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The effect of drugs stock out on discontinuity of antiretroviral therapy and type 2 diabetes mellitus treatment at the Coast Provincial General Hospital in Kenya.

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The effect of drugs stock out on discontinuity of antiretroviral therapy and type 2 diabetes mellitus treatment at the Coast Provincial General Hospital in Kenya.

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Declaration:

The thesis "**the effect of drugs stock out on discontinuity of antiretroviral therapy and type 2 diabetes mellitus treatment at the Coast Provincial General Hospital in Kenya"** is my own work.

Where other peoples' work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with the departmental requirements.

Signed_____Date 13/08/2012

Benard Nyaribo Miregwa

Kenya

48th International Course in Health Development (ICHD/MPH)

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ARVs	Antiretroviral drugs
AZT	Zidovudine
CD4	Cluster of Differentiation 4
CIs	Confidence Intervals
CNS	Central Nervous System
CPGH	Coast Provincial General Hospital
D4T	Stavudine
Disc	Discontinuation
EFV	Efavirenz
ENT	Ear Nose and Throat
FBOs	Faith Based Organizations
GDP	Gross Domestic Product
GHHE	Government annual expenditure on health
GNI	Gross National Income
GNP	Gross National Product
HbA1c	Glycated haemoglobin test

HIV	Human Immunodeficiency Virus
ICHD	International Course for Health Development
IR	Incidence Rate
IQR	Interquartile Range
KEMSA	Kenya Medical Supply Agency
KIT	Royal Tropical Institute
LMICs	Low and Middle Income Countries
MEDS	Missions for Essential Drug Supplies
MoMS	Ministry of Medical Services
MoPHS	Ministry of Public Health and Sanitation
MPH	Master in Public Health
NGOs	Non-Governmental Organizations
No.	Number
NVP	Nevirapine
PEPFAR	President's Emergency Plan for AIDS Relief
RR	Relative risk
SD	Standard Deviation
T_2DM	Diabetes mellitus type 2
TDF	Tenofovir
THE	Total Health Expenditure

TPE	Total pharmaceutical expenditure
UNAIDS	Joint United Nations Program for HIV/AIDS
USA	United States of America
WHO	World Health Organization

Abstract

Background: Drugs stock out may cause unwanted treatment interruption. This study will quantify the problem of discontinuities of antiretroviral therapy (ART) and type 2 diabetes mellitus (T_2DM) treatment due to drug stock outs in Kenya.

Methods: A retrospective cohort study of subjects starting ART and T_2DM treatment at the Coast Provincial General hospital between 6th September, 2010 and 6th January, 2012 was carried out. Follow up ended on 6th June, 2012. The primary outcome was first discontinuation of treatment (regimen switch, temporary or complete discontinuation). Incidence rates (IR) and 95% confidence intervals (CIs) were estimated and relative risks (RRs) were calculated to compare the two cohorts. Kaplan-Meier survival plots were created to depict time until discontinuation.

Findings: Overall, 57% of the167 T_2DM patients and 48% of the342 ART patients experienced at least one treatment discontinuity. Overall rates of discontinuation were 2.66 (95%CI 2.24-3.74) and 1.65 (95%CI 1.41-1.92) per 1000 patient-days for T_2DM and ART cohorts respectively, yielding a RR of 1.61 (95%CI 1.25-2.08).The RR of discontinuity due to drug stock out for T_2DM vs. ART was 8.92 (95% CI; 4.33-19.9).The median time to discontinue treatment due to drug stock outs was similar for both cohorts: 72 days for T_2DM (Interquartile range (IQR): 42-161) and 86 days (IQR: 32-177) for ART (p= 0.803).

Conclusion: Patients on T_2DM treatment were at a higher risk of discontinuation than those on ART. Drug stocks affected more patients on T_2DM treatment than on ART. Policy interventions are needed to avoid unnecessary treatment interruptions due to drug stock outs.

Keywords: Antiretroviral therapy, Diabetes type 2 treatment, treatment discontinuity, drugs stock out, Kenya.

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1. INTRODUCTION

1.1. Researchers Background

Having worked at the Coast provincial General Hospital (CPGH) from 2008-2009, my mission was inspired to contribute to improved treatment outcomes to the public and at the individual level. Moreover, I have also worked as the head of the Comprehensive Care and Research Centre (CCRC), collaborating closely with the Kenya Medical Research Institute at Kilifi. My professional career has been inspired by clinical puzzles in daily patient care and in research. While at Mombasa, I served as the head of the medicines therapeutic committee, besides, as in charge of medical supplies and commodities at the district, where CPGH was covered. One of my main challenges at that time was interrupted supplies of essential medicines, where chronic disease treatment shortages were augmented, thus affecting regular patient care and could yield serious clinical outcomes at the patient level. Currently, I work at the Ministry of Medical Services as health advisor and member of the pharmacovigelance team, and advisor to the International Centre for Health, Legal, Research and Governance foundation, based in Kenya. Drawing from my experience, I was motivated and inspired to conduct this research to understand the extent to which drug stock outs contribute to switches, short or long treatment interruptions of HIV and T_2DM therapies in Kenya, in order to support decision/policymaking to improve patient outcomes.

1.2. Introduction to Study topic

Chronic disease burden is exponentially increasing globally. Approximately 80 percent of the burden rests upon low and middle income countries (LMICs) (Quick et al., 2002). Human Immunodeficiency Virus (HIV) causes

Acquired Immune-Deficiency Syndrome (AIDS) and together with diabetes especially subtype 2 (T_2 DM) contribute a bulk share of chronic disease burden in Kenya. The prevalence of T_2 DM in rural areas is 8.6% and that of urban areas, 13.2%. Whereas, that of HIV/AIDS is 7.1% (Christensen et al., 2009; KAIS, 2007). Estimates of 100,000 adult new HIV infections are reported annually (NASCOP, 2012). For treatment success to be realized in diabetes and HIV/AIDS, continuity on treatments is essential. A number of factors have been described to contribute to treatment discontinuity. These factors include drug stock outs, high costs of treatment, adverse events and individual related factors such as pregnancy among others. In Kenya public health facilities have reported drug stock outs in many treatments. Medicines for chronic illness like diabetes were less available as compared to medicines for "acute" and infectious diseases including HIV/AIDS (Cameron, 2011).

Drug stock outs cause unplanned treatment interruptions. Further, repeated drug stock outs interrupt treatment which causes treatment discontinuity, and if not controlled could lead to drug resistance and/or treatment failure. Furthermore, treatment interruptions affect treatment efficacy and could compromise treatment effectiveness. This could cause first-line treatment to be switched, meaning other drugs belonging to the next step in treatment, for instance to those classified as second line, to guarantee efficacy. Moreover increased complications, hospitalizations and adverse events could follow, which possibly could lead to death. Thus regular and uninterrupted supplies of antiretroviral drugs (ARVs) and oral anti- diabetic drugs will considerably decrease treatment discontinuity, and therefore contribute to a decrease of morbidity and number of deaths related to HIV/AIDS and T_2 DM treatment discontinuation.

The study quantifies the problem of treatment discontinuity of HIV/AIDS and T_2DM and assesses reasons for switched regimens, temporary and complete

treatment discontinuation with a focus on the contribution of drug stock outs, at the Coast Provincial General Hospital in Kenya. Further the study suggests evidence based strategies from literature search to prevent drug stock outs and equally enhance continuity on treatment

2. BACKGROUND INFORMATION OF KENYA

2.1 Geography

Kenya is a low income nation as per the World Bank classification (World Bank, 2010). It is situated in East Africa within Sub Saharan Africa bordering Ethiopia, Somalia, Indian Ocean, Sudan, Uganda and Tanzania.

2.2 Demography and socioeconomic situation

Demographically it is home to circa 40 million citizens, with a median age of nearly 19 years. Over 40% of the total population is aged between 0-14 years, whereas, 55% ranges between 15-64 and the rest above 65 years, with the yearly growth rate of the population at 2.6% (World Bank, 2008). These statistics indicate that Kenya is dominated by a young population, with an average mortality of about 50 years (KNBS, 2010).

The average life expectancy at birth is 53 years for women, and 55 years for men. The infant and children under the age of five (5) is 52/1,000 live births and 74/1000 live births respectively. Whereas the maternal mortality rate is reported to be 488/100,000 live births (WHO, 2007; KDHS, 2009).

The gross national income per capita (GNI) is US $1,580 and the annual gross domestic product (GDP) growth rate is 3.6 percent. Total health expenditure (THE) in 2008 was KES 107,498 million (Kenya shillings) (US $ 1,502 million), which is 4.5% of gross domestic product (GDP). Yearly total

health expenditure per capita in is US $ 40 (KES 2,864). This is significantly below the 15% Abuja target (WHO, 2009; KIPPRA, 2009; KDHS, 2009).

2.3 Healthcare system and Administration

Kenyan healthcare system embodies a vision of *"efficient and high quality healthcare system that is accessible, equitable and affordable for every Kenyan"* through the governance of ministries of health namely the ministry of medical services (MOMS) and the ministry of public health and sanitation (MoPHS) coordinate the organized six (6) level tiered health system. This is leveraged through the eight provinces which have been replaced by 8 regions which are divided into 47 counties as per the new constitution, and then branched to many wards administratively. Public health facilities including hospitals in all these levels from level one are coordinated by community health workers to level six representing the national hospitals with specialty of services, all under the ministries of health governance.

According to the MoPHS (2009) summary report Kenya has a total of 6243 health facilities, of which, 2913 (46.7%) are directly owned and governed by MoPHS and MOMS , whereas 810 of the facilities (13%) are owned by Faith based organizations (FBOs), 99 (1.6%) by local government, 212 (3.4%) parastatals and other public institutions like the armed forces. Private institutions own 2079 facilities (33.3%), whereas, non-governmental organizations (NGOs) own 101 centres (1.6%) and 29 facilities are owned by specified owners (MoPHS, 2009).

2.4 Financing healthcare

The ministry of finance through its treasury department allocates funds to the MOMs and MoPHS, which then determine how the budget should be spent in the health sector. A parallel source of funding comes from donors, though these funds are project oriented thus decreasing the flexibility of the

allocation of these funds in other programmes. The ministry of medical services is responsible in providing most of the medicines for the public sector and HIV treatment for private and public institutions. HIV, Malaria and Tuberculosis treatments are funded by the government and many other donors and thus made free at point of delivery in public health facilities, though certain services are paid for in some hospitals. Contrastingly, treatments of other diseases such as diabetes are funded solely by the government, and patients make copayments to receive these treatments at the health facilities.

The yearly government expenditure on healthcare (GGHE) contributes to 37.4% of total expenditure on health, which is 7.1% of the total government budget. The remaining 62.6% is covered by the private health expenditure (WHO, 2008).

Total expenditure in pharmaceuticals (TPE) is about US $ 372 million, which is KES 714 (US $ 99) pharmaceutical expenditure per capita. TPE constitutes 1.65% of the GDP and accounts to 36.6 percent of the total health expenditure. (NHIF, 2010)

2.5 Procurement and distribution of medicines

The procurement and distribution of drugs in public institutions is mainly done by the Kenya Medical Supplies Agency (KEMSA). This is a semi-autonomous agency, which is government-private partnership agency. On the other hand, Mission of Essential Drugs (MEDS) supplies mostly FBOs and NGOs. MEDS is contracted by President's emergency plan for AIDS relief (PEPFAR) to procure and supply PEPFAR funded ART in private and public health facilities in Kenya. KEMSA covers 4,100 facilities all over the country. From its main central store in Nairobi distributes to 8 satellite stores situated

in all regions in Kenya, where hospitals from different levels receive their orders according to their needs (pull system). Level 4 facilities which are mostly district hospitals, act as central sites where satellite facilities including level 3- health cent
res and level 2- dispensaries (acting as the first contact point in the formal health system) make their orders. Similarly utilization reports follow the same order upwards through level 4 and level 5 facilities which are mostly district hospitals and provincial hospitals serving as regional referral facilities. Figure 1 below provides an overview of the distribution system.

2.6 Copayments and User fees

At the point of delivery, patients make copayments/ user fees for health consultations and drugs. Level 2 and 1 primary care facilities, patients remit a fee of US $0.14 and 0.28 respectively, whereas in other levels there are no guidelines for copayments and so fees is fixed by the health facility. The amount collected is used to supplement facility running costs. Medicines for chronic diseases except HIV/AIDS are copayed for, and usually their costs are higher than other medicines for acute illnesses. Most of the acute illnesses medicines are manufactured locally and mostly are generics.

The National Health Insurance Fund (NHIF) exists though it does not cover medicines costs, though it provides inpatient hospital bed fees. On the other hand, private health insurance schemes may cover medicines exists, but not linked to the essential medicines list (WHO/HAI, 2004; NHIF, 2009).

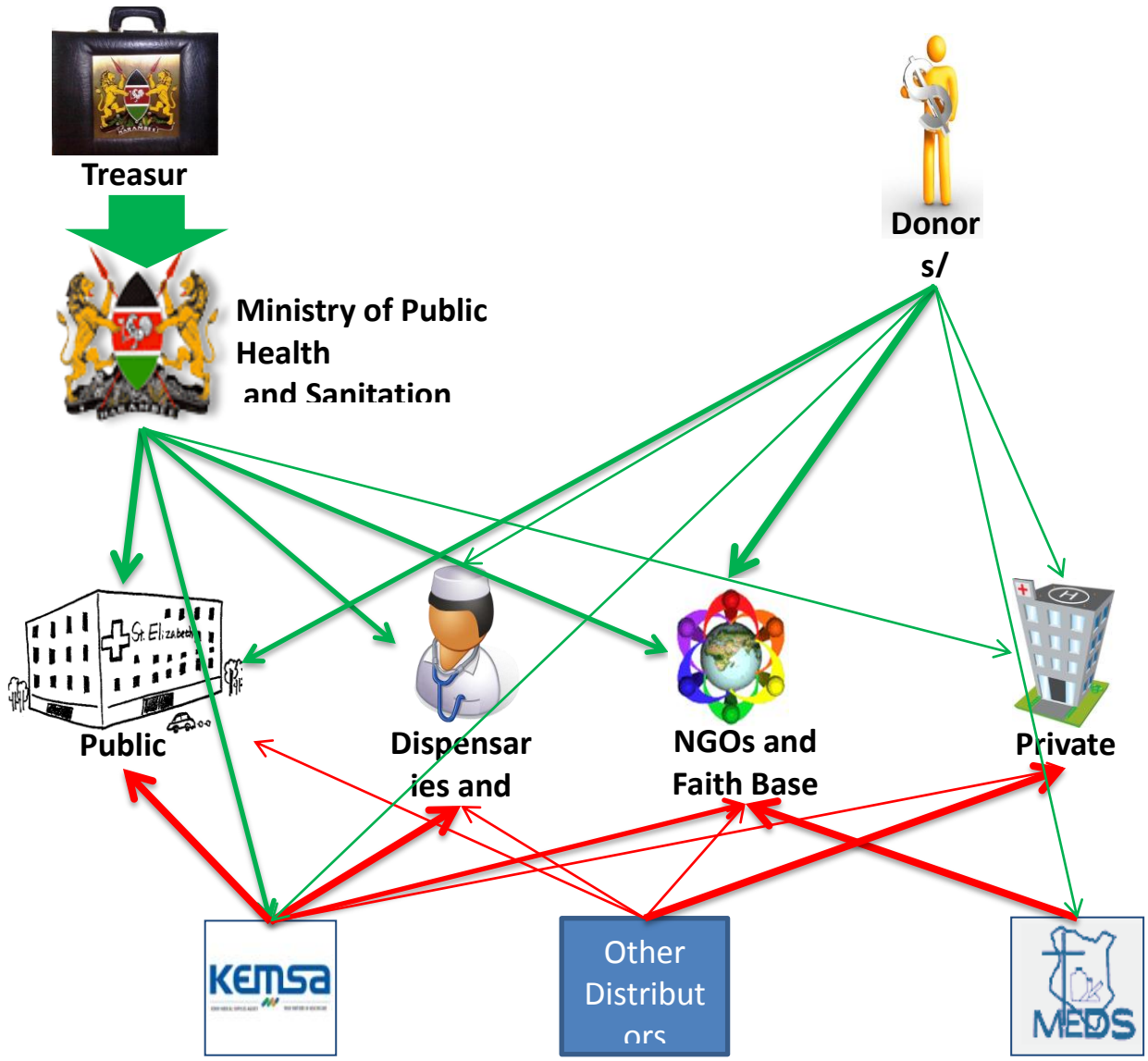

Figure 1 Healthcare Overview in Kenya

3. PROBLEM STATEMENT AND JUSTIFICATION

3.1. Problem statement

Globally about 35 million deaths, accounting to about 60 percent of all deaths each year, are attributed to chronic diseases and approximately 80% of all these deaths occur in low and middle income countries (LMICs) (Quick et al., 2002). The burden on chronic disease has exacerbated as diabetes and HIV and AIDS hugely contribute to the pool. Worldwide, 3.2 million deaths are attributed to diabetes and 3.1 million deaths relate to AIDS (WHO, 2004; JUNP, 2004).

The prevalence of diabetes in Kenya is estimated to be 3.3 percent by the International Diabetes Federation, though studies within the country have indicated a prevalence of 4.2 percent (IDF, 2006). Increasing prevalence disparities exist between the rural areas being 2.2% and that in the urban areas being 12.2%, whereas that of diabetes type 2 (T_2DM) among diabetes subtypes is the highest with the prevalence of rural areas being equally high (8.6%) and urban areas (13.2%). Therefore, T_2DM poses the greatest public health chronic disease threat in Kenya together with HIV and AIDS (Christensen et al., 2009). HIV/AIDS prevalence is estimated to be 7.6% in 15-49 age group and 7.1% in 15-65 age group (KAIS, 2007). Every year, approximately 100, 000 adult new HIV infections are reported (NASCOP, 2012). Of the eligible groups to be enrolled on antiretroviral therapy (ART), only 26% of the children and 38% of the adults are covered (WHO, 2010).

Diabetes and HIV/AIDS require continuity on treatment, since these diseases are not self-limiting and are usually ongoing over an augmented span of time because they do not have cure (Cabana and Jee, 2004; Garcia et al, 2002). For optimum benefits to be attained continuity on treatment is mandatory and retention of care has proven necessary to improve

functioning, minimize discomfort and equally lengthen life (Saultz and Lochner, 2005). Interruption on medication could lead to unnecessary discomfort, repeated hospitalization, premature disability and even death (Christakis et al., 2001; Parchman, 2002; Oyugi et al., 2007).

To ensure continuity on treatment, factors influencing discontinuity of chronic disease treatment, need to be understood. This can be discussed through the lenses of borrowed constructs from Wekesa (2007) and Fogarty et al. (2001), both frameworks on adherence in resource poor settings. Non-adherence causes treatment interruption and treatment discontinuity (WHO, 2006).

Discontinuity factors could be categorized to: Structural related such as drug stock outs of medicines; socioeconomic and community related such as cost of treatment; medical or treatment related such as adverse events; and individual related such as pregnancy (Wekesa, 2007). In resource poor settings, most of the discontinuity may likely be because drugs are not affordable and not available; this is often demonstrated by drugs stock outs, being a health system related issue (Weiser et al., 2003)

Little is known about whether patients have access to drugs for chronic disease in Kenya. A number of studies confirm that chronic disease medicines in Kenya are not affordable to patients and their availability remains low (Madden et al., 2003). The World Health Organization (WHO) initiative response, purposes to improve access to chronic disease medicines in Kenya and other LMICs countries (WH0, 2005). Cameron et al (2009) report surveyed 36 LMICs including Kenya which confirmed poor availability of medicines. Public sector availability varied between 29.4 and 54.4 % across WHO regions. Medicines for chronic illness like asthma, diabetes,

cardiovascular diseases were less available as compared to medicines for "acute" and infectious diseases including HIV/AIDS (Cameron, 2011).

Procurement and distribution of ART in Kenya is done by KEMSA (government funded) and MEDS (PEPFAR funded). Access to ART in Kenya has considerably improved due to multiple donors that fund antiretroviral drugs (ARVs), mainly by PEPFAR, UNAIDS, Global Fund including the government through KEMSA. This has substantially reduced the cost of ARVs, improved its availability and thus making them more accessible financially in most public health facilities (Walgate, 2002; News in brief, 2003). In light of the above, we hypothesize that discontinuities in treatment due to drug stock outs (leading to unavailability) and financial constraints (unaffordability) will occur more frequently in T_2DM patients, because diabetes treatments are less available and less affordable since their supply solely relies on government funding unlike ART.

3.2 Justification

Kenya bears a huge and increasing burden of chronic diseases especially diabetes and HIV/ AIDS. Treatment discontinuation among T_2DM and HIV patients could be attributed to drugs stock out, which is a major problem in Kenya, among other reasons.

Drug stock outs contribute to treatment discontinuity among other factors such as treatment costs, insufficient human resources, poor infrastructure, and adverse events etc. (Eholie, 2007; Diabate et al., 2007; Weidle et al., 2006). Repeated drug interruptions could cause drug resistance which in-turn lead to switching of drug regimens or substitutions. For instance first line antiretroviral therapy (ART) drug regimen are cheaper and switching patients to second line or higher regimens which are more costly could infer

that the government budget on these medicines will hike (Cameron et al., 2012; Fischer et al., 2006; Sokol et al, 2005). Some of these higher line regimens could be more toxic which could lead to increased adverse events, thus encouraging further treatment discontinuity (Garcia, 2002). These drug interruptions hamper adherence which is key for any treatment efficacy, where ART demands > 95% and diabetes > 80% of adherence (Oyugi et al, 2007; Pladerall et al., 2004). Drug interruptions could further increase the occurrence of opportunistic infections, especially in HIV, and even deaths (Garcia, 2002).

The study compares discontinuation on HIV and T_2DM treatments because of the differences in supply chains structure and funding exhibited by the two chronic disease treatments. Moreover HIV/AIDS and T_2DM pose a public health threat in Kenya. Although we know unavailability is an important issue, we do not know to what extent drugs stock out contribute to switches or short or long discontinuation of therapy. And none of the studies we know has quantified these outcomes of drugs stock out on discontinuity of HIV and T_2DM treatments in Kenya. In order to support decision making/policy making it is important to quantify the problem by conducting this study (fieldwork) and come up with evidence based solutions to prevent drug stock outs (literature search). Further, the study will draw recommendations based on the study findings.

The study will be conducted at the Coast Provincial General Hospital (CPGH), one of the three largest referral hospitals in Kenya situated in the coastal region where HIV and diabetes, particularly T_2DM, prevalence's are relatively high.

4. STUDY OBJECTIVES

4.1 General objective

To quantify the effect of drugs stock out on discontinuity of HIV and T_2DM treatments at the Coast Provincial General Hospital in Kenya. Further, the study will draw recommendations depending on the study findings to enhance treatment continuity.

4.2 Specific objective

1. To quantify the number of new HIV and T_2 DM patients that discontinue treatment (absolute risk),
2. To establish the percentage of discontinuities caused by drug stock outs, and
3. To assess the outcomes of drug stock outs in terms of switched regimens, temporary or complete treatment discontinuation at the CPGH in order to make policy recommendation and prioritize decision making.

4.3 Research questions

The research will answer the following research questions:

1. What are the overall rates of discontinuation in HIV and T_2 DM treatments and how do they compare between the two cohorts?
2. What are the discontinuation rates according to sex, age and initial treatment regimen?
3. What percentage of treatment discontinuation that can be attributed to either a regimen switch or temporary and complete discontinuity?
4. What proportion of discontinuation is caused by antiretroviral drugs and oral anti-diabetic drugs stock out?
5. Is the time to discontinuation of HIV and T_2 DM treatments different, also when stratifying by reason for discontinuation (with a focus on drugs stock out)?

5. METHODS

5.1 Search Strategy

A broad scoping search was conducted to assess the depth and breadth of literature to ensure a broad coverage of the topic. It was then limited to electronic media since they are generally accessible, thoroughly indexed, and mostly, have the potential links to retrieve much more up- to- date evidence than paper based resources. Searching was done in Cochrane, PubMed, Science Direct, Medline, and Embase databases. The Boolean/ phrase or keywords for the searches were *"antiretroviral therapy or ART, diabetes treatment, oral anti diabetic drugs, drug stock outs, unavailability, continuity on treatment, sub Saharan Africa and Kenya"*. Further refining was effected by year of publication from 2006 to 2012 to retrieve the most current evidence. Further filtration was done to identify full-text, randomized control trials, reviews and observational studies in English language. Country reports were also included. Additional literature was searched for by checking references of obtained sources (snowballing).

5.2 Research framework

The study adapts a conceptual framework which borrows constructs from Wekesa (2007) to study factors influencing chronic disease adherence particularly those of ART in sub-Saharan Africa. The constructs can be utilized to discuss discontinuity on treatment since non-adherence could lead to treatment interruption and discontinuity. Similarly the model has been used in Tanzania, Uganda and Botswana as exhibited by Fogarty (2001).

This study will be guided by the conceptual framework partly. The focus will mainly be on discontinuation of HIV and T_2 DM treatments caused by drug stock outs and indirectly other factors. Data collection, analysis, discussion

of findings and drawing of recommendations will be navigated through the lenses of the framework.

The framework categorizes factors as:

5.2.1. Medical or treatment related factors

These include: adverse events (side effects), regimen complexity and pill burden, undesired drug formulations, lifestyle inconveniences, poor interaction and relationship between providers and patients.

5.2.2. Structural related factors

Include: interrupted treatment supplies (drugs stock outs), higher user fees (copayment), lack of medical insurance, inaccessibility to health facility due to geographical location, poor or lack of confidentiality at the health centers and negative attitude of health workers. Others are shortage of staff which may lead to high workloads and augmenting the waiting time.

5.2.3. Socio-economic and community level factors

These include: high cost associated to treatment (including transport & opportunity cost), discrimination and stigma, lack of functional support networks, poor patterns of disclosure, lack of food (hunger), poverty, funerals, and family appointments.

5.2.4. Individual related factors

Include: negative attitudes on treatments, lack of faith on efficacy of treatment, not educated and illiteracy, ill lifestyle behaviors such as alcohol or substance use, patient forgetfulness, stress and depression, disappearing of symptoms, and interruption due to pregnancy

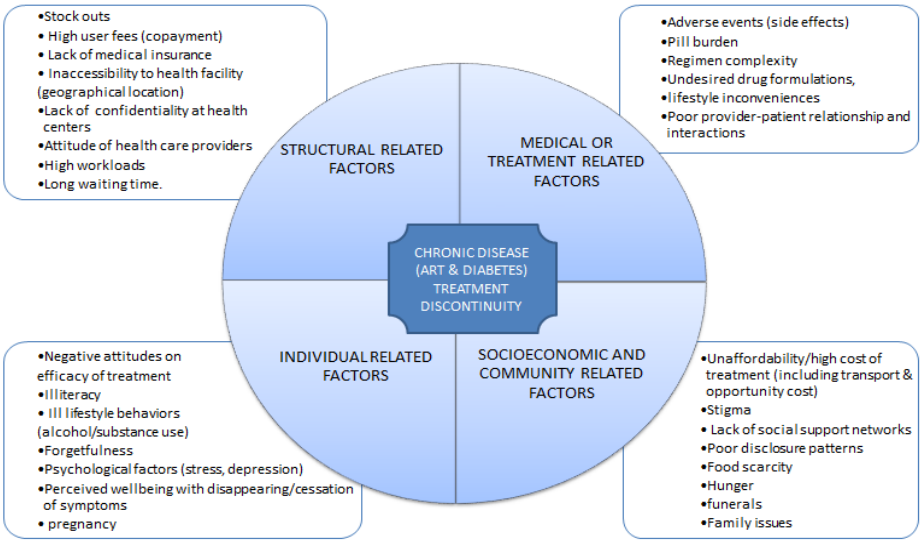

Figure 2 Conceptual framework for analysis of factors influencing chronic disease discontinuation on treatment (ART and diabetes treatment), Adapted from Wekesa (2007)

5.3 Study design

Retrospective cohort

Conducted a retrospective cohort study at the Coast Provincial General hospital (CPGH). Study population were HIV and T2 DM adult patients aged ≥19 years, which is above the legal age in Kenya, who initiated ART and T2 DM treatment between 6th September 2010 and 6th January 2012. Follow up began at ART or T2 DM treatment initiation as the index date and ended on 6th June, 2012 to ensure enough time of follow up to capture sufficient numbers to attain a feasible pilot study before the end of the study. To avoid bias due to loss to follow up (e.g. due to death, moving out of the catching area, etc.), patient follow up time was censored at time of last contact with the hospital (e.g. for appointment or filling of other medication). The primary outcome was treatment discontinuation, either switched treatment, temporary or complete treatment discontinuation.

5.4 Ethics Statement

Ethical approval was sought and obtained from the Research and Ethical Committee at the Royal tropical institute (KIT) in the Netherlands and from Coastal Research Ethics Board in Kenya before the study was conducted. Also permission was sought and granted from the study Centre, the Coast provincial General hospital.

5.5 Definitions

Treatment was defined as a specific medicine or combination of medicines that constituted a complete therapy.

Treatment discontinuity was defined as interruption of a specific medicine or combination of medicines beyond the theoretical end date for filling up medication either by: a regimen switch, temporary discontinuation, or complete discontinuation.

A regimen switch was defined as switching from one specific medicine to another medicine for the same disease or in case of combination treatment switching one or more of the medicines belonging to that combination to another medicine for the same disease. Addition of a new medicine while continuing the other medicines (add on) was not seen as a discontinuity.

Temporary discontinuation was further defined as a patient being late by more than 2 days and 6 days per month on ART and diabetes treatment respectively, but starting the same specific medicine or combination of medicines thereafter. The allowance of being 2 (ART) or 6 (diabetes) days late was justified by taking the required optimum adherence of ≥ 95% and ≥ 80% for HIV and type 2 diabetes, respectively, into account.

Complete discontinuation was defined as stop of a specific medicine or combination of medicines, without restart of any medication for that disease (either diabetes or HIV).

Drug stock out(s) was defined as the absence or lack of drug(s) at the health facility pharmacy store at the time of filling the prescription.

5.6 Data collection

The required patient information was collected from ART and T_2DM treatment databases and patient medical folders/files using a standardized clinical research form in Excel. The information collected retrieved demographic information of the inception cohort such as year of birth and sex. Further information on treatment start date, treatment regimen, type of treatment discontinuation (i.e. switch, temporary discontinuation or complete discontinuation), specific reason for discontinuation listed in the patient folders, categorized reason for discontinuation, date of discontinuation, HbA1c or CD4 results before and after discontinuation and their dates, restart of same treatment Yes/No, and restart date for recording multiple discontinuities within individuals was also collected using the clinical research form . All recruited subjects as per the set criteria were coded and made anonymous. Specific study outcomes were identified and recorded following the clinical research form. Specific reasons for discontinuation were recorded and categorised as per the conceptual framework and those not included were coded as others.

Drug stock outs were ascertained by: First, patients files including electronic patient databases were checked for information. When no information was available in a patient's file, the pharmacy drug stock out list was checked (if available) to see whether the drugs were out of stock at time of prescription.

If discontinuity occurred without mentioning any reason for discontinuity during the time of stock out, the reason was classified as "possibly related to drug stock out". To collect reliable information on drug stock outs the facility had electronic databases that showed when these medicines were unavailable.

5.7 Statistical analysis

First, we described the baseline characteristics of patients enrolled in the study.

Collected information as recorded by the clinical research form was analysed to quantify the problem of discontinuity by calculating the absolute (numbers) of discontinuities and of the relative (percentage) contributions caused by drug stock outs. Discontinuities from the total numbers of the inception cohorts within the start and end of entry calculated the incidence density rates (and 95% confidence intervals (CIs) and the relative risk (ratios) of discontinuation within and between HIV and T_2DM treatments and the incidence of discontinuity. Moreover, the percentage of treatment discontinuities that are caused by regimen switch, temporary and complete discontinuity was ascertained. Analysis was done for the first discontinuities to occur for individual patients following the index date of starting treatment. Further, associations with sex, age and treatment started variables were analyzed including the reasons for discontinuity.

In addition Kaplan-Meier curves were used to display a time to event analysis, stratified by age, sex, treatment started and reason for discontinuity of ART and T_2DM with a focus on drug stock outs. Median time to discontinuity and interquartile ranges (IQR) were calculated and compared using a Mann-Whitney's-U-test between cohorts and within groups. The statistical analysis was done by Epi- Info 7 software, Graph pad prism 5, Epi-open, SPSS and Excel.

6.0 RESULTS.

6.1 Baseline characteristics by age, sex and treatment started of inception cohorts

A total of 167 patients were initiated T_2DM treatment and 347 on ART between 6th September 2010 and 6th January 2012. Baseline characteristics are illustrated in Tables 1 and 2. The mean age for T_2DM cohort was 50.27 with SD of 12.49 and for the HIV cohort the mean age was 36.72 with SD of 10.14 ($p< 0.0001$).

The vast majority of the patients started on T_2DM treatment during the study period were ≥ 40years in age (n=134; 80.2%) and the rest were < 40 years, while 229 (79.4%) of the patients initiated on ART were < 40 years and the remaining ≥ 40 years in age. There were no patients aged 19 years.

In both cohorts more women than men started treatment, but the difference was larger for HIV than T_2DM. A total of 122 (35.7%) of the males initiated on ART, whereas 76 (45.5%) started on T_2DM treatment (table 1).

Table 1 Baseline characteristics on age and sex distribution of the inception cohort.

Description	T2DM cohort (n = 167), n (%)	HIV cohort (n = 342), n (%)
Age (Mean, SD)	50.27 (12.54)	36.72 (10.14)
20-29	5 (3.0)	89 (26.0)
30-39	28 (16.8)	140 (40.9)
40-49	48 (28.7)	72 (21.1)
50-59	44 (26.3)	31 (9.1)
60-69	32 (19.2)	6 (1.8)
≥ 70	10 (6.0)	4 (1.1)
Sex		
Male	76 (45.5)	122 (35.7)
Female	91 (54.5)	220 (64.3)

SD: standard deviation; *No patient was 19 years.

Most of T_2DM patients (59.3%) were started on metformin only, followed by metformin + sulfonylurea combination (28.7%). Most of those enrolled on ART were started on a combined ART regimen of AZT/3TC/NVP and AZT/3TC/EFV (33% each), followed by TDF/3TC/EFV (25.1%) as shown by Table 2.

Table 2 Baseline description of treatment regimen started.

T2DM cohort (n=167)		ART cohort (n =342)	
Treatment started	**No. started n (%)**	**Treatment started**	**No. started n (%)**
Metformin only	99 (59.3)	AZT/3TC/NVP	113 (33.0)
Metformin + Sulfonylurea	48 (28.7)	AZT/3TC/EFV	113 (33.0)
Metformin + thiazolidinedione	7 (4.2)	TDF/3TC/NVP	22 (6.4)
Sulfonylurea + thiazolidinedione	5 (3.0)	TDF/3TC/EFV	86 (25.1)
Others*	8 (4.8)	D4T/3TC/NVP	2 (0.7)
		D4T/3TC/EFV	5 (1.5)
		Others*	1 (0.3)

n (%). * Any combination of the treatment drugs other than the above (Abacavir/Lamuvidine/Alluvia for ART and sulfonyl ureas only like glibenclamide and metformin + insulin for T2DM). SD: standard deviation. AZT: zidovudine; 3TC: lamuvidine; NVP: nevirapine; EFV: efavirenz; TDF: tenofovir; D4T: stavudine.

6.2 Discontinuation rates by age, sex and type of discontinuation

6.2.1 Discontinuation rates by age and sex within the cohorts

HIV and T_2DM patients were followed up from the index date, when initiated treatment till the date of first discontinuity, end of study (6^{th} June, 2012) or last contact in the clinic for those who were lost to follow up, whichever came first. Of the 167 T_2DM patients, 56.9% of them experienced a discontinuity of treatment. Whereas, out of the 342 ART patients, 47.7% of the patients discontinued treatment as illustrated in table 3 (see appendix 5-9 for alternative analysis of cumulative incidence).

Table 3 Rates of at least one discontinuation by sex, age and risk ratios between sex and age categories.

Description	Disc in treatment n (%)		Rate*	95% CI	RR*	95% CI
	Yes	Patient days				
T2DM (n =167)						
Disc (overall)	95 (56.9)	35,655	2.66	2.17-3.24	-	-
Sex						
Female (n=91)	56 (61.5)	19084	2.93	2.24-3.78	1.25	0.83-1.89
Male (n=76)	39 (51.3)	16571	2.35	1.70-3.19	1 (ref)	
Age (years)						
< 40 (n=32)	15 (46.9)	6700	2.24	1.30-3.61	0.81	0.46-1.40
≥ 40 (n=135)	80 (59.3)	28955	2.76	2.21-3.42	1 (ref)	
ART (n= 342)						
Disc (overall)	163 (47.7)	98748	1.65	1.41-1.92	-	-
Sex						
Female (n=220)	103 (46.8)	65613	1.57	1.29-1.90	0.86	0.63-1.19
Male (n=122)	60 (49.2)	33135	1.82	1.40-2.33	1 (ref)	
Age (years)						
< 40 (n=229)	116 (50.7)	66113	1.76	1.46-2.10	1.22	0.87-1.72
≥ 40 (n=113)	47 (41.6)	32635	1.44	1.07-1.90	1 (ref)	

*per 1000 patient days; Disc: Discontinuation; RR: Risk ratios of discontinuation within T2DM and ART; ref: reference

Out of the 95 T_2DM patients who overall discontinued treatment, 56 (58.9%) were female and 39 (41.1%) were male. Also, of the 163 ART patients who discontinued treatment, 103 (63.2%) were female and 60 (36.8%) male. The proportion of females and males who discontinued T_2DM was higher than that of ART. Further, the relative risk of discontinuation for female diabetes patients to males was 1.25 (95% CI; 0.83-1.89), while that of HIV females to that of males was 0.86 (95% CI; 0.63-1.19), though the results were not statistically significant.

Discontinuation by age varied within the groups. Most of the patients who discontinued T2DM treatment were ≥ 40 years in age (84.2%). Contrary to ART, where the vast majority of patients who discontinued were < 40 years in age (71.2%). About 46 % of the patients who discontinued T_2DM treatment were < 40 years, and 59% were ≥ 40 years. While, 50.7% of ART patients who discontinued were < 40 years and 41.6% were ≥ 40 years in

age. T_2DM patients below the age of 40 years were 19% lesser likely to discontinue treatment than those of ≥ 40 years cluster, whereas the risk of discontinuation of treatment for HIV patients of < 40 years cluster was 22% greater than that of age ≥ 40 years (though the results were not significant because none of the 95% confidence intervals excluded 1, which means that the observed differences were not statistically significant).

6.2.2 Relative risk (ratios) of discontinuation between T_2DM and HIV

The risk of discontinuation between the T_2DM and HIV by sex, age and type is summarized in table 4. Overall, the risk of discontinuation of T_2DM treatment was 61% greater than that of ART (p=0.0002). Females on T_2DM treatment were 87% more likely to experience a discontinuation than those on ART (p=0.0001). Moreover, the likelihood of discontinuation of males in T_2DM was 29% higher than those of ART, though the results were not statistically significant (p=0.20). Discontinuation rates in age clusters differed in ART and T_2DM. The risk of discontinuation in T_2DM ≥ 40 years cluster was greater by 92% than that of ART (P=0.0003), while that of T_2DM < 40 years cluster was 28% greater than that of ART (p=0.37), although the latter was not statistically significant.

Table 4 Relative risk of discontinuation by sex and age between ART and T2DM cohorts

	T2DM (n =167)			**ART (n= 342)**					
Description	Disc in treatment n (%)		Rate*	Disc in treatment n (%)		Rate*	RR*	95% CI	P value
	Yes	Patient days		Yes	Patient days				
Disc (overall)	95 (56.9)	35655	2.66	163 (47.7)	98748	1.65	1.61	1.25-2.10	0.0002
Sex									
Female	56 (61.5)	19084	2.93	103 (46.8)	65613	1.57	1.87	1.34-2.58	0.0001
Male	39 (51.3)	16571	2.35	60 (49.2)	32935	1.82	1.29	0.86-1.93	0.20
Age (years)									
< 40	15 (46.9)	6700	2.24	116 (50.7)	66113	1.76	1.28	0.72-2.14	0.37
≥ 40	80 (59.3)	28955	2.76	47 (41.6)	32635	1.44	1.92	1.34-2.77	0.0003

*per 1000 patient days; Disc: Discontinuation; RR: Relative risk of discontinuation.

Kaplan-Meier plots were presented to depict the proportion of patients not having had a 1st discontinuity over time for the two cohorts of patients with ART and T_2DM treatment. Figure 3 depicts the overall time to discontinuity in ART and T_2DM cohorts.

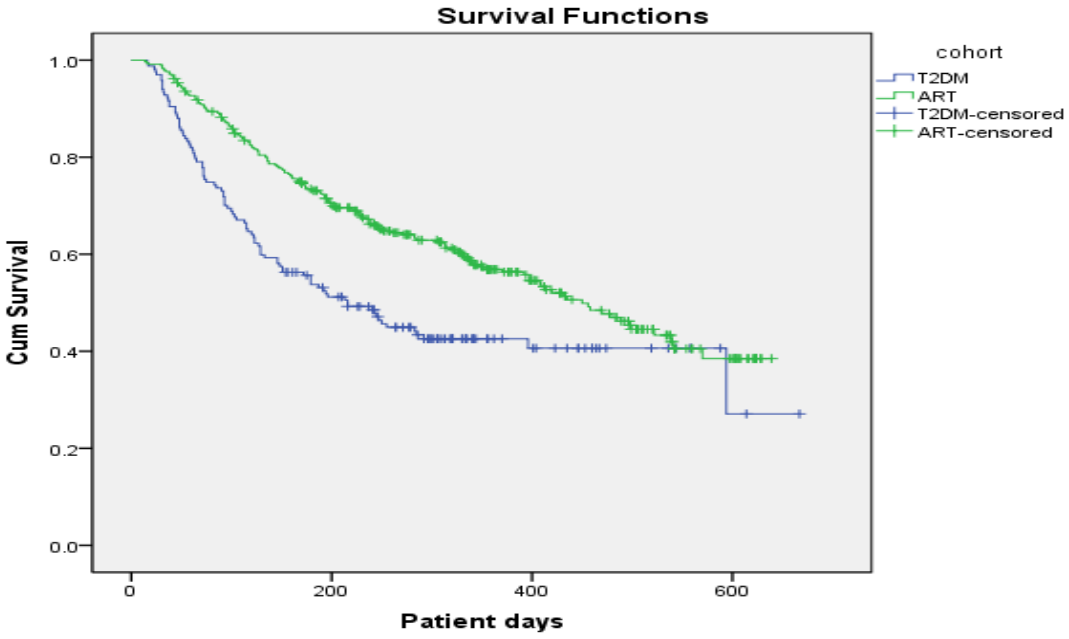

Figure 3 Kaplan-Meier survival plot for overall time to discontinuity between ART and T_2DM cohorts

Analysis for time to discontinuity of treatment was also presented, stratified by age and sex (figures 4-11).

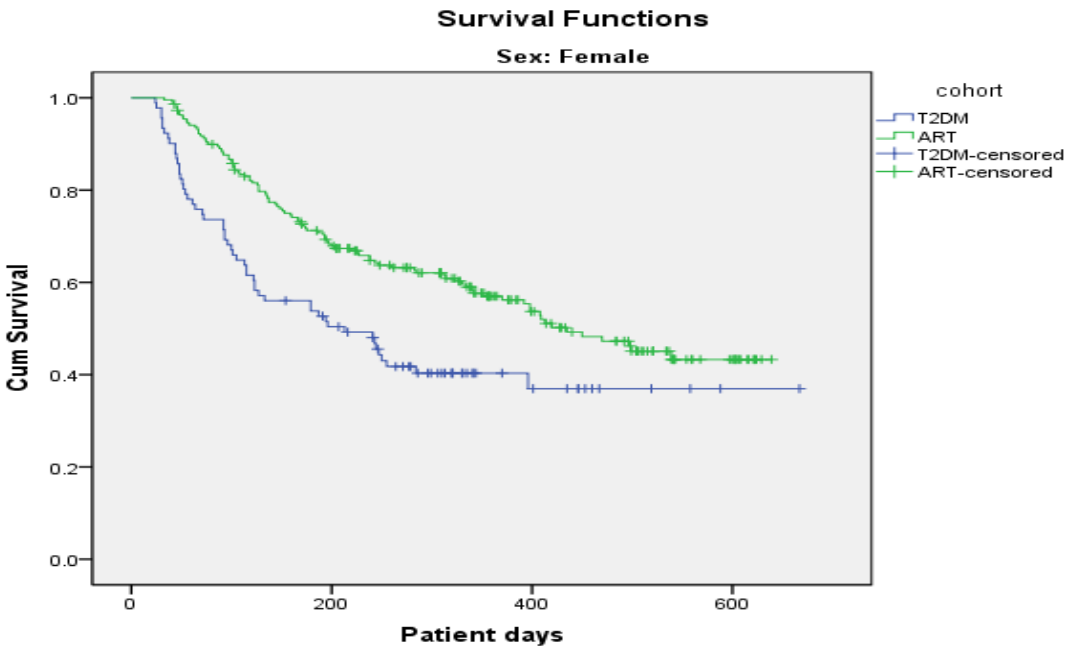

Figure 4 Kaplan-Meier plot for time to discontinuity between females in ART and T_2DM cohorts

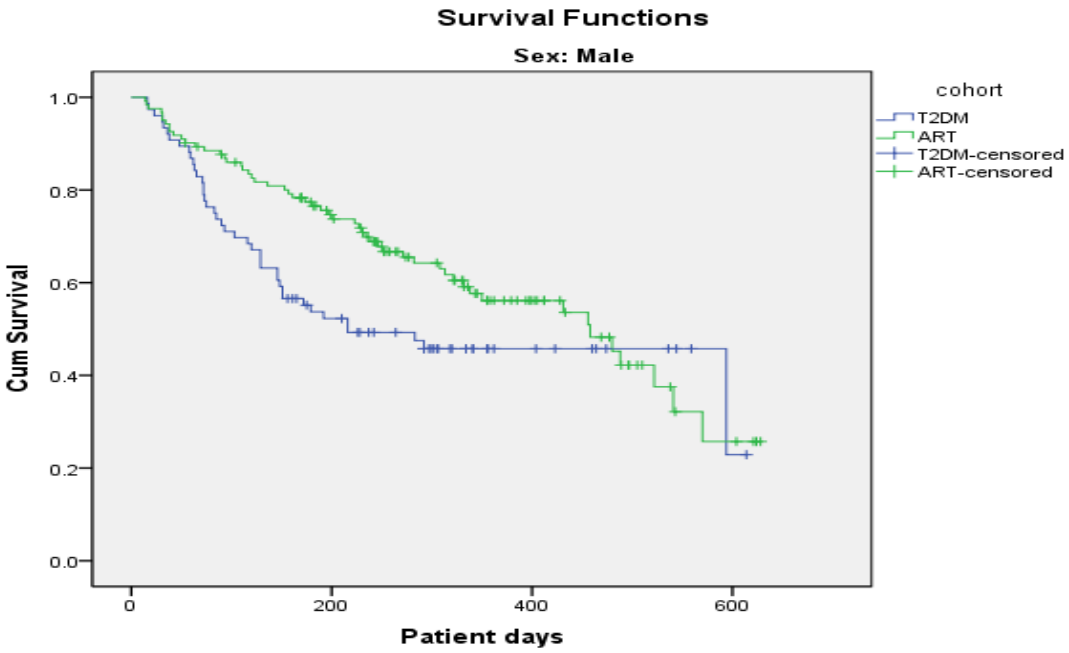

Figure 5 Kaplan-Meier plot for time to discontinuity between males in ART and T_2DM cohorts

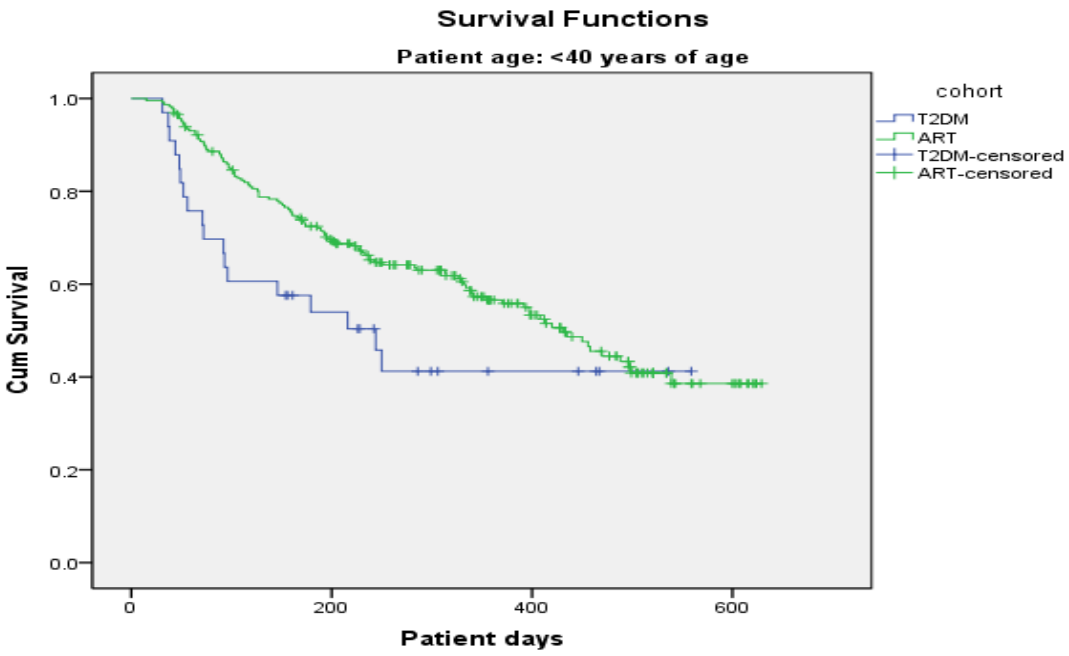

Figure 6 Kaplan-Meir plot for time to discontinuity between age cluster of <40 years in ART and T_2DM cohorts

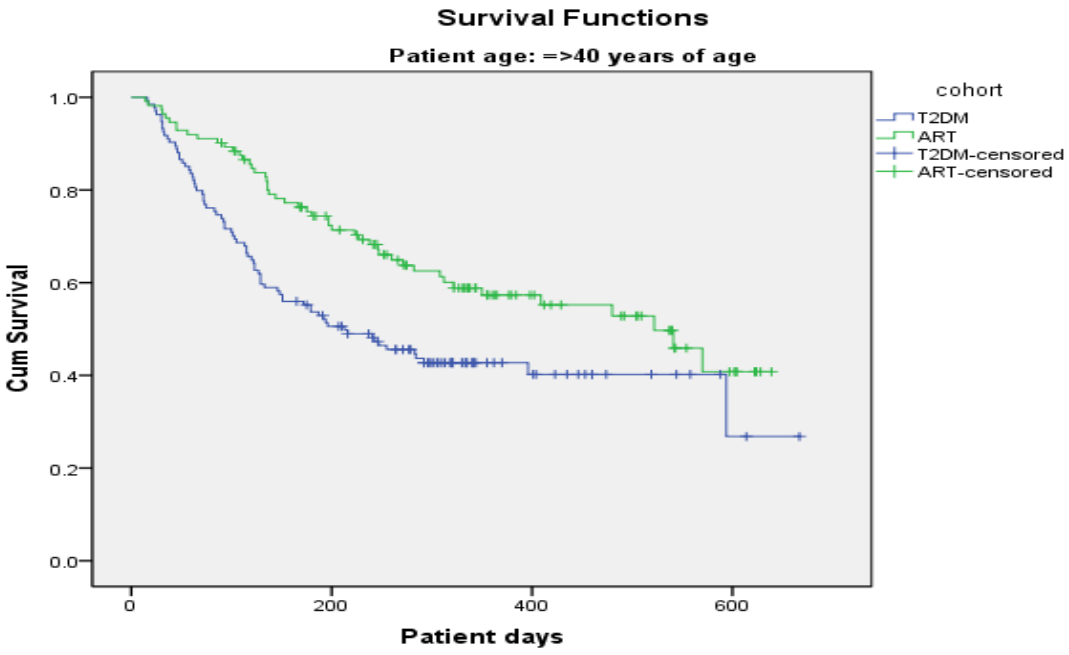

Figure 7 Kaplan-Meir plot for overall time to discontinuity between age cluster of ≥40 years in ART and T_2DM cohorts

6.2.3 Discontinuation rates by type of discontinuation within and between groups

Of the 258 patients who discontinued treatment in ART and T_2DM, 95 T_2DM patients stopped treatment, of which 7 (7.4%) were because of switched regimen, 88 (92.6%) discontinuations (temporary discontinuation, n=61; complete discontinuation, n=27). Whereas, among the 163 ART patients that discontinued treatment, 34 (20.9%) were because of switched regimen and 129 (79.1%) were due to discontinuation (temporary discontinuation, n=113; complete discontinuation, n=16).

In absolute terms, 4.2% of the patients who started on T_2DM treatment switched regimens and 52.7% experienced at least a discontinuation. Whereas, 9.9% of patients started on ART switched regimens and 37.7% discontinued treatment. The relative risk (RR) of experiencing a discontinuation (either complete or temporary) to that of switching a regimen was 12.57 (95% CI; 5.82-27.14) in T_2DM (p<0000001), whereas in ART, the RR was 3.79 (95% CI; 2.60-5.54) (p<0000001) respectively. The absolute rates within the cohorts are shown in table 5.

Table 5 Absolute rates of discontinuation by type of discontinuation

	T2DM (n=167)			ART (n=342)		
	n (%)	**Absolute rate***	**95% CI**	**n (%)**	**Absolute rate***	**95% CI**
Total patient days	**35655**			**98748**		
Overall 1st disc	95 (56.9)	2.66	2.17-3.24	163 (47.7)	1.65	1.41-1.92
Switched treatment	7 (4.2)	0.20	0.09-0.39	34 (9.9)	0.34	0.24-0.48
Temporary discontinuation	61 (36.5)	1.71	1.32-2.18	113(33.0)	1.14	0.95-1.37
Complete discontinuation	27 (16.2)	0.76	0.51-1.09	16 (4.7)	0.16	0.10-0.26

*per 1000 patient days

Discontinuation rates by type differed significantly between T_2DM and ART. The risk of a regimen switch was 43% lesser in T_2DM than in ART, that of

temporary discontinuation was greater by 50% in T_2DM than in ART (though former results were not statistically significant as shown in table 6), and the risk of complete discontinuation was about 5 times more in T_2DM than in ART (p=0000001),. The combined risk of experiencing a discontinuation (either complete or temporary) was 89% greater in T_2DM than in ART (P=0.000003).

Table 6 Relative risk of discontinuation by type of discontinuation between ART and T2DM cohorts

	T2DM (n=167)		ART (n=342)				
	n (%)	Rate*	n (%)	Rate*	RR*	95% CI	P value
Total patient days	**35655**		**98748**				
Overall 1st disc	95 (56.9)	2.66	163 (47.7)	1.65	1.61	1.25-2.08	0.0002
Switched treatment	7 (4.2)	0.20	34 (9.9)	0.34	0.57	0.23-1.24	0.17
Temporary discontinuations	61 (36.5)	1.71	113(33.0)	1.14	1.50	1.09-8.86	0.01
Complete discontinuation	27 (16.2)	0.76	16 (4.7)	0.16	4.67	2.53-8.86	<0.0000001

*per 1000 patient days; RR Relative risk of discontinuation

6.3 Reasons and rates of discontinuation

The rates of discontinuation per reason, stratified by category as per the conceptual framework, was analyzed and presented as illustrated by table 7. The categories were classified as: structure related factors (SRF; drug stock outs and financial constraints), medical or treatment related factors (MTRF; adverse events, other illnesses, and others which included patient felt better and patient too ill), socioeconomic and community related factors (SE&CRF; Travel problems, work appointments, out of town and family issues which included attending funeral, family wedding, other family appointments), individual related factors (IRF; depression, forgot/missed/stopped/defaulted in treatment) and others (OF) which included reasons not indicated from the medical folders. Structural related reasons in general in T_2DM affected discontinuity about 10 times more than in ART (p<0000001). Drug stock outs and financial constraints due to copayments affected discontinuity in

T_2DM treatment about 9 and 12 times more respectively than in ART (both with a p value of <0000001). Other reasons were not significantly different between the cohorts. Adverse events affected T_2DM treatment 55% lesser than ART (95% CI; -85%-8%), although not statistically significant. Besides, adverse events affected the majority of ART discontinuities.

Table 7 Rates of discontinuation of ART and T2DM by categorized reasons

	T2DM (n =167)			ART (n= 342)					
Category& reasons	Disc in treatment	Rate	95% CI	Disc in treatment	Rate	95% CI	RR*	95% CI	P value
Total patient days	35655			98748					
Disc overall	95	2.66	2.17-3.24	163	1.65	1.41-1.92	1.61	1.25-2.08	0.0002
SRF	49	1.37	1.03-1.80	14	0.14	0.08-0.23	9.69	5.45-18.14	<0000001
Drug stock	29	0.81	0.56-1.15	9	0.09	0.05-0.17	8.92	4.33-19.9	<0000001
Financial	20	0.56	0.35-0.85	5	0.05	0.02-0.11	11.08	4.35-33.11	<0000001
MTRF	19	0.53	0.30-0.82	64	0.65	0.50-0.82	0.82	0.48-1.35	0.4530
Adverse events	5	0.14	0.05-0.31	31	0.31	0.22-0.44	0.45	0.15-1.08	0.0858
Other illnesses	10	0.28	0.14-0.50	20	0.20	0.13-0.31	1.39	0.62-2.93	0.3985
Others	4	0.11	0.04-0.27	13	0.13	0.07-0.22	0.85	0.24-2.51	0.7794
SE&CRF	11	0.31	0.16-0.54	28	0.28	0.19-0.40	1.09	0.52-2.15	0.8125
Travel problems	4	0.11	0.04-0.27	12	0.12	0.07-0.21	0.92	0.26-2.76	0.8899
Family issues	6	0.17	0.07-0.35	9	0.09	0.04-0.17	1.85	0.61-5.25	0.2373
Others	1	0.03	0.04-0.27	7	0.07	0.03-0.14	0.40	0.02-2.56	0.3688
IRF	4	0.11	0.04-0.27	23	0.23	0.15-0.34	0.48	0.14-1.30	0.1680
Forgot/missed	4	0.11	0.04-0.27	13	0.13	0.07-0.22	0.85	0.24-2.51	0.7794
Depression	0 (+0.5)	0.01	0.01-0.00	9	0.09	0.04-0.17	0.00	0.00-1.09	0.07144
others	0 (+0.5)	0.01	0.01-0.00	1	0.01	0.01-0.05	0.00	0.00-52.62	0.5479
OF	12			34					
Not indicated	12	0.34	0.18-0.57	34	0.34	0.24-0.48	0.10	0.05-0.19	0.94

per 1000 person time; Disc: Discontinuation; RR: Risk ratios of discontinuation within T2DM and ART.

Among the 'not indicated' category, 5 discontinuities in T_2DM could have possibly occurred as a result of drug stock when comparing to drug stock out lists from the pharmacy and none in ART. If added, they could contribute to 4.5% of the discontinuities, thus could increase discontinuities due to drug stock outs by 4.5%.

Discontinuation rates differed by reason and type of discontinuation as classified in table 8.

Table 8 Number of patients discontinued on treatment by type and reason for ART and T2DM cohorts at CPGH

Reasons for discontinuation	T2DM cohort, n=95 (%)			ART cohort, n=163 (%)		
	Switched treatment	Temporary disc	Complete disc	Switched treatment	Temporary disc	Complete disc
Drug stock outs	6 (85.7)	7 (11.5)	16 (59.3)	2 (5.9)	6 (5.3)	1 (6.3)
Financial	0 (0.0)	14 (22.9)	6 (22.2)	0 (0.0)	5 (4.4)	0 (0.0)
Drug side effects	1 (14.3)	4 (6.6)	0 (0.0)	15 (44.1)	15 (13.3)	1 (6.3)
Other illnesses	0 (0.0)	8 (13.1)	2 (7.4)	16 (47.1)	2 (1.8)	2 (12.5)
Family issues	0 (0.0)	6 (9.8)	0 (0.0)	0 (0.0)	8 (7.1)	1 (6.3)
Forgot/missed/stopped/defaulted	0 (0.0)	4 (6.6)	0 (0.0)	0 (0.0)	13 (11.5)	0 (0.0)
Travel problems	0 (0.0)	2 (3.3)	2 (7.4)	0 (0.0)	12 (10.6)	0 (0.0)
Out of town	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	5 (4.4)	0 (0.0)
Depression & stigma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (7.1)	1 (6.3)
Patient felt better	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Patient worsened	0 (0.0)	2 (3.3)	0 (0.0)	1 (2.9)	4 (3.5)	6 (37.5)
Work	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Substance use	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Not indicated	0 (0.0)	11 (18.0)	1 (3.7)	0 (0.0)	31 (27.4)	3 (18.8)
	7 (100.0)	**61 (100.0)**	**27 (100.0)**	**34 (100.0)**	**113 (100.0)**	**16 (100.0)**

Most of the T_2DM patients who discontinued treatment were due to drug stock outs (26.1%) and financial issues (22.7%), while those who switched regimens were mostly as a result of drug stock outs (85.7%). On the other hand, those in ART discontinued treatment mostly due to adverse events (12.4%), and mostly those that switched regimens, 44.1% were affected by adverse events and other illnesses (47.7%). Drugs stock out affected 5.9%

of the ART patients who switched regimens and 5.4% of those who discontinued treatment.

About 85 percent of the switched regimens in T_2DM patients occurred due to drugs stock out and the rest because of adverse events. Besides, 23 (26.1%) of treatment discontinuation was due to drug stock outs (7 due to temporary discontinuation and 16, complete discontinuation). The rest were due to adverse events 4 (4.6%), 6 (6.8%) family issues, 10 (11.3%) other illnesses (ENT checkup, dental review and others not indicated), 1 (1.1%) out of town, 4 (4.6%) travel problems (facility far from home, weather changes such as raining, long distance), 20 (22.7%) financial issues (inability to pay for drugs, lacked fare to pick meds), 2 (2.3%) patient improved (felt better), 2 (2.3%) patient worsened (too ill), 4 (4.6%) forgot/missed/stopped/defaulted, 12 (13.6%) 'not indicated' (see appendix 1).

In ART, 2 (5.9%) of the patients switched regimens due to drugs stock out, 16 (47.1%) other illnesses (anemia, pregnancy, tuberculosis), 15 (44.1%) adverse events (Stevens Johnson syndrome, vomiting, nausea, CNS manifestations), 1 (2.9%) worsened (too ill) (see appendix 2). Among the 129 ART patients who discontinued, 7 (5.4%) were due to stock outs (6 temporary and 1 complete discontinuation). Besides, 16 (12.4%) were due to adverse events (Stevens Johnson Syndrome, vomiting, nausea, CNS manifestations), 2(1.5%) patients improved (felt better), 10 (7.8%) patients worsened (too ill), 5 (3.9%) financial issues (lack of fare to facility), 9 (7.0%) depression and stigma, 9 (7.0%) family issues, 4 (3.1%) other illnesses (anemia, pregnancy, tuberculosis, 5 (3.9%) out of town, 13 (10.1%) forgot/missed/stopped/defaulted, 12 (9.3%) travel problems (home far from facility), 2 (1.5%) work, 1(0.8%), and 34 (26.3%) 'not indicated' category.

6.4 Overall discontinuation and discontinuation due to drugs stock outs by treatment regimen started.

Overall discontinuation rates and drug stock out rates varied significantly by initiated treatment, as exhibited in table 9. Those started on metformin only, 41.4% of them discontinued, metformin + sulfonylurea (79.2%), metformin + thiazolidinedione (85.7%), sulfonylurea + thiazolidinedione (100.0%) and others (62.5%).

Table 9 Rates of overall discontinuation and drugs stock out by treatment started

	Rates of discontinuation in ART and T2DM treatments							
Treatment regimen started	Disc in general n (%)		Rate*	95% CI	Disc due to drug stock outs		Rate*	95% CI
	Yes	Patient days			Yes	Patient days		
Oral anti-diabetics drugs								
Overall (n=167)	95 (56.9)	35655	2.66	2.17-3.24	29	35655	0.81	0.56-1.15
Metformin only (n=99)	41 (41.4)	24419	1.68	1.22-2.26	1	24419	0.04	0.00-0.20
Metformin + Sulfonylureas (n=48)	38 (79.2)	7741	4.91	3.52-6.67	17	7741	2.20	1.32-3.45
Metformin + thiazolidinedione (n=7)	6 (85.7)	1382	4.34	1.76-9.03	6	1382	4.34	1.76-9.03
Sulfonylureas + thiazolidinedione (n=5)	5 (100.0)	358	13.97	5.12-30.96	4	358	11.17	3.55-26.95
Others (n=8)	5 (62.5)	1755	2.85	1.04-6.32	1	1755	0.57	0.03-2.81
Antiretroviral drugs								
Overall (n=342)	163(47.7)	98748	1.65	1.41-1.92	9	98748	0.09	0.04-0.17
AZT/3TC/NVP (n=113)	63 (55.8)	35813	1.76	1.36-2.24	1	35813	0.02	0.00-0.14
AZT/3TC/EFV (n=113)	52 (46.0)	31385	1.66	1.25-2.17	2	31385	0.06	0.01-0.21
TDF/3TC/NVP (n=22)	8 (36.4)	5924	1.35	0.63-2.56	0	5924	0.08	0.04-0.00
TDF/3TC/EFV (n=86)	32 (37.2)	23615	1.36	0.94-1.89	0	23615	0.02	0.01-0.00
D4T/3TC/NVP (n=2)	2 (100.0)	430	4.65	0.78-15.37	2	430	4.65	0.78-15.37
D4T/3TC/EFV (n=5)	5 (100.0)	1446	3.46	1.27-7.66	4	1446	2.77	0.88-6.67
Others (n=1)	1 (100.0)	135	7.41	0.37-36.53	0	135	3.69	1.79-0.00

*Per 1000 patient days

Also in the ART cohort, 163 patients discontinued treatment, among those discontinuing 63 (38.7%) were on AZT/3TC/NVP, 52 (31.9%) on AZT/3TC/EFV, 32 (19.6%) on TDF/3TC/EFV, 8 (4.9%) on TDF/3TC/NVP, 5 (3.1%) on D4T/3TC/EFV, 2 (1.2%) on D4T/3TC/NVP and 1(0.6%) on

alluvia/abacavir/lamivudine. 55.8% of patients started on AZT/3TC/NVP discontinued, AZT/3TC/EFV (46.0%), TDF/3TC/EFV (37.2%), TDF/3TC/NVP (36.4) and those started on D4T/3TC/EFV, D4T/3TC/NVP and alluvia/ abacavir/lamivudine all discontinued.

The rates of discontinuation in T_2DM increased gradually with metformin only (lowest rates) to sulfonylurea+ thiazolidinedione (highest rates) and likewise their rates of discontinuity due to their respective stock outs. Whereas in ART, stavudine based regimens had the highest rates of discontinuity. These results are graphically displayed in figures 8 and 9 (see appendix 10 for all ART treatments)

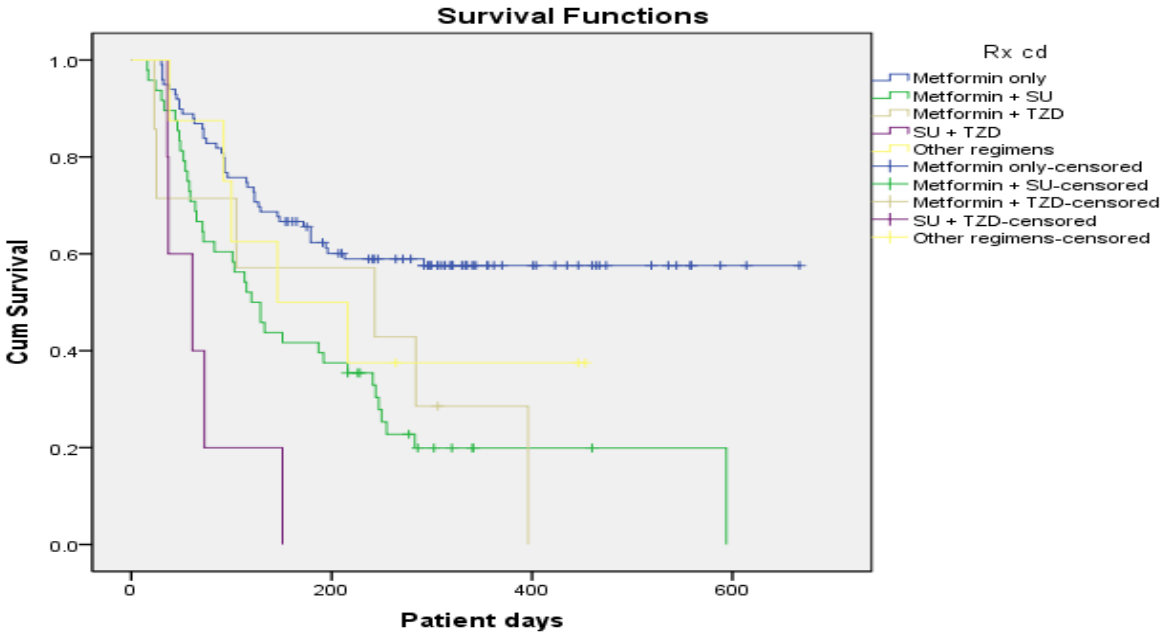

Figure 8 Kaplan-Meir plot for time to discontinuity by treatment started in T_2DM cohort

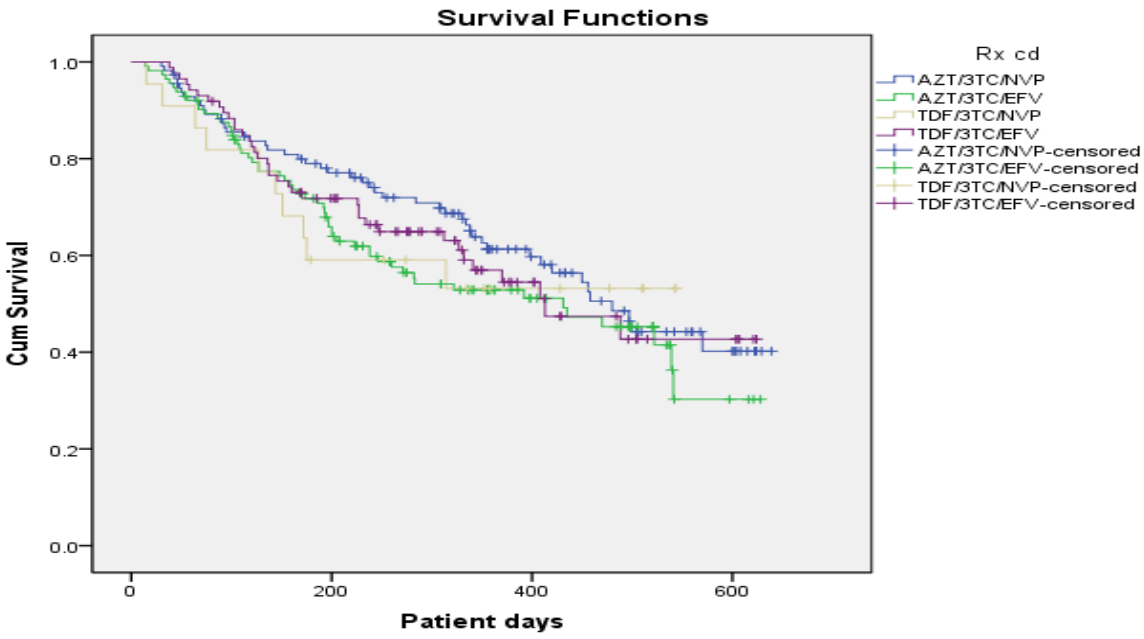

Figure 9 Kaplan-Meier plot for time to discontinuity by treatment started in ART cohort

Among the T_2DM patients who discontinued in metformin only group, 1(2%) was because of drug stock outs; in metformin + sulfonylurea, 17 (45%) due to drug stock out; in metformin + thiazolidinedione, all the 6 discontinued due to drug stock outs; 4 of the 5 who discontinued in sulfonylurea + thiazolidinedione group were because of drug stock outs; and in those classified as others, 1 of the 4 was due to drug stock outs. In ART, drugs stock out affected 1 (1.6%) of the 63 who discontinued on AZT/3TC/NVP, 2 (3.8%) of the 52 who discontinued on AZT/3TC/EFV, 4 (80%) of the 5 who discontinued on D4T/3TC/EFV and all who discontinued on D4T/3TC/NVP were due to drug stock outs. TDF/3TC/NVP, TDF/3TC/EFV and alluvia/ lamivudine/abacavir were not affected by drug stock outs.

The major drug stock out in T_2DM treatments was a shortage of sulfonylureas and thiazolidinedione's at the facility. Out of the 6 patients who switched regimens, 2 were as a result of pioglitazones classified under thiazolidinediones, 1 due to glipizide and 1 as a result gliclazide

(sulfonylureas) and 2 because of gliquidone + pioglitazone and glipizide + pioglitazone (sulfonylureas+ thiazolidinedione's). Drugs stock out led to discontinuation as well. 15 of the 23 patients discontinued because of sulfonylureas drugs stock out: glimepiride (8), glipizide (3), gliclazide (2) and gliquidone (2). Three (3) were thiazolidinedione's (all pioglitazone) and 2 were combination of thiazolidinedione and sulfonylurea (rosiglitazone +glimepiride and pioglitazone + glimepiride), and others comprised of 1 (metformin+ glibenclamide), metformin (1), glibenclamide + metformin (1).

Based on the scrutiny of drug stock out lists, it was ascertained that, most of the prescribed branded or originator treatments were out of stock or patients were unable to pay for the T_2DM treatments, thus contributing to either a switch or a discontinuation (see appendix 4). The facility pharmacy recorded mostly metformin and glibenclamide to be available consistently during the study period, and lacked most of the other oral anti-diabetic drugs. Although one week after the end of the study, glibenclamide went out of stock, thus could have affected a number of patients.

Stock outs in ART occurred for a combined dose regimen, stavudine and lamivudine (D4T/3TC) from 22nd June 2011 and by the time of the end of study it was still out of stock, stavudine (D4T) single dose, was out of stock from 30th August, 2010 until 23rd September, 2010 and then phased out on 6th December, 2010 due to issues of toxicity. Lamivudine (3TC) single dose went out of stock on 20th June, 2011 until 23rd July, 2011, tenofovir (TDF) single dose was out of stock from 20th July 2011 up to the time the study ended, zidovudine single dose (AZT) went out of stock from 17th February 2012 to 23rd march 2012, no stock out was registered for nevirapine single dose (NVP), all fixed doses were in stock throughout the study period except D4T/3TC/NVP. TDF/3TC, TDF/3TC/NVP, TDF/3TC/EFV, AZT/3TC/NVP, AZT/3TC were all in stock. Patients were affected less in ART compared to T_2DM treatment. The 2 switched ART regimens were due to D4T/3TC/EFV,

and out of the 7 discontinuations, 2 were caused by D4T/3TC/EFV, 2 of D4T/3TC/NVP, 2 of AZT/3TC/EFV and 1 of AZT/3TC/NVP. Most of the discontinuations during the period when single dose formulations were out of stock were avoided due to replacement by the fixed or combined dose regimens which were most of the time in stock

6.5 Time to discontinuity of ART and T_2DM treatments

Time to discontinuity of ART and T_2DM treatments among those who experienced such a discontinuity, stratified by reason and categories was calculated and presented in table 10. The median time to discontinue treatment due to T_2DM drug stock out was 72 days (Interquartile range (IQR):42-161) and that of ART was 86 days (IQR: 32-177) (p=0.03), which was not significantly different between the cohorts.

Table 10 Time to 1st discontinuity of ART and T2DM by categorized reasons

	T2DM (n =167)			ART (n= 342)			
Category& reasons	No. of disc in treatment	Median time	IQR	No. of disc in treatment	Median time	IQR	P value
Disc overall	95			163			
SRF	**49**	**93**	**50-149**	**14**	**111**	**46-201**	**0.692**
Drug stock	29	72	42-161	9	86	32-177	0.803
Financial	20	100	64-146	5	186	59-334	0.337
MTRF	**19**	**105**	**51-187**	**64**	**171**	**89-284**	**0.042**
Adverse events	5	72	38-213	31	127	46-260	0.410
Other illnesses	10	114	53-194	20	200	120-139	0.035
Others	4	100	52-178	13	174	93-292	0.089
SE&CRF	**11**	**127**	**48-216**	**28**	**131**	**101-328**	**0.391**
Travel problems	4	173	128-273	12	154	102-345	0.808
Family issues	6	69	28-147	9	127	68-169	0.289
Others	1	196	-	7	134	91-458	0.827
IRF	**4**	**69**	**38-181**	**23**	**104**	**66-199**	**0.290**
Forgot/missed	4	69	38-181	13	136	71-287	0.193
Depression	0	-	-	9	104	57-143	-
others	0	-	-	1	31	-	-
OF	**12**			**34**			
Not indicated	12	89	45-121	34	160	100-228	0.03

The median time to discontinuity of treatment for T_2DM MTRF was 105 days (IQR: 51-187) and that of ART was 171 days (IQR: 89-284) (p=0.042),

while that of OF was 89 days (IQR: 45-121) for T_2DM and 160 days (IQR: 100-228) for ART (p=0.03). In other categories there was no statistically significant association between the time to discontinuity and reason affecting discontinuity.

Figure 10 focuses on time to discontinuity due to drugs stock outs. As indicated above, no differences exist between the two cohorts in time to discontinuation among those who experience a discontinuity for this reason.

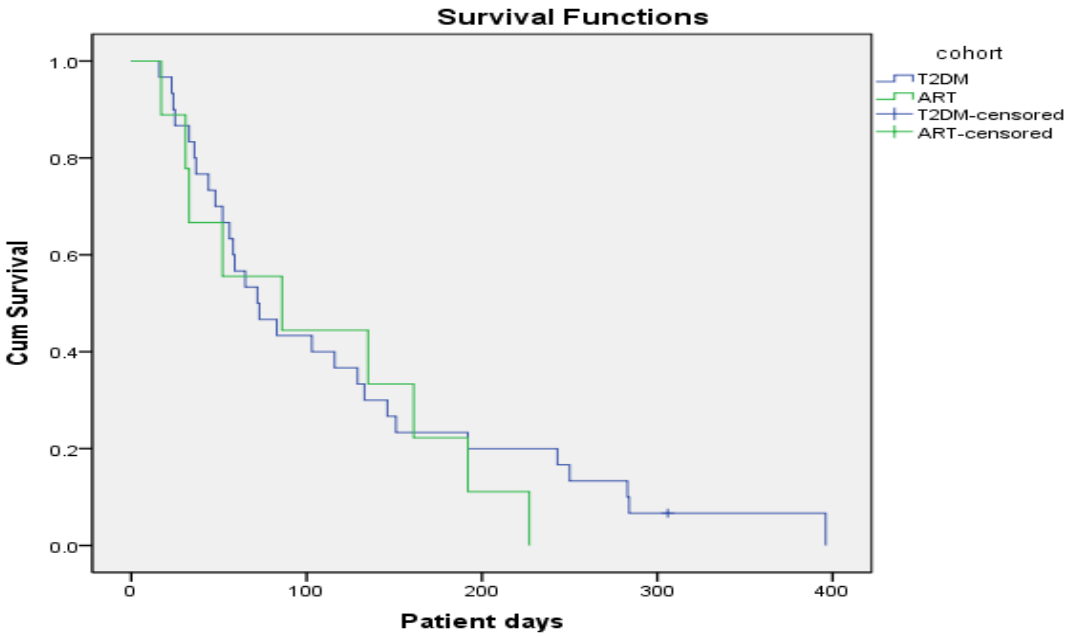

Figure 10 Kaplan-Meier plot for overall time to discontinuity due to drug stock outs between ART and T_2DM

Figures 11 and 12 depict time to discontinuation for the four categories according to the conceptual framework, within the cohorts of T2DM and ART, respectively (see appendix 11 for SRF comparison).

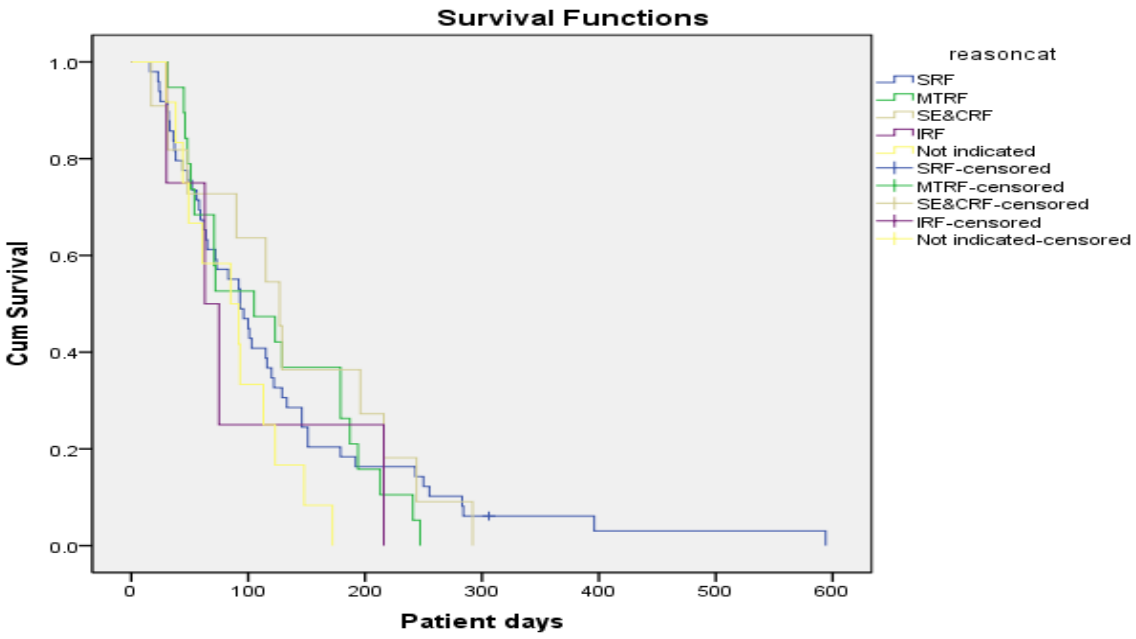

Figure 11 Kaplan-Meir plot for time to discontinuity by categorized reason in T_2DM cohort

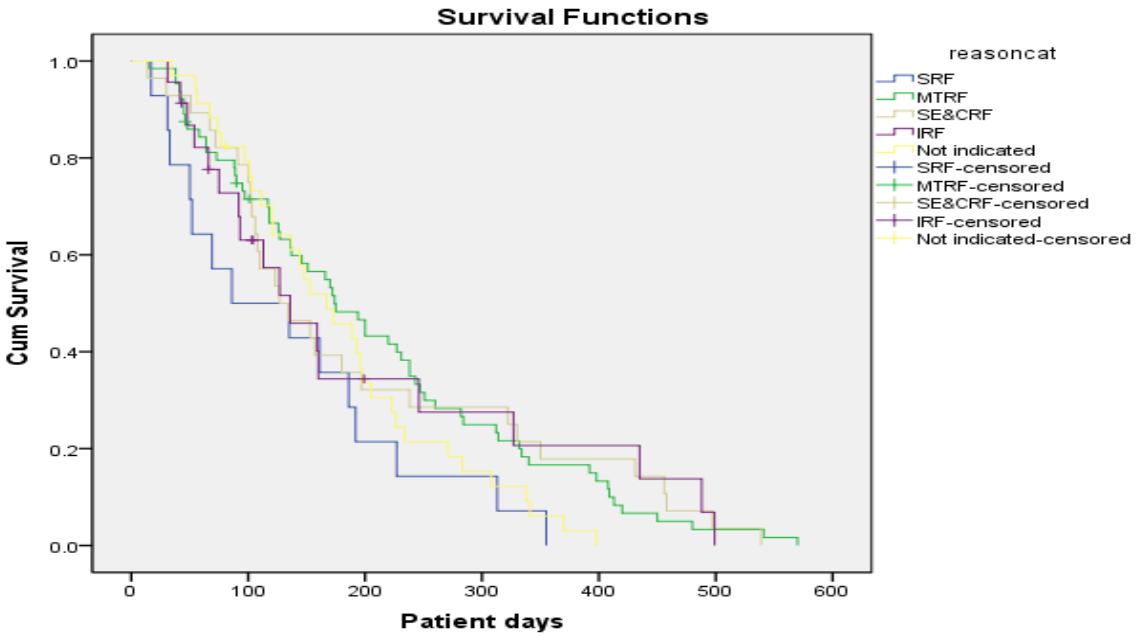

Figure 12 Kaplan-Meir plot for time to discontinuity by categorized reasons in ART cohort

7.0. DISCUSSION

In this study at Coast General Hospital in Kenya, 56.9% of the 167 T_2DM patients and 47.7% of the 342 ART patients who started treatment between 6th September 2010 and 6th January 2012 discontinued their treatment at least once. The overall incidence of discontinuation at least once for T_2DM patients and HIV patients was 2.66 per 1000 patient days and 1.61 per 1000 patient days respectively. Thus, the risk of treatment discontinuity at least once in T_2DM patients was 61% greater than that of HIV patients. The rate of treatment discontinuity due to drugs stock out was 0.81 per 1000 patient-days in T_2DM, while that of ART was 0.09 per patient-days. Most of the discontinuations in ART were affected by adverse events.

The higher rates of discontinuation in T_2DM treatment can be attributed to structural and funding variations as anticipated. The combined risk of experiencing a discontinuation (either complete or temporary) was 89% greater in T_2DM than in ART. Females diabetes patients were 25% more likely to discontinue than males, while HIV females were 14% lesser likely to discontinue compared to men. The ART results are in line with other studies, which suggested that men are at higher risk of discontinuation in treatment than women (Wools et al, 2006; Calmy et al, 2006; Lawn et al, 2006). Evidence supporting the higher rate of discontinuation among T_2DM females than males is scarce and more studies are required to explain the variation.

The present study depicted rates of discontinuation across age clusters. The rate for ≥ 40 year cluster was 2.24 and 1.28 per 1000 patient-days in T2DM and ART respectively, while those for < 40 year cluster were, 2.76 and 1.96 per 1000 patient-days for T2DM and ART respectively. The rate of discontinuation is higher in T2DM than ART, which is in line with our hypothesis. Most of the patients who discontinued T2DM treatment were ≥

40 years in age, while in ART, the vast majority of patients who discontinued were < 40 years in age. This is not surprising, following the baseline demographic characteristics of the study, where the majority of patients initiated on ART were < 40 years in age and those on T2DM treatment were ≥ 40. Alternative explanation could be due to epidemiology of HIV and T2DM, where the age cluster < 40 years is more at risk of HIV infection (more sexual active) and T2DM risk increases markedly with age (Denys and David, 2004).

The observed discontinuation rates and reasons for discontinuation are fairly consistent with other sources in literature. Cesar et al (2010) et al, for example, reported in their study that about 28 percent of 5,026 patients who initiated ART in a Latin American and Caribbean cohort switched their first line treatment one year after starting, mostly due to adverse events.

Studies reporting on frequency and impact of drug stock outs are scarce in sub-Saharan Africa. No studies focusing on T2DM and/or a comparison of T2DM and ART in this respect could be retrieved. In Rwanda, Fischer et al, 2006 and in Cote d'Ivoire, Pasquet et al, 2010 reported mainly on ART adherence indicating that drug stock outs led to 10%-52% of ART discontinuations. The current study showed that stock outs led to 5.4 % of ART and 26.1% of T_2DM discontinuations. The variations between these studies may change over time and healthcare setting too. Further explanation could be due to differences in definitions of drug stock outs. Since we could not assess some of the reasons for treatment discontinuation for several patients in medical files and databases, which were not recorded, the proportion of those affected by drug stock outs could be even higher than the current 26.1% in T_2DM and 5.4% in ART. Although drug stock out lists were scrutinized at the study Centre pharmacy and possibly 5 drug stock outs yielded to possibly have affected T_2DM treatment and none for ART, this was still much lower than reported in the studies mentioned above.

The higher contribution of drugs stock out to T_2DM treatment switches and discontinuations is in line with our hypothesis, that T_2DM treatments were less available, which could be explained by the structural differences within the KEMSA supply chain. This argument is in line with the results from the study done by Cameron et al who reported less availability of chronic disease medicines as compared to acute disease medicines including ART. Also from the present study, 22.7% of discontinuities (temporary and complete) were contributed by financial issues such as patients unable to pay for medicines due to higher copayments at the facility, which supports our former claims that T_2DM treatments are less financially accessible and unaffordable. Indeed, for T_2DM treatment, SRF (as per the conceptual framework) contributed to most of the treatment discontinuities.

The frequency of drug stock outs and rates of discontinuation between HIV and T_2DM treatments may partly be attributed to structural problems and to differences in funding between the two treatments at the national level. The Presidential emergency plan for AIDS relief (PEPFAR), the Global Fund and the government through KEMSA have been at the fore front to fund HIV treatment, while T_2DM treatments are funded solely by the government budget. Following the current global economic crisis, most governments and international organizations have withdrawn funding on treatment programs in low and middle income countries (BBC, 2011). For HIV, the Global fund has pledged to support treatments for only those already enrolled on ART and no more on starters. Moreover, recently the USA ambassador Scott, affirmed that PEPFAR budget will be slashed after 2 to 3 years. He further reiterated, " we believe that we have an obligation to help, we do also believe that the Kenyan government has to take more responsibility as do all African nations.....We do not want to make the abnormal normal". We foresee from these trends, drug stock outs and treatment discontinuations may exacerbate, if sustainable interventions are not sought.

In the current study, ART single dose formulations were more frequently out of stock than combined or fixed dose formulations. For fixed dose regimens, drug stock outs were due to D4T/3TC/NVP. Nevirapine and other fixed and combined dose formulation were regularly in stock. This contrasts with the Pasquet et al (2010) study in Cote d'Ivoire which reported in their ART cohort, that most stock outs that occurred frequently were as a result of nevirapine and zidovudine/lamivudine, while fixed dose D4T/3TC/NVP was always in stock. This differences may be attributed due to the current WHO updated guidelines on ART (WHO, 2009),which recommended that sub-Saharan countries adopt the use of tenofovir or zidovudine based first-line treatments instead of those with stavudine, with the aim to avoid drug toxicity due to stavudine. Kenya phased out the use of stavudine on 6th December 2010, as a result of the recommendation.

The current results showed that T_2DM treatment stock outs frequency was recorded to be higher with sulfonylurea and thiazolidinedione derivatives. Moreover, clinicians prescribed originator and branded treatments for T_2DM which were not distributed by KEMSA leading to increased chances of discontinuity of treatment. This can be explained because KEMSA procures and distributes glibenclamide and metformin mainly among other oral anti-diabetic generic treatment. Further, stock outs could be due to a lack of national guidelines that recommend a standardized first line therapy for all patients starting treatment and generic prescribing policies, which are effective at the health facility level and adhered to by prescribers.

The current study results depicted reduced effects on treatment discontinuation, despite the stock outs in ART, which were mainly recorded for single dose ART treatments regimens. The study pharmacy reports indicated that during the period of drugs stock out, alternative fixed dose or combined dose treatment regimens replaced the out of stock treatment, and in case no replacement was possible then switching treatment regimen was

encouraged rather than a discontinuation. Thus, fewer discontinuities due to drug stock outs were realized for most of the HIV patients. For T_2DM treatments, most treatment regimens were out of stock and so replacement was not possible and thus might have contributed to treatment discontinuity.

Stock outs can be prevented if resource poor settings adapt sustainable strategies to prevent T_2DM treatment stock outs, and even further decline those of ART by ensuring proper management and establishment of guidelines to have all patients initiated on treatment on fixed dose standardized regimens. Harries et al (2007) illustrated a model that ensures rational forecasting of ART treatments in Malawi, which suggests the use of fixed dose regimens as standard combined ART first line treatment. Similar model has been adopted by the country's tuberculosis control program. So far, the authors did not report any stocks outs during the follow up. Similarly, Pasquet et al (2010) indicated that standardizing first line treatments reduced drug stock outs and treatment discontinuations. Evidence in this area is scarce and further studies are required on evidence based solutions to prevent drug stock outs.

Medical records of a number of patients that discontinued treatment indicated that clinicians prescribed originator and branded T_2DM treatments which were not supplied by KEMSA. And at times, originator and branded products that had generic alternative at the facility, for example, a number of patients had been prescribed 'Glucophage' an originator for metformin which is more costly than generic metformin, 'glibomet' (a branded product of glibenclamide and metformin) while metformin and glibenclamide generic equivalent were in stock at the study Centre. For instance, some discontinuities were due to 'glucophage 850 mg'. Though, the national drug policy allows for generic substitution at the point of delivery unless indicated 'do not substitute', this was not possible for some patients, since the prescribed strength of treatment was 850 mg for 'Glucophage', and only the

strength of generic metformin available for metformin was 500mg at the pharmacy. Also some patients were on 'glurenorm' (branded product for gliclazide), pioglitazone and gliquidone which were not in stock which resulted to discontinuation. . This prescribing of drugs that are not in stock may be due to lack of proper communication at the health facility between clinicians and pharmacists regarding what is in stock and possible alternatives. Therefore proper communication and follow up of patients between the facility clinic and pharmacy is essential and could avoid possible treatment discontinuity.

KEMSA supplies mostly generic and some branded products. In their Lancet paper, Cameron et al (2009) showed that branded medicines are usually more expensive than the lowest priced generics. Thus, value for money can be realized and a lot saved if KEMSA could switch from procuring brands and focus entirely on generics where alternatives exist. Cameron et al (2012), similarly confirms the value in health care costs that can be gained if people could switch from brands to generics.

In addition, if patients discontinue because of financial constraints, which means that drugs are in stock but too expensive for patients, having cheaper generics than branded products could make most T_2DM treatments including other chronic disease treatments affordable at KEMSA level and at the patients level, as well as avoid discontinuities due to financial constraints for patients. Moreover, at KEMSA level, this will mean that the quantity of medicines procured by pharmaceutical budget will be 6 times more than when paying for branded products and thus could lead to less drug stock outs.

The HbA1c and CD4 count results were not consistently recorded in the patients' files and databases at the time before and after discontinuation and so no reliable information was retrieved for these values as planned. But it is

an important issue, since treatment discontinuity affects the patient and could yield serious clinical outcomes. Therefore clinicians should monitor the effects of discontinuation and so further research work is required in this area to understand the clinical outcomes of treatment discontinuities.

The study had several limitations. First, the results can't be generalized because it only includes one health facility and country, and healthcare systems vary in setting and structure. However, it is likely that other facilities in Kenya and other sub Saharan countries have similar experiences. Second, the sample size captured was small and we did not calculate for sample size. Therefore, in some cases observed trends did not reach statistical significance and should be interpreted with caution. Third, several patient files and databases used were incomplete and so we were not able to assess the reasons for discontinuations for some patients. This was the case in approximately 12% and 20% of all discontinuities in T2DM and in HIV respectively. This might have underreported the proportion of subjects of whom treatment switches or treatment discontinuations who were due to drug stock outs and other reasons, thus not heavily affecting the association presented between drug stock out switched regimens and treatment discontinuations. That in itself is an important finding from a clinical point of view that needs to be reported and needs action in daily clinical practice. On the other hand, drug stock out lists had been maintained quite well and adequately reflected the actual situation in the pharmacy. Fourth, since the study design was retrospective and mainly focusing on patient records it was not possible to find out those patients who received treatments elsewhere, for example private pharmacies or other health facilities to continue their treatments.

The conceptual framework was helpful in guiding the study though some reasons could not be easily classified, for instance, patient stopped

treatment because of other illnesses like anemia, tuberculosis. Others reasons included patients being too ill, weather changes like raining, and feeling better. Some reasons for discontinuities were not indicated and so for the analysis a category of others was introduced, to include other reasons that the framework did not capture.

8.0. CONCLUSION

This study indicates that patients on T_2DM treatment were at a higher risk of discontinuation than those on ART and that drug stocks affects a bulk proportion of patients on T_2DM treatment and lesser percentage of those on ART at the Coast provincial general hospital in Kenya. The effect due to stock outs was significant and standardizing first line treatment regimens and adopting policies to promote use of generic medicines may avoid further drug stock outs and its outcomes.

9.0. RECOMMENDATIONS

9.1. Policy implementation

Policies should be implemented: First, the ministries of health should standardize first line treatment regimen and update treatment guidelines to prevent drug stock outs and its outcomes. In case stock outs happen for standardized first line regimens, written protocols should be available to offer an alternative provision without necessarily affecting patients' treatment outcomes. Such protocols should ensure favorable patient outcomes, for example switching to a second option would be better than a temporary or complete discontinuation. Secondly, Policies that encourage procurement and use of generic medicines should be implemented to ensure affordability of treatments at the patient level and value for money at the KEMSA level. Thirdly, Copayments/ higher user fees should be standardized or removed to avoid treatment discontinuity due to financial constraints and ensure financial accessibility of treatments.

9.2. Practice

At the Coast Provincial General Hospital, as part of good clinical practice, patient records need to be filled completely to ensure the patients information is up to date and reliable when required for patient follow up and research. This includes noting reasons for treatment discontinuities as well as clinical effects of discontinuities in terms of clinically important endpoints such as CD4 count for ART and HbA1c for T2DM. Also there should be good communication between the T2DM and HIV clinics and the pharmacy within the health facility, to ensure proper follow up of patients and to ensure that alternative treatment are well known by clinicians, which are in stock and out of stock, which may avoid prescribing treatments that are out of stock.

9.3. Further Research

Further research is needed: First, the study may need to be repeated with more patients and more facilities (including both public and private health facilities) to enhance generalizability and power. It is also important to understand why T2DM females are at higher risk of discontinuation than males. Second, a study needs to be done to fully understand the impact of influencing factors on discontinuities and measure CD4 and HbA1c results to determine their clinical outcomes. Third, an operational study needs to be done to understand why clinicians prescribe originator and branded products that have alternative generics within the health facility. Furthermore, a study following up patients, whether they get alternative treatment from private pharmacies and health facilities when not available at the health facility pharmacy and the possible outcomes will be necessary to have a clearer picture. Finally, studies that discuss evidence based strategies to avoid drug stock outs in chronic diseases also are required.

9.4. Supply chain structure

The government through the ministries of health should restructure and strengthen the procurement and distribution process within KEMSA and the supply chain to ensure essential ARTs and T_2DM treatments are supplied regularly and in an uninterrupted manner guided by evidence based criteria. This could be possible by ensuring KEMSA functions as an autonomous body, with the mandate and authority to make decisions regarding medical supplies and pharmaceuticals. Further, KEMSA should take responsibility of the funds to procure medical and pharmaceutical supplies and be fully accountable in case of any irregularity. Equally the capacity within KEMSA needs to be upgraded to meet the challenges of the task (human resources and infrastructure).

9.5. Sustainability

The government through the ministries of health, need to prioritize equitable access of essential medicines to its citizenry, and in ensuring sustainability and preventing a re-emerging crisis of ART and other donor supported treatments including T_2DM treatments, the total pharmaceutical expenditure (TPE) budget should be increased to guarantee equitable supply of essential medicines to all health facilities in Kenya. Procurement and supply should switch entirely to generic medicines which is in line with the pharmacoeconomic principles, so as to get maximum benefits in health and value from the scarce resources available, following drying of donor funding. The government also needs to create an enabling environment to promote local manufacturing of the pharmaceutical products.

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APPENDICES

Appendix 1 Reasons included in the categories for T2DM treatment discontinuation

Structural related	Treatment related	Socioeconomic & community related	Individual related	Others
Out of stock	Eye review	Travel problems	Pregnancy	Not indicated
Financial	Too ill/felt better	Far residence	Felt better	
	Side effects	Family issues	Forgot/missed/defaulted	
	Other illness	Out of town		
	other medical:			
	check up			
	ENT			
	Dental			

Appendix 2 Reasons included in the categories for ART treatment discontinuation

Structural related	Treatment related	Socioeconomic & community related	Individual related	Others
Out of stock	TB	Travelling problems	Pregnancy	Not indicated
Financial constraints	Anemia	Weather changes	Forgot	
	Pregnancy	Stigma	Stopped	
	Felt better	Out of town	Missed	
	Too ill	Career related	defaulted	
			Depression	
			Substance abuse	
	Adverse events:	Family issues:		
	Nausea	Funeral		
	Vomiting	Sick relative		
	Steven Johns S.			
	CNS manifestations			

Appendix 3 Examples of the T2DM drugs included in the categories below as per the study

Sulfonylureas	Thiazolidinedione's	Others
glipizide	rosiglitazone	glynase
gliclazide	pioglitazone	glibomet
glimepiride		glucovance
glyburide		
glibenclamide		
gliquidone		

Appendix 4 The drugs prescribed as originator or branded and discontinuity as per the study

Name of drug	Generic name/INN	Cohort	No of discontinuities
Glucomet	metformin	T2DM	2
Glucophage	metformin	T2DM	12
Glurenorm	gliquidone	T2DM	2
Glibomet	Glibenclamide+metformin	T2DM	2
gliben	glibenclamide	T2DM	2
Glucovance	glibenclamide	T2DM	1
Dimicron MR	gliclazide	T2DM	1

Appendix 5 Table for rates of at least one discontinuation by sex, age and risk ratios between sex and age

Description	Disc in treatment n (%)		Rate*	95% CI	RR*	95% CI
	Yes	No				
T2DM (n =167)						
Disc (overall)	95 (56.9)	72 (43.1)	0.57	0.49-0.64	-	-
Sex						
Female	56 (61.5)	35 (38.5)	0.62	0.51-0.71	1.20	0.91-1.58
Male	39 (51.3)	37 (48.7)	0.51	0.40-0.62	1	
Age (years)						
< 40	15 (46.9)	17 (53.1)	0.47	0.31-0.64	0.79	0.53-1.17
≥ 40	80 (59.3)	55 (40.7)	0.59	0.51-0.67	1	
ART (n= 342)						
Disc (overall)	163 (47.7)	179 (52.3)	0.48	0.42-0.53	-	-
Sex						
Female	103 (46.8)	117 (53.2)	0.47	0.40-0.53	1.00	0.76-1.20
Male	60 (49.2)	62 (50.8)	0.49	0.40-0.58	1	
Age (years)						
< 40	116 (50.7)	113 (49.3)	0.51	0.44-0.57	1.22	0.95-1.57
≥ 40	47 (41.6)	66 (58.41)	0.42	0.42-0.59	1	

per 1000 person time; Disc: Discontinuation; RR: Risk ratios of discontinuation within T2DM and ART.

Appendix 6 Table for relative risk of discontinuation by sex and age between ART and T2DM cohorts

	T2DM (n =167)			ART (n= 342)				
Description	Disc in treatment n (%)		Rate	Disc in treatment n (%)		Rate	RR*	95% CI
	Yes	No		Yes	No			
Disc (overall)	95 (56.9)	72 (43.1)	0.57	163 (47.7)	179 (52.3)	0.48	1.19	1.00-1.42
Sex								
Female	56 (61.5)	35 (38.5)	0.62	103 (46.8)	117 (53.2)	0.47	1.31	1.06-1.63
Male	39 (51.3)	37 (48.7)	0.51	60 (49.2)	62 (50.8)	0.49	1.04	0.79-1.39
Age (years)								
< 40	15 (46.9)	17 (53.1)	0.47	116 (50.7)	113 (49.3)	0.51	0.93	0.63-1.37
≥ 40	80 (59.3)	55 (40.7)	0.59	47 (41.6)	66 (58.41)	0.42	1.42	1.10-1.85

Disc: Discontinuation. RR* Relative risk of discontinuation

Appendix 7 Table for absolute rates of discontinuation

	T2DM (n=167)			ART (n=342)		
	n (%)	Absolute rate	95% CI	n (%)	Absolute rate	95% CI
Overall 1st disc	95 (56.9)	0.57	0.49-0.64	163 (47.7)	0.48	0.42-0.53
Switched treatment	7 (4.2)	0.04	0.02-0.09	34 (9.9)	0.99	0.07-0.13
Temporary discontinuation	61 (36.5)	0.37	0.30-0.44	113(33.0)	0.33	0.28-0.38
Complete discontinuation	27 (16.2)	0.16	0.11-0.23	16 (4.7)	0.05	0.03-0.08

Appendix 8 Table for relative risk of discontinuation by type between ART and T2DM cohorts

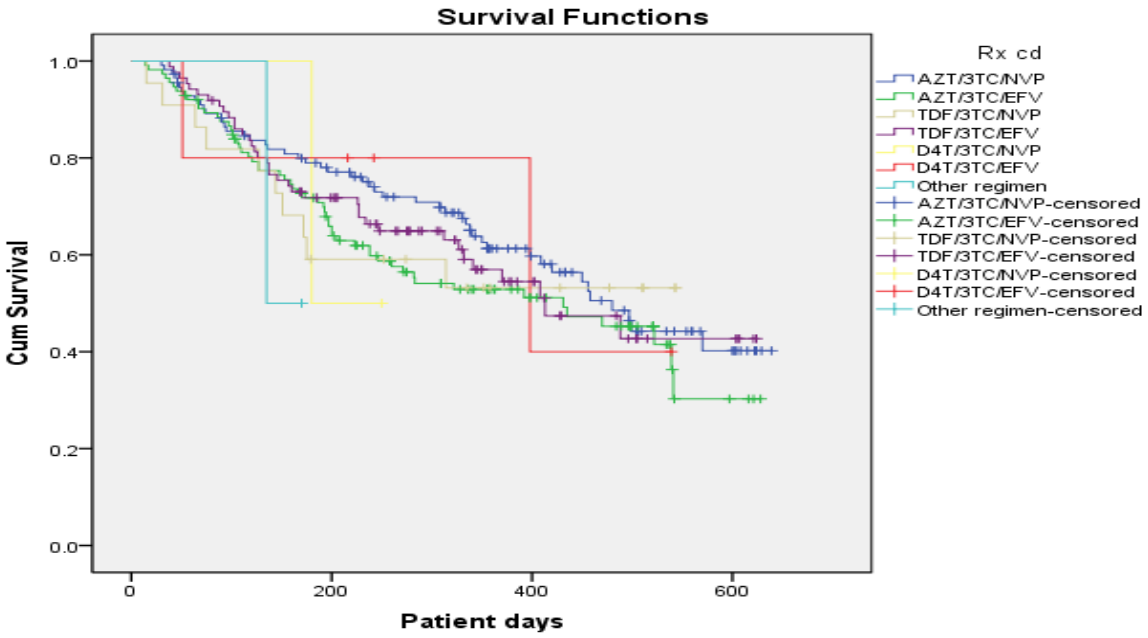
	T2DM (n=167)		ART (n=342)			
	n (%)	rate	n (%)	rate	RR*	95% CI
Overall 1st disc	95 (56.9)	0.57	163 (47.7)	0.48	1.19	1.00-1.42
Switched treatment	7 (4.2)	0.04	34 (9.9)	0.99	0.42	0.19-0.93
Temporary discontinuations	61 (36.5)	0.37	113(33.0)	0.33	1.12	0.86-1.42
Complete discontinuation	27 (16.2)	0.16	16 (4.7)	0.05	3.40	0.92-6.23

Appendix 9 Table for rates of discontinuation by treatment started and drugs stock out

Rates of discontinuation in ART and T2DM treatments

Treatment regimen started	Disc in general n (%)		Rate	95% CI	Disc due to drug stock outs		Rate	95% CI
	Yes	No			Yes	No		
Oral anti-diabetics drugs	N=95	N=72	-	-				
Metformin only	41 (41.4)	58 (58.6)	0.41	0.32-0.51	1	98	0.01	0.00-0.06
Metformin + Sulfonylureas	38 (79.2)	10 (20.8)	0.79	0.66-0.88	17	31	0.35	0.23-0.50
Metformin + thiazolidinedione	6 (85.7)	1 (14.3)	0.86	0.47-0.99	6	1	0.86	0.47-0.99
Sulfonylureas + thiazolidinedione	5 (100.0)	0 (0.0)	1.00	0.51-1.00	4	1	0.80	0.36-0.98
Others	5 (62.5)	3 (37.5)	0.63	0.30-0.87	1	7	0.13	0.00-0.49
Antiretroviral drugs	N=163	N=179						
AZT/3TC/NVP	63 (55.8)	50 (44.3)	0.55	0.47-0.65	1	112	0.01	0.00-0.05
AZT/3TC/EFV	52 (46.0)	61 (54.0)	0.46	0.37-0.55	2	111	0.02	0.00-0.07
TDF/3TC/NVP	8 (36.4)	14 (63.6)	0.36	0.20-0.57	0	22	0.00	0.00-0.18
TDF/3TC/EFV	32 (37.2)	54 (62.8)	0.37	0.28-0.48	0	86	0.00	0.00-0.05
D4T/3TC/NVP	2 (100.0)	0 (0.0)	1.00	0.29-1.00	2	0	1.00	0.29-1.00
D4T/3TC/EFV	5 (100.0)	0 (0.0)	1.00	0.51-1.00	4	1	0.80	0.36-0.98
Others	1 (100.0)	0 (0.0)	1.00	0.17-1.00	0	1	0.00	0.00-0.83

Appendix 10 Figure for Kaplan-Meier plot for time to discontinuity by treatment started in all ART treatment started



Appendix 11 Figure for Kaplan-Meir plot for time to discontinuity by SRF category in ART and T_2DM treatments