Evaluation of Second Line Antiretroviral Treatment Outcomes and Determinants in Epworth, MSF-OCA HIV Cohort, Zimbabwe

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Study proposal

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List of abbreviations

ADE	Adverse drug events
AIDS	Acquired immune deficiency syndrome
ATV	Atazanavir
ART	Antiretroviral Therapy
cART	Combined Antiretroviral Therapy
EPMS	Electronic Patient Monitoring System
HIV	Human immunodeficiency virus
LPV	Lopinavir
LTFU	Lost to Follow Up
MSF	Medicines sans Frontiers/ Doctors without borders
NRTI	Nucleoside reverse transcriptase inhibitors
OCA	Operation Center Amsterdam
PI	protease inhibitor
PLHIV	People living with HIV
R	ritonavir
RNA	Ribonucleic acid
SL	Second line
VL	Viral load
WHO	World Health Organization

Summary

Epworth poly-clinic is found in Epworth district, Harare. It is a clinic jointly run by Epworth local board (on behalf of the Ministry of Health and Child Care) and Médecins sans Frontiers (MSF). One of the major MSF activities in the clinic is early detection and management of patients who fail first line ART. Patients with elevated viral load (VL), HIV RNA greater than 1000 copies/ml, undergo five to six sessions of two weekly enhanced adherence counseling (EAC) support. After enhanced adherence counseling sessions, those with elevated repeat VL test result are then switched to second line ART. Since the number of patients on second line ART is growing, there is an increased need to know the outcomes of second line ART and predictors of treatment failure.

The main objective of this study is to evaluate the prognosis and determinants of second line ART regimen for cohort of HIV patients in Epworth MoH/MSF poly-clinic, Zimbabwe. The study will also identify cumulative incidence of SL ART treatment failure through clinical, immunological or virological criteria at 6, 12, 24 and 36 months of second line ART initiation for a cohort of patients enrolled from March 2009 to January 2016 in Epworth poly-clinic.

This is a retrospective cohort study of patients on second line ART in Epworth poly-clinic enrolled since 2009. We describe baseline characteristics and outcomes of treatment using descriptive analysis. Multivariate cox proportional hazard modeling is used to model predictors of time to treatment failure. Kaplan–Meier curve is used to calculate cumulative incidence of treatment failure at 6, 12, 24 and 36 months of second line ART initiation.

The study is expected to be finished and communicated to relevant stakeholders in December 2016. The report will be published on peer reviewed journals in January 2017. All the costs needed for this study will be covered by MSF OCA.

Introduction

Zimbabwe initiated its national ART program in April 2004. According to Zimbabwe national HIV/ AIDS report 2015, the total number of PLHIV receiving ART was 787,980 and 63.4% of eligible adults were on ART by the end of 2014. Zimbabwe adopted HIV viral load (VL) testing as gold standard to monitor patients on ART in December 2013 but roll out in the country is still very low, achieving only 3% of the expected patients in 2014. In all, routine VL monitoring in first, second and third line ART has been remained a challenge in the country.

MSF-OCA started working in Zimbabwe in 2005 on a Water and Sanitation project in Harare at Hopely Farm. The HIV program in Epworth Poly-clinic developed in 2007, giving services to people living in and around Epworth. The total population, area and density of Epworth district, according to 2012 census, were 167,462, 35.35km2 and 4,736.7 inh/km2 respectively.
From a comprehensive HIV program, long term ART management is been growing with the years and maturation of the ART cohort and currently the number of patients in need of second and third line treatment is increasing. Unfortunately, access to second and particularly third line treatment regimens remains very limited not just in Zimbabwe, but in many other resource limited settings. Epworth Poly-clinic has ever enrolled more than 13,000 patients in ART program. Second line ART (containing a ritonavir-boosted PI) has been available in our setting since 2009 and by June 2016 about 550 patients are receiving it. Timely transition between ART lines and adequate regimen selection, guarantee long term positive outcomes in ART recipients. In this regard routine VL monitoring is proven a key tool for retention in care, in conjunction with immunological and clinical monitoring.
In Epworth Clinic, our model of care requires that all patients are switched from first line ART to second line ART based on a comprehensive package of care that includes laboratory and clinical parameters. All patients with elevated VL levels >1000copies/ml are referred to counsellors for enhanced adherence counseling as per the standard of care. A patient passes through an average of 6 adherence counseling sessions in 3 to 4 months. After that, a second VL test is repeated and if the result remains 1000copies/ml, the patient is switched to second line ART. MSF uses WHO recommended second line ART regimen for treating patients who failed first line ART in Epworth poly-clinic.

There is limited knowledge about the clinical, immunological and virological outcomes of patients who are on second line ART regimen in our setting. Also little is known about the predictors of treatment failure in our clinic. Understanding these components of our program will provide us with a great opportunity to take operational decisions to maintain the quality of or ART service delivery and to offer the MoH a platform to learn about how to plan treatment strategies and forecast treatment options beyond first and second line therapy.

This study aims to evaluate the second line treatment outcome and identify predictors of treatment failure among patients on the second line antiretroviral treatment. As Epworth is one of the ART centers with high number of patients on second line ART, conducting this study at this center is an added value.

This study is not comparing the outcome of second line HIV treatment between children and adults, treatment outcome between ATV and LPV based second line regimens. There should be further study on those topics to get a better overview about these regimens in Zimbabwe.

Study hypothesis

Second line ART based on ritonavir- boosted Lopinavir (LPV/r) or Atazanavir (ATV/r) provided in our setting has good clinical, immunological and virological outcomes if initiated timely after first-line failure and provided within our simplified model of care.

Objectives

General Objective

To describe the longitudinal outcomes and identify risk factors for unfavorable outcomes in a cohort of second line ART patients enrolled in Epworth MoH/MSF poly-clinic in the period of March 2009 to January 2016.

Specific objectives

1. To describe the MSF model of care for long term ART retention in Epworth.
2. To describe the baseline characteristics of the patients started on second line ART regimen.
3. To describe treatment response to SL ART through clinical, immunological, and virological treatment outcomes at 6, 12, 24 and 36 months intervals after initiating second line ART.
4. To describe rates and types of adverse drug events (ADE) reported while on second line ART.
5. To describe genotype profile in those failing second line ART.

Literature review

HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. At the end of 2015, there were approximately 36.7 (34.0–39.8) million people living with HIV and 2.1 (1.8–2.4) million people becoming newly infected with HIV globally. Sub-Saharan Africa is the most affected region, with 25.6 (23.1–28.5) million people living with HIV in 2015, accounting for two-thirds of the global total of new HIV infections. At the end of 2013, more than 11.7 million people were on antiretroviral therapy (ART) in low and middle income countries, with only 6% of all individuals receiving first-line therapy in sub-Saharan Africa needed to switch to second-line regimens in any given year.

Access to second-line antiretroviral therapy (ART) for HIV-positive patients remains limited in sub-Saharan Africa. WHO recommends a second-line ART for adults that contains two

nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI). On the course of treatment, viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure and if viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.
A study from Brazil showed that in a middle-income country with universal access to ART, having a detectable HIV RNA at the start of second-line ART, young age and low level of education negatively impact second-line outcomes and efforts should be put to find strategies would that help maximize the durability of these regimens.

In low and middle income settings, the vast majority of patients on first-line ART with immunologic or virological failure are still not detected and such patients continue to take the failed regimen for long time, amplifying resistance to other drugs and minimizing treatment options for the future. The need to lengthen the durability of the each ART regimen is at the base of the WHO recommendation to use viral load as a preferred treatment response monitoring strategy. A recent collaborative analysis on strategies to monitor and switch of ART in adult cohorts in sub-Saharan demonstrated that ART switch happened late in the absence of routine viral load monitoring and transition between first and second lines was more common and happened earlier after initiation of ART with targeted or routine viral load testing.

In the overall strategy for treatment of patients on second line ART, a comprehensive package of care that includes attention to long-term adherence plays a major role in viral (re)suppression. Novel adherence interventions in South Africa may usefully target patients on second-line ART to prevent accumulation of minor PI drug mutations and achieve viral re-suppression. Another study from Vietnam also indicated that adherence was one of the factors affecting outcome of second-line treatment and overall treatment failure rate using immunological and clinical criteria is 18.4% after a median follow-up of 29 months. Early AIDS-associated death is the main result of treatment failure and is predicted by older age, history of Intra-venous drug Use, lower CD4 count at therapy switch, and medication adherence levels <95%. Finally, in a close by similar setting in a hospital-based cohort in Harare conducted on first line ART also showed that poor adherence to treatment was related to early treatment failure.

Age is a factor that heavily impacts on frequency of ART failure and adolescents on ART are a key population in this regard: adolescents are at high risk of treatment failure and addressing factors associated with poor adherence in this group should be a priority to maximize viral suppression and long term treatment outcomes.

Study design and methods

Study design

This is a retrospective cohort analysis of a cohort receiving second line ART in our operational setting in the Epworth MoH/MSF HIV program.

Study site and setting

The study site is Epworth Poly-clinic which provides medical service to people living in Epworth. Epworth is a township located about ten kilometers outside Harare city and administered by Epworth local board. It is a densely populated area with a total population of 167,462 according to 2012 census. The clinic has been providing ART program since 2007 and more than 13,000 patients were ever enrolled in the program since then. Patients are initiating first line ART according to Zimbabwe MoH ART treatment guideline. MoH runs first line ART program in the clinic. MSF takes over patients who failed first line ART for management and follow up. Since March 2009, 550 patients where switched from first line regimen to second line regimen. CD4 count is done at the lab in Epworth poly-clinic at second line ART initiation and repeated every six months in the subsequent follow up visits. HIV RNA test is done at National Microbiology Reference Laboratory (NMRL) and Beatrice Infectious Disease Hospital Laboratory (BRIDH) in Zimbabwe. HIV RNA results are available at the baseline and repeated six months after initiation. HIV RNA test is repeated every year in the subsequent visits. Patient treatment and other laboratory tests are done according to standard of care. Patient on second line ART has clinic review by MSF HIV doctor once in three months. MSF primary care counselor do adherence counseling and pill count during each three monthly follow up visit. The main activities of MSF in Epworth Poly-clinic are management and follow up of patients on second line ART, pediatrics and adolescents HIV care, severe immunocompromised patients care and MDR TB treatment.

Study participants

Adult and pediatric patients who commenced second line ART in Epworth Poly-clinic from 1st of March 2009 to 30th January 2016 will be included in the study. Pediatric, adolescents and adult ages will be defined by the new 2016 WHO age groups . We estimate the size of the cohort in the study will be approximately 700 patients.

Source of data, data collection and management:

When a patient comes for a clinic visit, primary care counselor and clinician collect demographic, adherence and clinical data using MoH HIV follow up booklet. All data from this paper based booklet are transferred to electronic patient monitoring system (EPMS) database used by MoH by 3 trained data encoders. Data on second line ART has been collected since 2009 and the last day to update the database will be on 30th of August 2016. Data on adherence is collected using pill count and it is documented as percentage of pills taken by the patient over total pills dispensed to the patient. The EPMS has an in-built data quality monitoring system. Data is exported from EPMS and imported to STATA for further data cleaning and analysis. Data related to HIV RNA result will be obtained from NMRL and BRIDH database. HIV RNA database from the above two laboratories will be merged with the database from EPMS using STATA software. STATA version13.1 will be used for all data analysis.

Variables, outcomes and data analysis strategies:

Data will be abstracted from existing patients' medical records. We will measure negative treatment outcomes, defined as time from second-line ART initiation to death, LTFU or to a new or reoccurrence of a virological, immunological or a clinical failure event, whichever occurred first. Immunological failure is defined by the WHO as a decrease of CD4 count to or lower than baseline or a persistent CD4 count of<100 cells/mL after at least 6 months of continued ART. Clinical failure is defined as new occurrence or reoccurrence of a WHO stage IV disease after six months of effective treatment. Virological failure is plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support. LTFU is defined as loss of patient from treatment for 90 days after the last scheduled appointment. For the analysis, event-free transferred patients will be censored at the time of transfer.

The following lists of covariates are pre-defined for analysis: Sex, age at second line ART initiation, education, marital status, CD4 at second line initiation and follow up, VL at second line initiation, interval between first high VL and initiation of second line ART regimen, BMI at second line initiation, WHO staging at second line initiation, TB status, adherence (percentage) and duration on first line regimen.

Univariate analysis using log-rank test of equality across strata for all the categorical predictors and univariate Cox proportional hazard regression for continues variables, are used to analyze association between baseline factors and time to treatment failure. factors with P<0.3 in univariate analysis will further be analyzed in a multivariate cox proportional hazard modeling using backward step-by-step exclusion, removing the least significant variable, until all remaining variables have a P<0.05. Kaplan-Meier curves will be used to ensure that all variables included in the model fulfill the proportional hazards assumption. The cumulative incidence of treatment failure rates at 6, 12, 24 and 36 months and corresponding 95% confidence intervals will be calculated using the Kaplan–Meier method.

The description of the model of care will gather information from project-based documents.

Table 1 briefly outlines the list of variables considered for this analysis:

Table 1 List of variables

Demographic variables	Descriptions	Source of data
Demographic variables	• Age at the second line initiation • Sex • Marital status • Level of education • Indicator of social status or economic capacity • Distance to the clinic (if available routinely) • Transfers in failing or on second line (if available)	EPMS, patient booklet
Medical	**Descriptions**	**Source of data**

variables		
Physical examinations	• Weight • BMI • W/H • MUAC	EPMS
Clinical data	• WHO staging at the beginning of second line ART • WHO staging at the time of outcome	EPMS
First line ART	• Last recorded first line ART regimen the patient was taking • Duration on first line ART (mean, interquartile range and SD) • Recorded NRTIs substitutions during first line	EPMS
Second line ART	• Most recent second line ART regimen • interval between first viral load and second VL in management of treatment failure • Time from second VL.1000 and initiation of second line ART regimen	EPMS, BRIDH & NMRL VL database
TB status	• TB status while on second line ART • Date of TB diagnosis • TB and ART co-treatment.	EPMS, TB registers
Adherence	• Percentage of adherence by pill count while on second line ART • Disclosure status	EPMS, patient booklet (counseling forms)
Laboratory tests (CD4 and VL)	• CD4 at second line initiation and follow up • VL at second line ART initiation and follow up	EPMS, BRIDH & NMRL VL database
Side effects	• Recorded adverse drag events while on second line ART	patient booklet
Outcome variables	**Descriptions**	**Source of data**
Negative treatment outcome variables	• Number of deaths in second line ART patients • Number of LFU in second line ART patients • VL >1000 rate • Stage T4	EPMS, BRIDH & NMRL VL database
Positive treatment outcome variables	• Number of active and in care second line ART patients • Viral load suppression rate in second line ART • T staging • Immunological improvements	EPMS, BRIDH & NMRL VL database
Time to treatment outcome	• Time from second line ART initiation to treatment outcome (positive or negative outcomes)	EPMS
Descriptive analysis	**Descriptions**	**Source of data**
Model of care	• Number health care workers by cadre • Patient flow description • Best practices	Clinic administrative documents, clinic observation, clinic staffs

Outcomes definition

Table 2 describes outcomes for this analysis:

Table 2 outcomes

Outcome	definition
Positive	• Active in care
Negative	• Death • Lost to follow up (LFU): defined as a patient who is lost to care for >90 days • Treatment failure as defined in the WHO guidelines (clinical, immunological and virological)

Collaborative partnership

MSF has had a robust relationship with the Zimbabwe Ministry of Health and Provincial Health Authorities that allowed implementation of health activities and Health Policy design along the years. At this crucial time of the MSF project in Zimbabwe the partnership includes description of lessons learnt, successes and challenges in collaboration with key representatives of the regional/national ART program. A team of relevant MSF staff has been selected to support this project and the relevant counterparts in the MOH will support and contribute their time to critically appraise the results, narrate and extract conclusions from the experience and contribute to the dissemination of the results at designated provincial, national and international forums.

Ethics and human subject issues

This research fulfils the exemption criteria set by the MSF Ethical Review Board (ERB) for a posteriori analyses of routinely collected clinical data, and thus does not require MSF ERB review. It will be conducted with permission from the Medical Director of the MSF Operational Centre Amsterdam. and MSF Scientific Ethical Review Boards. In addition, ethical clearance will be sought from medical research counsel of Zimbabwe (MRCZ).

Patient's data will be and coded in the database using a unique identifier. As this study is conducted on retrospective existing secondary data collected under programmatic conditions, individual consent will not be seeked.

Time frame

Finalization of the protocol and ethics reviews will happen during August and September 2016. Analysis and writing will be happen from September to November 2016 after we receive the needed approvals. In December 2016 final report will be finalized and shared with relevant stakeholders. Around the same time a paper will be submitted for publication on targeted peer reviewed journals.

activities	July 2016	Aug 2016	Sep 2016	Oct 2016	Nov 2016	Dec 2016	Jan 2017
Finalization of protocol and							
Proposal submission to MRCZ for approval							
Proposal submission to MSF OCA for approval							
Data cleaning, analysis and report writing							
Sharing final research report and submission for peer reviewed journals							

Benefits and risks of the study

Current HIV treatment strategy is a life-long decision and there is a need to understand how to best use the existing ART combinations to have positive outcomes, measured as viral suppression. Understanding second line ART treatment outcome and risks of second line treatment failure in the cohort of HIV patients in the Epworth project will build up to the existing body of evidence that documents best practices and bottlenecks in the care of these patients in low resource settings. Documenting our experience in Epworth is critical to guide program strategies and policy making in the Zimbabwe HIV Program. Moreover, it gives evidence for the national program forecast treatment options beyond second line therapy.

The Information will strengthen the relationship between the MoH and MSF-OCA in the spirit of collaboration to provide the best care possible for ART patients.

There are no risks for conducting this study, other than general operational risks for the whole program. There should be no harm to participants as this is a retrospective cohort analysis of routinely collected data in MSF's HIV project.

Confidentiality of the patients will be highly respected as no patient names or any other patient personal identifiers are used.

Results will also be communicated to the patients and the community using the existing channels of engagement in the project. IEC materials will be designed including simplified messages to distribute to the patients and their health care workers when attending clinical care. The community will be engage through the community support groups and simplified messages that focus on long-term adherence to therapy will be distributed.

Strength and weakness of the study

Strengths are related with the capacity of this study to generate evidence in an operational clinical setting. The findings can be relevant to many other similar settings, especially in Sub-Saharan Africa. Multivariate cox proportional hazard modeling will help to control confounder variables and identify the independent effect of covariate variable on the outcome.

This is a retrospective study and limitations include incomplete data and missing records. In this operational research project, however, we believe that the information will provides an accurate second line ART management best practices and challenges that will be comparable to similar settings. Although this is a clinic-recruited cohort, significant selection bias is unlikely as, during the study period, Epworth Poly-clinic functioned as the only point of access to second line ART in the surrounding areas.

This study is not intending to compare the second line HIV different treatment options between ATV/r and LPV/r.

Public health significance

Documenting the successes and bottlenecks within our *simplified* clinical environment can have a wider impact on programs that are expanding access to gold standard interventions (viral load roll out) and access to second and third ART lines in low resource settings.

This is a time where the core of the global HIV strategy uses the best ART combinations to 1) decrease morbidity and mortality in HIV-infected individuals and 2) decrease new HIV infections by decreasing viremias and, therefore circulating HIV viruses: "*ART for treatment and for prevention of transmission*". It is, therefore vital that programs understand the underlying factors that influence disengagement of the continuum of care in their local context.

This study aims to reveal key treatment success factors that assure long term viral suppression for patients, within the context of our model of care situated in a HIV high burden country. Moreover; it is a good opportunity to collaborate with the Zimbabwean MoH in ART program evaluation initiatives that will influence national and regional HIV strategies.

Dissemination plan

The ultimate goal of this proposal is to review the MSF ART model of care that aims to assure long-term retention in a high burden setting. Dissemination of results ambitions to have key messages available at relevant levels. We aim to benefit and generate change in individuals, communities, health care workers and policy makers. At individual and community level

simplified key messages will be extracted and disseminated using existing channels of communication, health care workers will be targeted in designated forums for continual medical education and relevant other meetings where lessons learnt will be disseminated. Lastly, policy makers will be targeted through existing regional, national and international technical working groups.
Information will also be disseminated within the MSF network to contribute to the existing body of knowledge.

Budget

Since this is a retrospective study utilizing secondary data, there would be little / minimum cost implication which will be covered by MSF OCA. Further costs may be related to publication fees.

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