the provision of ART in Tanzania follows a public health approach, HIVDR will pose a threat to the health system in terms of patient outcome and increase health care cost for new medication due to reduced efficacy of the first line regimens.

Individual, socio-cultural, health delivery and structural factors have been identified to influence occurrence of HIV drug resistance in Tanzania. Lack of clear information about HIV and ART use coupled with certain treatment beliefs affect adherence. Stigma and some religious and traditional practices on the other hand have been shown to negatively influence health seeking behaviour of PLHIV leading to treatment interruption and therefore development of HIVDR.

How the services are delivered also has effect on patients' ability to continue treatment or stop. Services need to be easily accessible, affordable and provided by skilled HCWs. Long waiting hours due to large number of client load may lead to non retention in care. HRH, health information system, procurement and supply of ARVs, governance and health financing have also been shown to be important determinants of HIVDR.

Several interventions have been identified to address the determinants of HIVDR in SSA. The interventions have taken several approaches which include hospital based and community based approaches. The interventions resulted in improving adherence, clinical outcome and retention. They also resulted in reduced indirect cost for the patients and reduced workload for HCWs through task shifting. PPM has also proved to be useful in other set up in East Africa but the results have not been shown in Tanzania due to lengthy government processes. There were also several limitations which need to be considered when adapting such interventions.

The success of HIVDR prevention requires clearly set interventions based on an in depth understanding of the determinants of HIVDR. The above mentioned findings indicate how determinants occurring at different levels can be linked and influence each other. Current efforts to address HIVDR in Tanzania are minimal although some of these factors are already identified in the HRH strategic plan and NMSF III. NACP need work closely with other departments such to address these determinants.

5.3 Recommendations

In order to reduce occurrence of HIVDR in Tanzania it is important to address the most important determinants of HIVDR. Addressing these determinants will help to improve the quality of care, retain more clients in HIV care, and reduce health care worker's burden and stock out of ARVs. The following recommendations also have considered the review of the interventions that have tried to address these determinants in the rest of SSA. The recommendations will be put in Policy, Intervention and Research groups.

5.3.1 Policy

- The MoHSW should develop policy on task shifting among HCWs in order to make it formal with clear duties and responsibilities defined as it has been conducted without any formal rules or regulations. Task shifting should be careful planned in such a way that it does not shift the burden of work from one health care cadre to the other.
- The MoHSW should also develop policy on task shifting which will allow lay persons such as community health workers/HBC to be trained and perform duties which do not require clinical expertise. The policy should also recognize them as part of health workforce with proper remuneration and their roles and responsibilities should be clearly defined.

5.3.2 Interventions

- The National AIDS control program should change the appointment system of CTCs so as to reduce the number of unnecessary visits to patients who are already doing well on treatment. This appointment system should be in such way that the number patients visiting the clinic should not overburden the health worker and at the same time the health of the patient should not be compromised due to long clinic intervals. There should be clearly set criteria to identify those who need frequent visits and those who need less frequent visits.

- As long term plan, NACP should set up ART refilling centres in areas that are far from the existing CTCs in order to bring the services close to the community. The refill centres should be operated by trained CHWs and clear linkage to the health facilities should be made.

- Ministry of health should set a budget for transport of ARVs for facilities which don't receive ARVs directly from MSD zone offices so as to reduce delays in receiving orders and prevent stock out.

5.3.2 Research
- NACP should conduct feasibility study in order to find out if the adaptation of community based ART programs in Tanzania settings give the available resources is feasible.
- NACP should ensure quarterly analysis of the early warning indicators at facility and national level for prompt action when there is need since these indicators are part of routinely collected data at facility level.

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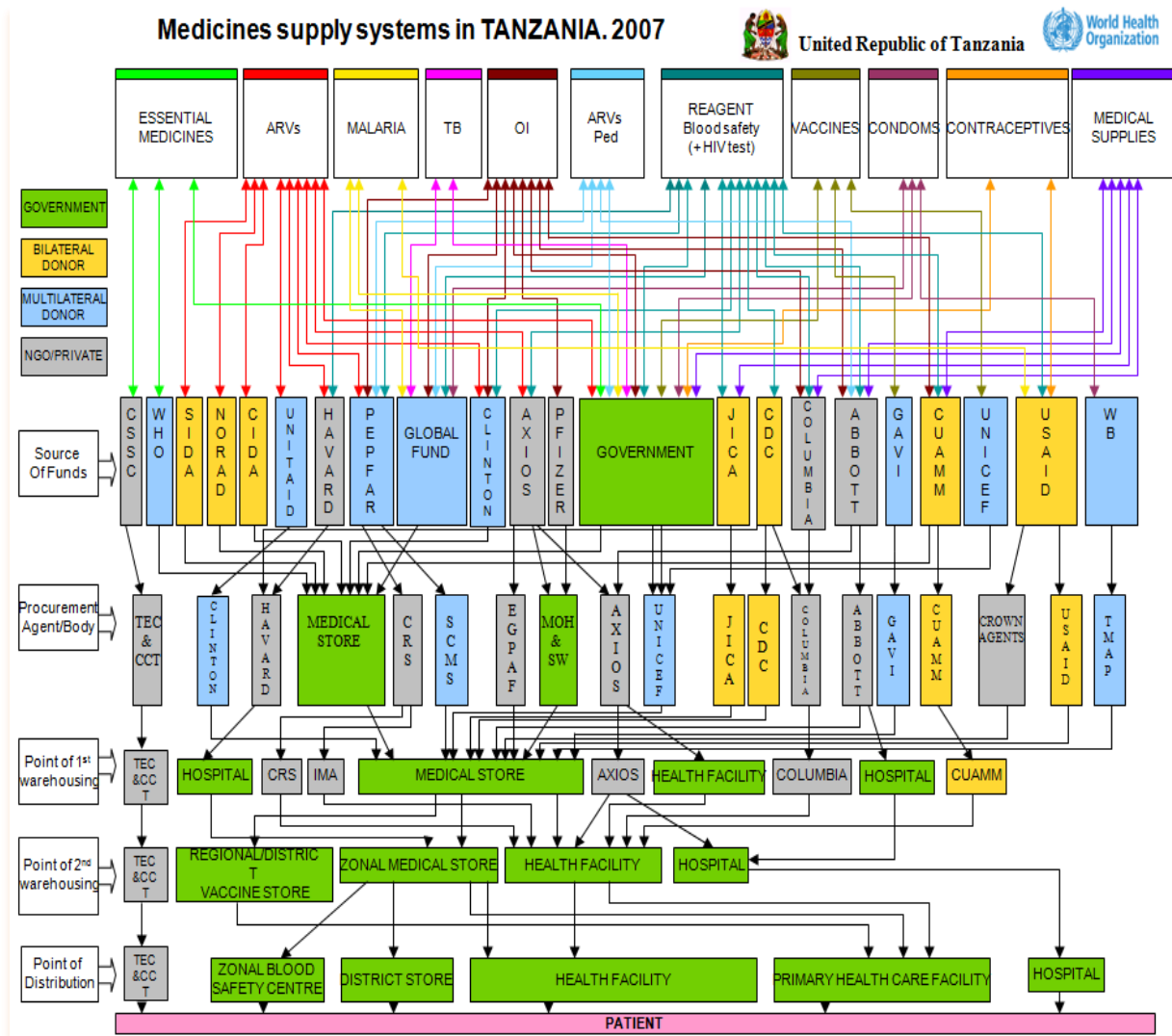81. NBS, OCGS. Population Distribution by Age and Sex. Dar es Salaam: NBS; 2013.

ANNEXES

Annex 1: Map of Tanzania showing administrative boundaries and international borders

Source: National Bureau of Statistics (81)

Annex 2: Medicine procurement and supply systems in Tanzania

Source: Mapping of the medicines procurement and supply management system in Tanzania (65)