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Treatment Outcomes and Risk Factors Associated With Low Level Viremia among Adults on First Line Antiretroviral Therapy - A Case of Harare Central Hospital, Zimbabwe

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Abstract

Background: The study sought to determine the treatment outcomes of patients on first line ART with low level viremia (51-1000 copies/mL) as well as the risk factors for subsequent treatment failure at Harare Central Hospital in Zimbabwe.

Method: A cohort of 300 medical records of patients who were on first line ART between 01 January 2013 and 31 December 2016, and who had low level viremia at least 6 months post ART initiation were followed up to determine the treatment outcome.

Results: While only a single individual died, 11% had persistent low-level viremia, 74% suppressed, 8% failed treatment, and 6% had been transferred out and thus their treatment outcome could not be established. Only 17% recorded new opportunistic infection. The hazard of treatment failure were 3.37 times higher in subjects with 0-200 CD4 when compared to those with CD4 > 350 at baseline, while there were no significant differences in the hazard of treatment failure between subjects with 201 to 350 and >350 CD4 count at baseline. The hazard of treatment failure were 2.06 times higher in subjects taking ABC-N when compared to those on TENOLAME while there were no significant differences in the hazard of treatment failure between subjects on TENOLAME and TENOLAMN. There was no association between hazard of failing treatment and WHO stage, marital status, employment and duration on ART.

Conclusion: Patients with low level viremia must be closely monitored for timely switch to second line ART in the event of treatment failure.

Keywords: Low level viremia; Treatment failure; Virological suppression; Treatment guidelines; Drug resistance

Introduction

Viral load monitoring is now widely recognized as the surrogate marker of the Human Immune Deficiency Virus (HIV) virological suppression. The goal of antiretroviral therapy (ART) in HIV management is to suppress the viral load to levels below the limit of detection of the assay used. To ensure that patients are deriving the most clinical benefit out of ART, there is needed to routinely monitor for efficacy of treatment and for early virological replication by quantifying HIV RNA [1]. Of paramount importance is the ability to detect when ART is no longer effective. To detect virological failure and manage it, there is need to define clear end points of treatment success and treatment failure [2]. However, threshold definitions evolve over time, and may vary significantly across the continents.

Virological success is widely accepted as a viral load below the limit of detection of the assay used, and the threshold used in clinical practice, treatment guidelines and in literature is below 50 copies/mL. According to the World Health Organization (WHO), virological failure is defined as plasma viral load above 1000 copies/ml based on two consecutive viral load measurements 3 months apart, with adherence support in a patient who has been taking ART for at least 6 months [3,4]. On the other hand, the Centers for Disease Control and Prevention (CDC) defines virological failure as the inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL [5]. Universally, HIV guidelines present a collection of dissimilar notions lacking overall homogeneity regarding the management of patients with viral load levels between the lower limit of detection of an assay and the chosen threshold for defining virological failure. This case is commonly referred to as low level viremia (LLV). WHO defines low level viremia as a viral load between 51 and 1000 copies/mL, whereas CDC defines it as viremia between 51 and 200 copies/mL [3].

Zimbabwe, like most resource limited nations closely follow the WHO threshold definitions. A lot of questions arise when it comes to the management of those with low level viremia. The Zimbabwe national HIV guidelines do not advise on the management of these patients despite the vast evidence in literature of the possible consequences of low-level viremia. Hence, clinical judgement developed through practice, experience, knowledge and continuous critical analysis has been the basis for the management of patients with low level viremia in Zimbabwe [6]. This has led to variations in the clinical management of these patients. Field and Lohr put forward the view that variations in clinical practices depending on geographical region and the clinical judgement of the attending clinician has seen patients with similar clinical conditions receiving different care [7]. To close the gap between what clinicians do and what scientific evidence supports, there is need to determine the outcomes as well as the risk factors associated with low level viremia in Zimbabwe. The present study sought to determine treatment outcomes for people with low level viremia at Harare Central Hospital.

Research Methodology

Research design

This was a quantitative observational retrospective cohort study on

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HIV positive patients who were on antiretroviral therapy (ART) for at least 6 months between January 2013 and December 2016, and whose initial viral load was between 51 and 1000 copies/mL.

Participants and setting

Three-hundred and thirty-nine (339) participants needed to be enrolled in the study to have 80% power at 95% confidence intervals and 20% attrition rate. However, only 300 patients met the eligibility criteria for the study, who were all included in the study. Thus the study consisted of 300 adult patients (19 years old and above), on first line ART for at least 6 months, with low level viremia (that is documented plasma viral load between 51 and 1000 copies/ml measured at least 6 months post initiation of ART), and with adherence history of >95.0% on scheduled visits. Patients with undetectable viral load at 6 months post ART initiation, those with a documented history of poor adherence (<95.0% on 3 visits or more) as well as those on second- and third-line ART, were excluded from the study.

The study was conducted at Harare Central hospital adult opportunistic infections clinic, which is a tertiary hospital, and one of the largest in Zimbabwe. The facility provides HIV/TB/STI services to patients who are 19 years and above. The clinic provides comprehensive healthcare services to 6 733 patients from across the country. Of these patients, 6 549 patients are on first line ART, 173 patients are on second line, and 11 are on third line.

Data collection tools and data sources

An assessment form was used to guide in the collection of relevant study variables. Data were electronically captured and cleaned using excel spreadsheet. The study sought to measure all variables on treatment outcomes and risk factors associated with Low Level Viremia among Adults on first line ART including demographic and time dependent variables. Time dependent variables that were updated at each visit were death, weight, WHO stage, TB status, pregnancy/ contraceptive method, new opportunistic infection, Isoniazid Preventive therapy (IPT) status, pill count, adherence %, ART regimen, laboratory investigations requests, referrals outside the clinic, as well as next review date.

The data sources were the electronic Patients Monitoring System (ePMS), and the client ART Care booklets (Green books) [8]. Harare Central Hospital has been using the ePMS since 2012, with the aim of enhancing improved access to data, security of patient data, elimination of multiple patient information and easier data analysis. However, one of the challenges was inconsistent availability of laboratory service resulting in incomplete records. These incomplete records were excluded from the study. Validation checks were carried out by the researcher as part of the data scanning and data entry process.

Procedure

The study was approved by the Harare Central Hospital Ethics Committee. Since secondary data was used, informed consent was waived. However, privacy and confidentiality of patients' electronic data was ensured through the removal of personal identifiers on data collection and data entry and use of an encrypted password protected hard drive for storage.

Data analysis

Descriptive statistics was performed using STATA version 13.0 software package. Statistical tools such as graphs, tables, charts were used to present the data. Survival analysis was performed using R statistical package to determine the survival curves. To determine the risk factors associated with low level viremia and progression to treatment failure, Cox proportional hazard model was employed because of its robustness. Cox-proportional hazard assumption was tested and validated before performing survival analysis. Stepwise regression approach was used in the selection of the final model. Interaction terms were tested and removed if they were insignificant and fail to improve the model fit. All statistical tests were concluded at 5% level of significance.

Results

The baseline characteristics of the study population are summarized in Table 1. A total of 300 medical records of patients who were on first line antiretroviral therapy for at least 6 months between 1st January 2013 and 31st December 2016 met the eligibility criteria and were recruited. Most participants (52.7%) were females with 48.3% being males. In this study patients were on treatment for a median of 9 months (range: 6-19 months) prior to their first low-level viremia episode.

Baseline CD4 count and WHO Clinical Staging

Table 2 summarizes the Baseline CD4 and WHO clinical staging frequency distribution for study participants. As shown in Table 2, CD4 count categories of less than 200 c/umL, 200 to 350 c/umL and over 350 c/umL, all had patient proportions over 30.0%. The majority of participants (54.0%) were WHO stage 1, while 16.0%, 22.7% and 7.3% were stage 2, 3 and 4 respectively. The distribution of CD4 counts reflects the eligibility criteria that were used to initiate patients on ART during the study period. Between 2013 and 2016, the eligibility criteria for ART in Zimbabwe were: CD4 count <500 c/umL or WHO clinical stage 3 and 4. Only 7.3% of the subjects presented with an AIDS defining illness (WHO stage 4), whereas the majority (54.0%) did not have any opportunistic infection at the time of ART initiation. Less than 50% of the participants (46.3%) reported to have contracted an opportunistic infection during the follow-up period. The most common opportunistic infections reported were chronic gastroenteritis (16%),

Variables	Category	Frequency n (%)
Age	19-29	101 (33.7)
	30-39	86 (28.7)
	>40	113 (37.6)
Sex	Male	145 (48.3)
	Female	155 (52.7)
Marital status	Divorced	36 (12.0)
	Married	170 (56.7)
	Single	70 (23.3)
	Widowed	24 (8.0)
Occupation	Formal	77 (25.7)
	Informal	94 (31.3)
	Unemployed	129 (43)

Table 1: Frequency distribution of the baseline characteristics (N=300).

Variables	Category	Frequency n (%)
CD4 count	0-200	95 (31.7)
	201-350	110 (36.7)
	>350	95 (31.6)
WHO stage	1	162 (54.0)
	2	48 (16.0)
	3	68 (22.7)
	4	22 (7.3)
Opportunistic infections	Yes	139 (46.3)
	No	161 (53.7)

Table 2: Baseline CD4 and WHO clinical staging frequency distribution (N=300).

herpes zoster (20%), pulmonary TB (16%), oral candidiasis (6%) and unexplained weight loss (23%). The median baseline CD4 was 289 c/umL (range 8-952 c/umL). The median viral load at low level viremia was 474.2 copies/ml range (60-988 copies/ml).

ART regimen and retention in care

Table 3 shows the distribution by ART regimen, adherence and retention. Most of the study participants (82.3%) were on TENOLAME compared to 10.7% who were on the alternative regimen, TENOLAMN, and lesser proportions for the remaining regiments. The majority (93.7%) of the study subjects were still in care compared to those who died (<1%) or transferred out (6.0%) during the study period; a high retention rate of 93.7% being an indicator of good quality of service. History of changing drugs within first line was less common among study participants (12.0%).

Treatment outcome analysis

Table 4 illustrates the treatment outcomes that were observed when medical records of 300 patients who were on First line ART for at least 6 months between January 1, 2013 and December 31, 2016 were abstracted. Treatment outcomes included death (<1%), persistent LLV (11.0%), viral suppression (74.3%), treatment failure (8.3%) and unknown status (6.0%). The proportion of participants who developed new opportunistic infection was 16.7%. Only 1(<1%) died during the study period. Although the cause of death could not be established from the medical records, the results suggest mortality due to low level viremia was significantly very low. Eleven percent (11.0%) of the patients maintained their low-level viremia, which is characteristic of patients who need longitudinal follow up for drug resistance assessment.

Most of the patients who participated in the study (74.3) achieved full virological suppression (below 50 copies/mL). A significant number of patients (n=25; 8.3%) with low level viremia progressed to treatment failure during the research period. From the findings, 8.3% of low-level viremia patients who initiate treatment fail between 19 months follow-up.

The treatment outcome of 18 participants (6.0%) could not be established due to their transfer to other facilities prior to the second viral load test. The most common reasons for transferring patients to other facilities in Zimbabwe are relocation, decentralization of stable patients to decongest higher institutions, patient's request for transfer for financial constraints and convenience. In this study, the reasons could not be determined.

Variables	Categories	Frequency (%)
ART regimen	ABC-E	6 (2.0)
	ABC-N	2 (0.7)
	TENOLAMN	32 (10.7)
	TENOLAME	247 (82.3)
	ZIDOLAME	8 (2.7)
	ZIDOLAMN	5 (1.6)
Adherence	Yes	300 (100)
Retention	Died	1 (<1)
	In care	281 (93.7)
	Transfer out	18 (6.0)
History of changing drugs	Yes	36 (12.0)
	None	264 (88.0)

Table 3: Summary of the distribution by ART regimen, adherence and retention (N=300).

Variables	Categories	Outcome n (%)
Follow-up treatment outcome	Died	1 (<1)
	Persistent LLV	33 (11.0)
	Suppressed	223 (74.3)
	Failure	25 (8.3)
	Unknown	18 (6.0)
New opportunistic infection	Yes	50 (16.7.)
	No	250 (83.3)

Table 4: Summary of the treatment outcomes of patients who were on first line ART for at least 6 months between January 1, 2013 and December 31, 2016 (N=300).

Survival analysis

Survival analysis was performed using R statistical package. Cox-proportional hazard assumption was tested and validated before performing survival analysis. The assumption was that, participants who had a follow-up period of less than 19 months were regarded as loss-to-follow-up. Stepwise regression approach was used in the selection of the final model. All statistical tests were concluded at 5% level of significance.

The distribution of the hazard rate from 6 months to 19 months

The overall hazard of failing treatment with a follow-up period of up to 20 months was slightly above 10% when assessed from 6 months of initiating therapy. Hence only an estimated of about 10% of study subjects who initiate treatment fail between 19 months follow-up (Figure 1).

The distribution of the hazard and survival rate from 6 months to 19 months

Figure 2 shows that participants who experienced viral load failure occurred within 15 months of ART initiation whereas it took up to 20 months follow-up for a few individuals to fail treatment.

Factors associated with treatment failure from 6 months follow-up

Sex had a significant association with treatment outcome, the hazard of treatment failure were 2.44 times higher in males when compared to females (HR=2.44; 95% CI: 1.06-6.26; p=0.049). Baseline CD4 had a significant association with treatment outcome, the hazard of treatment failure were 3.37 times higher in subjects with 0-200 CD4 when compared to those with CD4 > 350 at baseline (HR=3.37; 95% CI: 1.07-10.7, p=0.039), while there were no significant differences in the hazard of treatment failure between subjects with 201 to 350 and >350 CD4 count at baseline (p=0.436). Age had a significant association with treatment outcome. The hazard of treatment failure were 0.26 times less in subjects with > 40 years of age (HR=0.26; 95% CI: 0.07-0.93, p=0.038), while there were no significant differences in the hazard of treatment failure between subjects with 19-29 and 30-39 years of age (p=0.746). ART regimen had a significant association with treatment outcome; the hazard of treatment failure were 2.06 times higher in subjects taking ABC-N when compared to those on TENOLAME (HR=3.14; 95% CI: 0.41-24.04), while there were no significant differences in the hazard of treatment failure between subjects on TENOLAME and TENOLAMN (p=0.878), ABC-E (p=0.410) and ZIDOLAME/N (p=0.977). There was no association between hazard of failing treatment and WHO stage, marital status, employment and duration on ART (Table 5).

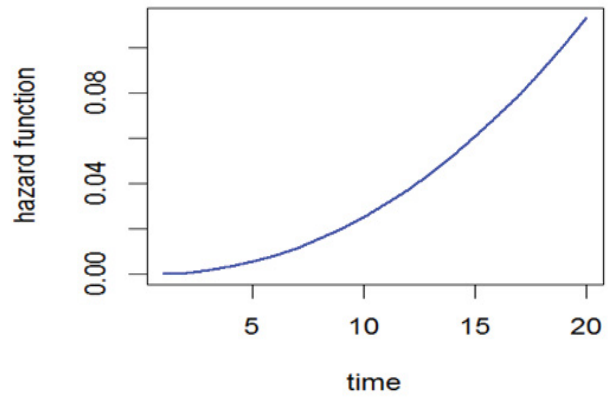

Figure 1: Hazard function.

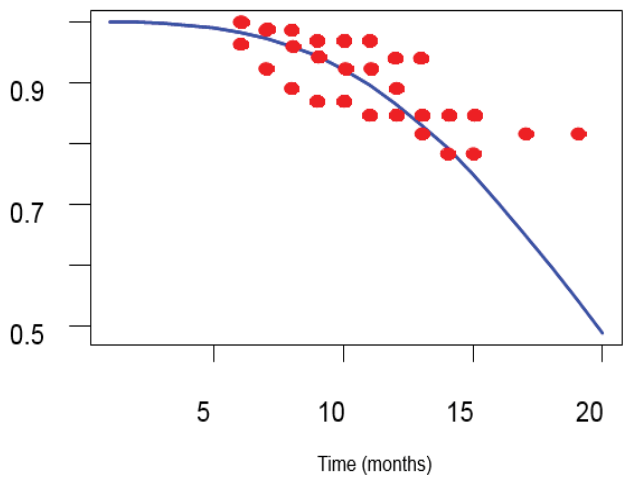

Figure 2: Survival function.

Factors*	Category	Hazard Ratio (HR) (95% CI)	p-value
Sex	Female	--	--
	Male	2.44 (1.06-6.26)	0.049**
Baseline CD4	(>350)	--	--
	0-200	3.37 (1.07-10.7)	0.039**
	201-350	1.64 (0.47-5.68)	0.436
WHO stage	-1	--	--
	2	1.24 (0.34-4.51)	0.741
	3	2.16 (0.86-5.38)	0.099
	4	4.37 (0.92-7.45)	0.087
Age	19-29 years	--	--
	30-39	0.86 (0.35-2.14)	0.746
	>40	0.26 (0.07-0.93)	0.038**
Marital status	Married	--	--
	Divorced	0.78 (0.17-3.59)	0.746
	Single	1.31 (0.50-3.40)	0.581
	Widowed	1.51 (0.33-6.83)	0.596
Employment	Formally	1.36 (0.32-5.68)	0.677
	Informally	2.51 (0.72-8.72)	0.149
	Unemployed	0.99 (0.89-1.09)	0.793
Duration on ART Regimen	TENOLAME	--	--
	ABC-E	3.14 (0.41-24.04)	0.41
	ABC-N	2.06 (2.50-169.41)	0.005**
	TENOLAMN	1.12 (0.26-4.91)	0.878
	ZIDOLAME/N	1.03 (0.13-8.20)	0.977

Table 5: Factors associated with treatment failure (N=300). *Factor level in bracket is considered as the reference level.

Discussion

The mean time to viral load testing was 9 months versus the recommended 6 months, probably reflecting limited capacity to perform viral load testing in Zimbabwe. Again, time to second viral load testing was around 8 months versus the recommended 6 months. Further inquiry is required to assess health system and patient-level factors influencing delays in viral load testing. Again, it might be worthwhile for implementation science research to assess risk factors or predictors of high viral load and treatment failure in people living with HIV so as to prioritize viral load testing to those at risk of high viral load and treatment failure, for provision of prompt care.

It was established that 8.3% of patients who had low level viremia during the research period progressed to treatment failure, and 11% of the patients maintained low level viremia. A retrospective cohort study found a rate of virological failure in patients with persistent low-level viremia of 38.2%, and 22.1% of patients still had persistent low-level viremia at the end of study [9]. Hence, the rate of failure obtained in this study was much lower compared to other studies that were done in WHO guided countries. This could be a good indicator of positive progress towards 90-90-90 target by 2020 for Zimbabwe. However, reliable statistics also rely on availability of well-maintained data capturing systems and good screening and diagnostics services. In Zimbabwe genotyping resistance testing services are not easily accessible and are costly, thus close monitoring of these patients is recommended.

The results indicated that the probability of failing treatment for males was 2.44 higher compared to females. This could be explained in part by the differences in health seeking behavior by gender. An in-depth analysis of the influence of gender and other patient characteristics on health-seeking behavior and the results obtained confirms that women tend to visit their primary healthcare providers more frequently than males [10].

Patients who were over 40 years were 26% less likely to fail treatment compared with those below 40 years. Though the prevalence of chronic diseases tends to increase with age, this age group tends to have better outcomes due to better health seeking behavior implying more frequent visits to healthcare facilities. This reduces their likelihood of missing clinic appointments and running out of medication. ART regimen had a significant association with treatment outcome confirming what is already known in the medical arena about the ineffectiveness of ABC based regimens when used as first line regimen [11]. Patients on ABC-N were 2.06 times more likely to fail treatment compared with those who were on TENOLAME.

Baseline CD4 was also an important predictor of progression to treatment failure. Both in literature and in clinical practice, patients who present late (CD4 < 200, and WHO stage 4) have a greater risk of failing treatment, mortality, and incomplete immune recovery [12]. Similarly, from this study, patients with baseline CD4 < 200 c/umL were 3.37 times more likely to progress to treatment failure compared to those with CD4 > 350 c/umL.

Almost 75% of the study participants achieved full virological suppression. Possible causes of low level viremia include patient factors (adherence, absorption, food requirements); medication factors such as drug-drug interactions; virological factors such as intermittent activation of latently infected cells, ongoing replication at sanctuary sites, viral mutations, non-B sub type virus, and collection/assay factors such use of plasma preparation tubes [13,14]. Most of these risk factors can be prevented, minimized or avoided. However, owing to the retrospective nature of the study, these variables could not be determined.

Conclusion

Basing on the indication that 8.3% of patients with low level viremia progress to treatment failure, it is recommended more attention regarding CD4 count and viral load monitoring be given to them where possible, these should be retained in care. Decentralization must be strictly for patients with an undetectable viral load. More research can be done on the survival analysis of patients with persistent low-level viremia (>2 LLV results) to determine their treatment outcome. These will require longer durations of follow of the cohort. In addition, comparison studies are needed to investigate if there is any difference in treatment outcomes when lower threshold definitions are adopted. Again, studies on baseline resistance testing are recommended as it has been shown to predict treatment failure.

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