Factors Associated with ART Outcomes among Adult (15+) Persons Living with HIV in Zimbabwe in the Multi-Month Scripting (MMS) Regime

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Introduction

Acquired Immuno Deficiency Syndrome (AIDS) continue to be a major global public health concern. There are an estimated 1.3 million people living with in Zimbabwe and 1,100,000 million are estimated to be on Antiretroviral Therapy (ART) by 2018, which translates to over 80% ART coverage [1]. This study explores the factors associated with ART outcomes among adult (15+) persons living with HIV in Zimbabwe.

A synopsis from literature on the subject

Below is a summary of the factors from prior studies across the globe.

Factors associated with treatment failure: Several studies have explored the factors associated with ART outcomes across the globe. The United States' Department of Health and Human Services (2013) reported that treatment failure may occur in PLHIV due to various risk factors. These include poor adherence to treatment, poor absorption of ARVs, previous treatment failure, drug resistance, co-morbidities, drug toxicity and drug interactions, poor health prior to initiation of ART, as well as substance abuse (e.g. tobacco smoking or excessive alcohol consumption) leading to poor adherence. Other studies [2-4] also seem to suggest that other factors such as advanced HIV disease, gender, ARV regimens low baseline CD4, age, and long periods on ART are strongly associated with treatment failure.

A study by Haile, et al. [5] investigated the predictors of treatment failure among adult ART clients in the Bale Zone Hospitals, South Eastern Ethiopia. The study used a retrospective cohort study from four hospitals of Bale zone. The study results showed that male ART clients were more likely to experience treatment failure as compared to females [AHR=4.49; 95% CI: (2.61 ± 7.73)]. In addition, lower CD4 count (<100 m³/dl) at initiation of ART was found to be significantly associated with higher odds of treatment failure [AHR=3.79; 95% CI: (2.46 ± 5.84)]. Similarly, bedridden [AHR=5.02; 95% CI: (1.98 ± 12.73)] and ambulatory [AHR=2.12; 95% CI: (1.08 ± 4.07)] patients were more likely to experience treatment failure as compared to

patients with working functional status. As expected, TB co-infected clients also had higher odds of experiencing treatment failure [AHR=3.06; 95% CI: (1.72 ± 5.44)]. The study further showed that patients who developed TB after ART initiation had higher odds to experience treatment failure as compared to their counter parts [AHR=4.35; 95% CI: (1.99 ± 9.54]. Having other opportunistic infections during ART initiation was also found to be associated with higher odds of experiencing treatment failure [AHR=7.0, 95% CI: (3.19 ± 15.37)]. Having fair [AHR=4.99 95% CI: (1.90 ± 13.13)] and poor drug adherence [AHR=2.56; 95% CI: (1.12 ± 5.86)] were significantly associated with higher odds of treatment failure as compared to clients with good adherence.

Overall, the study by Haile, et al. [5] shows two sets of variables: one with narrower confidence intervals (implying less variability) e.g., having a lower CD4 count, ambulatory status, TB co-infection and poor drug adherence. The other set of variables have wider confidence intervals (implying higher variability) e.g., bed ridden, developing TB after initiation, other OIs and fair drug resistance. This study explores some of the major factors being investigated in this study and provides critical insights into what to potentially expect. That it is a recent study adds value to what is being investigated in this study. However, the study report does not show whether these findings are reflective of a post multi-month scripting era or not. Nonetheless, other reviews done by this researcher show that Ethiopia has adopted the differentiated models of care.

Factors associated with survival: A retrospective study conducted by Ram Bajpai, et al. [6] assessed the survival rates and factors associated with survival among adult PLHIV in Andhra Pradesh, India. This research piece used data from 139 679 PLHIV aged ≥ 15 years on ART, registered between 2007 and 2011. These were followed up through December 2013. The outcome of interest was death of the client. The Kaplan-Meier was used to estimate survival, while the Cox-regression models were used to explore the factors associated with survival.

The study results show that approximately 13% of those newly initiated on ART died during follow-up with 56% of all deaths occurring within the first three months. From the study, the CD4 count (adjusted hazard ratio of 4.88; 95% confidence interval of 4.36 to 5.46 for <100 cells/mm³ *vs.* >350 cells/mm³); functional status (adjusted hazard ratio of 3.05; 95% confidence interval of 2.82 to 3.30 for bed ridden *vs.* normal), and body weight (adjusted hazard ratio of 3.69; 95% confidence interval of 3.42 to 3.97 for <45 kg *vs.* >60 kg) were strongly associated with the survival of HIV patients. This study by Ram Bajpai, et al. [6] shares a lot of methodological similarities with the study undertaken by this researcher. This is exemplified by the following: a retrospective design, a relatively long follow up (which however is only half of what my study is looking at), and significantly larger sample size. It is also worth recognizing the narrower confidence intervals in this study (reflective of less variability owing to a large sample, among other factors). However, this study explores only a limited set of outcomes (primarily survival) in comparison to what this study is investigating. Nonetheless, it provides a rich repository for the current study.

Factors associated with immunological failure: Virologic failure remains one of the major ART outcomes for PLHIV on ART. Evidence shows that there is a myriad of factors associated virologic failure. These include, but not limited to the following: hazardous drinking of alcohol which affect adherence to ARVs [7]; opportunistic infections during ART [8]; previous exposure to ARVs before initiation of ART; advanced HIV disease (WHO clinical stage 4) [9]; change of ARVs due to toxicity; and baseline haemoglobin level less than 10g/dl [2]. On the other hand, other studies indicated that sexual orientation of the patient (comparing heterosexual and non-heterosexual); marital and employment status [2]; patient's residence (whether urban or rural), pre-ART opportunistic infections, co-infection with Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) [3].

In addition, other studies have also shown that non disclosure of HIV status, history of Tuberculosis (TB), socioeconomic status/class, history of smoking at time of viral load testing, herbal medicine use at the time of viral load testing [2] and co-morbidities are associated with virologic failure.

While the HIV epidemic remains a "gendered one", studies done in Massachusetts General Hospital out-patient HIV clinic in the USA; in Clinicas de Porto of Brazil and in Chiang Mai University Hospital in Thailand showed that male gender was not associated with virologic failure [3]. Similarly, a study done in Nigeria [2] showed that the male gender was not associated with virologic failure. However, a study done in the Americas (Mexico) showed different results i.e., the results showed that the female gender was marginally associated with virologic failure [4].

Methodology

Study design and data sources

This is a retrospective cohort analysis of treatment outcomes. Data were abstracted from the OI/ART patient care booklets for clients initiated on ART between October 2012 and March 2013.

Study population

Site selection: Data were collected from all five MOHCC facilities in Chitungwiza; namely Chitungwiza Central Hospital, Seke North Clinic, Seke South Clinic, St Mary's Clinic and Zengeza Clinic.

Patient inclusion criteria: All HIV positive clients 15 years and older, who were initiated on ART between the October 2012 and March 2013, at the five ART sites in Chitungwiza, regardless of treatment outcome, were included in the study.

Patient exclusion criteria: Patients initiated on ART after March 2013 was excluded from the study. Patients without a documented ART initiation date were excluded from the study.

Sample size

The following formula was used to come up with the sample size:

$$n = \left[p\left(100 - p\right) / \Delta^2 \times f\left(1 - \infty\right) \right]$$

n = computed sample size

p = estimate of the proportion

Δ = the desired width of the confidence interval

1-∝ = confidence level

This implied that the study needed to sample a minimum of 310 OI/ART Patient Care Booklets to generate 95% confidence intervals with +/- 2.5% bounds around the proportion of interest. The sample is distributed as follows, per site, using probability proportional to size (as per their ART volume the five health facilities in June 2013) (Table 1).

Data analysis

All analyses were performed using STATA 13 software. Univariate and multivariate regression modelling was used to identify the factors associated with treatment response of ART patients. Data were faced checked for completeness and consistency. Missing data were estimated using imputation techniques. Logistic regression was done to identify the factors associated with patient retention and linear regression was done to identify factors associated with weight gain. Poisson regression model was used to identify factors associated with immunological response. Univariate Cox proportional hazards model was run for covariate and factor variables. Variables for the multivariate Cox proportional hazards model were selected using the Lemeshow Hosmer statistic, all variables with p-value <0.25 from univariate analysis were considered for inclusion in the multivariate model. The proportional hazards assumption was checked using Kaplan Meir curves and verified using the log-rank test statistic. Post estimation diagnosis was also performed to test the adequacy of all the models.

Ethical Considerations

Clearance was sought from the MOHCC Head Office, the Chitungwiza Central Hospital CEO, the Superintendent at CITIMED Chitungwiza Hospital and the Chitungwiza City Health Department. To ensure confidentiality, no personally identifiable information relating to clients, such as patient name or clinic registration, number were collected during chart extraction. All the data was kept by the principal investigator on a personal computer with a password-protected login screen.

Results

Demographic characteristics

Three hundred and five (305) respondents were considered in the study. Sixty percent (60%) of the respondents were females. The majority (71%) of the clients attained a secondary level of education.

Table 1: Sample size per health facility.

Name of Health Facility	Proportion	Sample size
Chitungwiza Central Hospital	0.44337	137 (F=82; M=55)
Seke North Clinic	0.05673	18 (F=11; M=7)
Seke South Clinic	0.19602	60 (F=36; M=24)
St Mary's Clinic	0.12711	39 (F=24; M=15)
Zengeza Clinic	0.17679	56 (F=33; M=23)
Total	**1**	**310 (F=186; 124)**

Only one percent of both males and females reached tertiary level. In addition, only one percent did not have any level of education. Sixty-four percent (64%) of the clients were married, 18% were widowed, 10% were divorced and 7% were single. Table 2 shows other demographic characteristics of the respondents. Fifty-eight percent (58%) of the respondents were enrolled through Voluntary Counseling and Testing (VCT). Thirty-seven percent (37%) of the sampled clients were in WHO clinical stage III, see table 3 for more details. Of the total sample, 23% did not have a CD4 count done (42/183 women and 29/122 men). In 2012/13, where point of care CD4 counts was done, ART initiations were restricted to those with a CD4 cell count of 350 cells/µL or less. The exceptions to this rule were pregnant women as well as those who were TB-HIV co-infected regardless of sex. The proportion of those with/without a documented CD4 result was the same for both males and females. The average CD4 count at initiation was 334 cells/µL for females and 289 cells/µL for males.

Factors associated with the observed treatment outcomes

The section below highlights the critical factors associated with the observed outcomes.

Predictors of retention: Table 4 below provides a synopsis of factors associated with retention. As shown in the table 4, females were twice likely to be retained on ART than their male counterparts. Similarly, the odds of being retained in care among clients in WHO Stage II were 3.02 times that of clients in Stage IV. The odds of being retained in care among clients who received Cotrimoxazole were 1.8 times that of clients who did not receive it. Clients under Multi-Month Scripting (MMS) regime were 28% less likely to be retained than those who were not on MMS. Similarly, clients with a university level of education were 73% less likely to be retained in care compared to those with primary education. See table 4 for additional outputs.

Predictors of weight gain: Table 5 gives a synopsis of the key factors associated with weight gain (the clinical outcome of interest) using a linear regression model. Female patients have extra weight gain compared to male patients, holding other factors constant. Females were 3.72 times likely to gain weight than their male counterparts (1.313 kg; range of 0.347; 2.279 kg). Widows were 96% less likely to gain weight than those who were married. Similarly, PLHIV with no education were 96% less likely to gain weight compared to PLWHA who attended at least primary school.

Predictors of immunological outcomes (CD4): Table 6 below shows the factors associated with positive changes in CD4 count. The IRRs are the incidence rate ratios for the Poisson model which are obtained by exponentiating the Poisson regression coefficient. The IRR is the estimated rate ratio for one-unit increase in CD4 holding other variables constant in this model. If a widowed person living with HIV were to increase their CD4 by one point, his/her rate ratio for CD4 is expected to decrease by a factor of 0.68. This is statistically significant (CI: 0.57-0.81). The picture is the same for single persons (IRR=0.54; CI: 0.36-0.80); received Cotrimoxazole (IRR=0.69; CI: 0.63-0.76); on MMS (IRR=0.77; CI: 0.64-0.92). Clients in WHO stage IV are expected to have a rate of 1.71 times greater for loss in CD4 than clients in stage 1, while holding other variables constant (IRR=1.71; CI:1.48-1.96).

Predictors of survival: Table 7 below details the factors associated with survival. Using the Weibull regression for predictors, the data shows that women were 96% more likely to survive than male (HR=0.04; CI:0.00-0.28). Similarly, those who received Cotrimoxazole were 93% more likely to survive than those who did not (HR=0.07; CI: 0.02-0.24) as shown in table 7 below. PLHIV with no education were dying at a rate that was 60% more than those with some education (HR=0.4; CI: 0.03-5.72), while clients in WHO stage I were dying at a rate that was 96% lower than those in Stage IV (HR=0.04; CI: 0.01-

0.15). The hazard of dying was significantly higher in the 25-29 year olds compared to the 15-19 year olds (HR=11.64; CI: 1.67-81.15), albeit with a wider confidence interval. Other important factors are detailed in the same table.

Conclusion

The study confirms some of the findings from earlier studies in Zimbabwe, albeit with differences on some of the factors deemed

Table 2: Marital status and level of education of respondents.

Demographic Variable	Female ART Clients		Male ART Clients		Overall Sample	
Marital Status	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**
Divorced	24	13%	5	4%	29	10%
Married	99	54%	96	79%	195	64%
Single	13	7%	9	7%	22	7%
Widowed	47	26%	9	7%	56	18%
Unknown Status	0	0%	3	2%	3	1%
Total	**183**	**100%**	**122**	**100%**	**305**	**100%**
Level of Education						
None	2	1%	1	1%	3	1%
Primary	27	15%	10	8%	37	12%
Secondary	123	67%	95	78%	218	71%
Tertiary	2	1%	1	1%	3	1%
Unknown Level	29	16%	15	12%	44	14%
Total	**183**	**100%**	**122**	**10%**	**305**	**100%**

Table 3: Clinical characteristics of the sampled male and female clients.

Referral source for HIV care and Treatment	Female ART Clients		Male ART Clients		Overall Sample	
VCT	89	49%	87		176	58%
TB Clinics	5	3%	10	8%	15	5%
PMTCT	13	7%	0	0%	13	4%
Obstetrics Unit	10	5%	0	0%	10	3%
Hospitalization	62	34%	23	19%	85	28%
Home	1	1%	0	0%	1	0%
Other	3	2%	2	2%	5	2%
Total	**183**	**100%**	**122**	**100%**	**305**	**100%**
WHO Stage at Initiation	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**
Stage I	55	30%	20	16%	75	25%
Stage II	73	40%	40	33%	113	37%
Stage III	49	27%	59	48%	108	35%
Stage IV	6	3%	3	2%	9	3%
Total	183	100%	122	100%	305	100%
CD4+ Cell Count Done						
Yes	42	23%	29	24%	71	23%
No	141	77%	93	76%	234	77%
Total	183	100%	122	100%	305	100%
Pre-ART Exposure						
HAART	39	21%	21	17%	60	20%
PMTCT	7	4%	0	0%	7	2%
SD NVP	4	2%	1	1%	5	2%
None	133	73%	100	82%	233	76%
Total	183	100%	122	100%	305	100%
Exposure to OI prior to ART initiation						
TB	9	5%	21	17%	30	10%
Other OI	36	20%	16	13%	52	17%
None	138	75%	85	70%	223	73%
Total	183	100%	122	100%	305	100%

Table 4: Predictors of retention.

Covariates	Odds Ratio	SE	P-Value	95% CI	
Sex					
Female	2.01	0.84	0.09	0.89	4.55
Age					
Age group	0.38	0.07	0	0.26	0.55
WHO Stage					
II	3.02	0.68	0	1.94	4.68
Cotrim					
Yes	1.8	0.17	0	1.49	2.17
ART Regimen					
Lamivudine+ Stavudine+ Nevirapine	0.26	0.14	0.01	0.09	0.73
MMS					
Yes	0.72	0.28	0.4	0.34	1.54
Level of education					
Secondary	1.48	0.25	0.02	1.06	2.05
University	0.27	0.31	0.26	0.03	2.65
None	3.15	1.59	0.02	1.17	8.49

Table 5: Predictors of weight gain (clinical outcome of interest).

Covariates	Odds Ratio	SE	P-value		95% CI
Sex					
Female	3.72	1.37	0.02	1.41	9.76
Age					
(25-29)	0.01	0.02	0.02	0	0.28
(30-34)	0.01	0.01	0.01	0	0.21
Marital status					
Widowed	0.04	0.06	0.09	0	2.03
Level of education					
None	0.18	0.11	0.04	0.04	0.85
ART Regimen					
Lamivudine+ Stavudine+ Nevirapine	0.28	0.12	0.04	0.09	0.87

Table 6: Predictors of positive changes in CD4.

Covariates	IRR	SE	P-Value	95% CI	
Marital status					
Widowed	0.68	0.06	0	0.57	0.81
Single	0.54	0.11	0	0.36	0.8
Level of education					
Secondary	0.00	0	0	0	0
WHO stage					
IV	1.71	0.12	0	1.48	1.96
Cotrimoxazole					
Yes	0.69	0.03	0	0.63	0.76
On MMS					
Yes	0.77	0.07	0.01	0.64	0.92
ART regimen					
Lamivudine+ Tenefovir + Efavirenz	1.59	0.31	0.02	1.08	2.33
Zidovudine+ Lamivudine+ Nevirapine	1.52	0.12	0	1.31	1.76

Table 7: Predictors of survival.

Predictors	HR	SE	P-value	95% CI	
Sex					
Female	0.04	0.04	0	0	0.28
Cotrimoxazole					
Yes	0.07	0.04	0	0.02	0.24
Age					
(25-29)	11.64	11.53	0.01	1.67	81.15
(30-34)	0	0	0	0	0
(35+)	0	0	0	0	0
Level of education					
Secondary	0.05	0.03	0	0.01	0.2
University	0	0	0	0	0
None	0.4	0.54	0.5	0.03	5.72
Other	0	0	0	0	0
WHO stage					
I	0.04	0.03	0	0.01	0.15
II	0	0	0	0	0
ART regimen					
Zidovudine+ Lamivudine+ Efavirenz	0	0	0	0	0
Zidovudine+ Lamivudine+Nevirapine	0	0	0	0	0
/ln_p	-0.72	0.2	0	-1.11	-0.33
p	0.49	0.1		0.33	0.72
1/p	2.05	0.41		1.39	3.04

significant. This study contributes to the existing body of knowledge on critical factors affecting ART outcomes in Zimbabwe, albeit the need to explore the subject further given the transition to differentiated service delivery models as well as changes in ART regimens.

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