FACTORS ASSOCIATED WITH LACTIC ACIDOSIS IN HIV PATIENTS ON ANTIRETROVIRAL THERAPY IN HARARE CITY- 2012

BY

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DECLARATION

This dissertation is the original work of Emmaculate Choto. It has been prepared in accordance with the guidelines for MPH dissertations in the University of Zimbabwe. It has not been submitted elsewhere for another degree at this or any other university.

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ABSTRACT

Title: Factors associated with lactic acidosis in HIV patients on ART - Harare City 2012

Introduction: Antiretroviral medicines have side effects that can be life threatening. An unpublished study by Malunga in Harare City, showed a high incidence of hyperlactatemia in patients on stalanev. This research therefore aimed to determine the proportion of HIV patients on stalanev, the burden of lactic acidosis and factors associated with developing lactic acidosis in Harare City.

Methods: An analytic cross sectional study was carried out at Harare City's Wilkins and Beatrice road hospitals. A total of 250 HIV positive participants who had been on ART for more than four months were purposively selected. In addition to interviewer administered questionnaires blood samples were analysed for lactate levels. The frequencies of hyperlactemia and lactic acidosis were determined. Risk factors were determined by multivariate logistic regression.

Results: Of the 250 participants, 5.2%(13) had lactic acidosis and 29.2% (73) had hyperlactatemia. Patients on stalanev were 76% (190). Being on stalanev (p: 0.003) and having a low CD4 count of < 100cells/ml on ART initiation were found to be associated with developing lactic acidosis.

Discussion: HIV patients with CD4 counts of ≤ 100 cells/μl before the inception of ART were at risk of developing lactic acidosis. Monitoring of lactate levels may be useful during management of HIV patients.

Key words: lactic acidosis, stalanev, prevalence

TABLE OF CONTENTS

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LIST OF TABLES

LIST OF DIAGRAMS

LIST OF FIGURES

ABREVIATIONS

ARV	Antiretroviral therapy
HIV	Human immunodeficiency virus
WHO	World Health Organization
ART	Antiretroviral therapy
NRTIs	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitor
d4T	Stavudine
AZT	Zidovudine
3TC	Lamivudine
EFZ	Efavirenz
NVP	Nevirapine
FDC	Fixed dose combination
LDH	Lactate dehydrogenase
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide dehydrogenase
DNA	Deoxyribonucleic acid

mtDNA	Mitochondria deoxyribonucleic acid
γ	gamma
µL	micro-litre
OI	Opportunistic infection
OIC	Opportunistic infection clinic
BRIDH	Beatrice road infectious disease hospital
WIDH	Wilkins infectious disease clinic
nm	Nanometers
UZUCSF	University of Zimbabwe and University of California San Francisco
MRCZ	Medical research council of Zimbabwe
JREC	Joint Research Ethics Committee
BMI	Body mass index
ZLN	Zidovudine, lamivudine, neverapine
TLE	Tenofovir, lamivudine, efavirenz
TLN	Tenofovir, lamivudine, neverapine

DEFINITIONS

lactic acidosis

Lactate levels above 5mmols/L

Hyperlactatemia

Lactate levels between 2.5 and 5mmols/L

Normal lactate levels

Lactate levels below 2.5mmols/L

LIST OF APPENDICES

LIST OF LETTERS OF APPROVAL

INTRODUCTION

Background

Antiretroviral (ARV) medicines have been extensively used since 1996 as treatment for human immunodeficiency virus (HIV) with positive outcomes being reported, such as reduction in HIV-associated morbidity and mortality, but the side effects of the medicines can be life threatening and can cause a major drawback to drug adherence. The World Health Organization (WHO), in 2011, estimated that over 34 million people were infected with HIV globally, with 2.5 million new HIV infections per year and 1.8 million annual deaths due to AIDS [1,2]. Approximately 69% of the HIV infections are in the Sub Saharan Africa [1]. In 2012, more than 9.7 million people living with HIV were receiving antiretroviral therapy (ART) in low- and middle-income countries [1]. Zimbabwe has an HIV prevalence of 13.7% with an incidence of 0.4% [3,4]. Approximately 300 000 of these HIV patients were on ART in 2011 [3]. Of concern is the number of patients on ART experiencing side effects and the relative increase that will occur as the World Health Organization guidelines increased the threshold of ART initiation to a CD4 count of 500 cells/μL[5].

Zimbabwe is one of the 189 countries that have committed themselves to a comprehensive program of national commitment and action to fight HIV/AIDS epidemic by adopting the United Nations General Assembly special session declaration of commitment on HIV/AIDS of June 2001 [6]. The declaration established a number of goals for achievement of specific targets including health care and treatment [7]. Zimbabwe initiated its national ART program in April 2004 [7]. First line regimens consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a nucleotide reverse transcriptase inhibitors or a non-nucleoside reverse transcriptase

inhibitor (NNRTI); stavudine (d4T) or zidovudine (AZT); lamivudine (3TC); and efavirenz (EFZ) or nevirapine (NVP) [8].

Use of antiretroviral therapy offered several advantages to HIV patients. One of the major strength of ART was the increase of survival time: the increase of which was between 4 and 12 years on initiation of ART after AIDS development compared to 9.2 months in the absence of ART [9,10,11] . The survival time was increased as antiretroviral therapy allowed maximal and durable suppression of replication of HIV, restoration and /or preservation of immune function, reduction of HIV related morbidity and mortality thereby improving the patients' quality of life [8].

In addition to the afore mentioned advantages, use of regimens based on two NRTIs and one NNRTI also allowed several benefits which included being efficacious, less expensive, having generic formulations, often available as fixed dose combinations (FDCs) and not requiring a cold chain[14]. FDCs had also the advantage of reducing the patient's pill burden thereby improving medication adherence [14,15]. Despite these advantages offered by ART or NRTIs and NNRTI, more than fifty percent of patients on the therapy failed to reach optimal results, due to medication intolerance/side effects, prior ineffective antiretroviral therapy and infection with a drug-resistant strain of HIV [11,12,13] .

City of Harare ART program

In Harare, the capital and largest city of Zimbabwe, HIV and AIDS remains a significant public health problem.[8] With a national HIV prevalence of 13.6% and an urban population of 1.6 million people, the estimated number of people infected with HIV in Harare was 217 000 [8,].

Harare City initiated the antiretroviral therapy in 2004[9]. Antiretroviral initiation was conducted at the city's Wilkins and Beatrice Road Infectious Disease Hospitals. Nineteen of the city's clinics offered follow up services. In line with the national antiretroviral therapy guidelines, the city offered two nucleoside reverse transcriptase inhibitors and one non nucleoside reverse transcriptase inhibitor. Aproximately 17% of the people living with HIV and AIDS, in Harare City, were on antiretroviral therapy[9].

Problem statement

An unpublished study done by Malunga, at Wilkins Hospital in Harare City, has indicated a high incidence of hyper-lacticemia- > 2.5mmols/litre in patients initiated on stalanev - a stavudine based regimen. Malunga's cohort study followed 180 patients for four months that were initially ART naïve and had been initiated on ART. The study found that 20% and 30 % of the study participants developed hyperlactatemia by the second and third month after ART initiation respectively.

The standard treatment for first line adult antiretroviral therapy in Zimbabwe have removed stavudine[19] but despite these recommendations and the adverse effects of stavudine the Zimbabwe target for stavudine replacement is 20%[1]. This research therefore aimed to determine the prevalence of HIV patients on stalanev, the burden of lactic acidosis and factors associated with developing lactic acidosis in Harare City.

Literature review

The antiretroviral drugs differed in how commonly they caused particular side effects and duration of side effects. While some side effects such as nausea, diarrhea and headache appeared shortly after starting ART and disappeared within a few weeks, others like peripheral

neuropathy and lactic acidosis worsened over time and would persist for ever. Some problems emerged months or even years after treatment had started. The major toxicities of nrti therapy over the medium-term to long-term, were secondary to inhibition of mitochondrial DNA polymerase β, resulting in impaired synthesis of mitochondrial enzymes that generate ATP by oxidative phosphorylation[13]. These included neuropathy (stavudine, didanosine, zalcitabine) and lactic acidaemia (didanosine, stavudine, zidovudine)[13].

Lactic acidosis

Lactic acidosis is defined as venous blood lactate greater than or equal to 5 mmol/L and either arterial pH of less than or equal to 7.35[17,18] , whilst hyperlactatemia is defined as a mild to moderate (2-5 mmol/L) increase in blood lactate concentration [19,20,21,]. Lactate production is partially dependent on pyruvate concentrations. Pyruvate is produced from glycolysis (85%) and proteolysis (15%) [22]. Formation of lactate is catalysed by lactate dehydrogenase (LDH).

$$\text{Pyruvate} + \text{NADH} + H^+ \xleftrightarrow{\text{LDH}} \text{Lactate} + NAD^+$$

Lactate is produced at about 0.8mmols/ Kg per hour, while simultaneous metabolism in liver and kidneys ensures normal blood concentrations of less than 2 mmols/L [22].

The Cohen and Woods classification of lactic acidosis defined two subgroups depending on the presence (Type A) or absence (type B) of tissue hypoxia [20,23]. The type B lactic acidosis has been described in HIV patients on ART as a cause of severe and fatal adverse reaction [24,25,26,27]. The NRTIs, stavudine (d4T), zidovudine (AZT) and didanosine (ddI) have been linked to the type B

lactic acidosis[25]. Mitochondrial toxicity through the inhibition DNA polymerase γ led to mtDNA depletion and finally dysfunction with disturbance of oxidative phosphorylation and shifting of the pyruvate–lactate equilibrium to lactate[25,28,and 29].

Calza reported an estimated prevalence of 15% and 35% of mild to moderate hyperlactatemia in (HIV)-infected patients treated with NRTIs[25] while a lower prevalence of 8 % and 12.1 % of hyperlactatemia were reported by Moyle et al from Westminster Hospital database and the University of Nairobi from the Kenyatta national hospital [30,31]. Contrary, lower prevalence of lactic acidosis or severe hyperlactatemia was reported by the university of Nairobi (1.1 %) and Calza et al [25, 30]. Arenas – Pinto explains this variation as being attributed to differences in case definitions [32]. For example, a study conducted in Botswana by Wester et al (2012) categorized patients as no lactic acidosis symptoms, minor symptoms but lactate <4.4 mmol/L, and symptoms with lactate ≥ 4.4 mmol/L [moderate to severe symptomatic hyperlactatemia or lactic acidosis whilst another study by Barlow-Mosha categorised patients into mild to moderate asymptomatic hyperlactatemia with lactate levels below 5 mmol and fulminate life-threatening lactic acidosis with lactate levels >5 mmol/L[33,34]. The incidence rate of lactic acidosis ranged from 1.7 to 25.2 cases per 1000 person-years of antiretroviral treatment, and was associated with a remarkable mortality rate, which varied from 30% to 60% in different studies [25,36].

Reviews conducted by Arenas-Pinto et al (2003) and Barlow-Mosha et al (2013) on lactic acidosis in HIV infected patients showed that the major signs and symptoms of lactic acidosis included elevated lactic acid levels in the blood, nausea, vomiting, non specific gastrointestinal symptoms, abdominal pain, dyspnoea and tachypnoea, and severe weakening of muscles in the legs and arms [32,35]. Similarly, Calza et al (2004) and Patel et al (2007) reported the same

symptoms in HIV patients on ART with lactic acidosis[25,36]. Calza et al (2004) and Noguera et al (2003) also reported asymptomatic hyperlactatemia in ART patients with the mild to moderate condition [25, 37].

Several risk factors for causing hyperlactatemia and lactic acidosis in HIV patients on ART have been reported in several articles. Early case studies showed nucleoside reverse transcriptase inhibitors as the major causes of lactic acidosis in HIV patients on antiretroviral therapy [27,38,39], but later analytic studies showed stavudine as the major drug causing the acidosis [40,41]. The most widely used stavudine based generic form or fixed dose combination was stalanev which came in two concentrations: stalanev 30 and stalanev 40. Stalanev 30 contained 30mg of stavudine per dose whilst stalanev-40 contains 40mg of stavudine. Both, stalanev 40 and 30, contained 150mg of lamivudine and 200mg of nevirapine. Lower dosage of stavudine (30 mg stavudine dose versus 40 mg) was associated with fewer reports of stavudine-associated adverse events and also a lower risk of stavudine discontinuation within the first year on ART [40].

The duration on stavudine when hyperlactatemia or lactic acidosis was experienced by the HIV patients was almost similar in different studies. Osler et al (2010) reported a duration on stavudine of six to eighteen months and Sivadasan et al (2009) also reported similar durations of about twelve months [42]. Similarly Manosuthi et al (2008) reported a median duration on ART of 13 months [43]. Due to stavudine or stavudine-containing regimens having been associated with serious side effects, such as mitochondrial toxicities, notably peripheral neuropathy and lactic acidosis, the WHO initially recommended a lower maximum dose of stavudine for all adults in 2007 and in 2009[44], recommended that it no longer be used for initial treatment of HIV infection

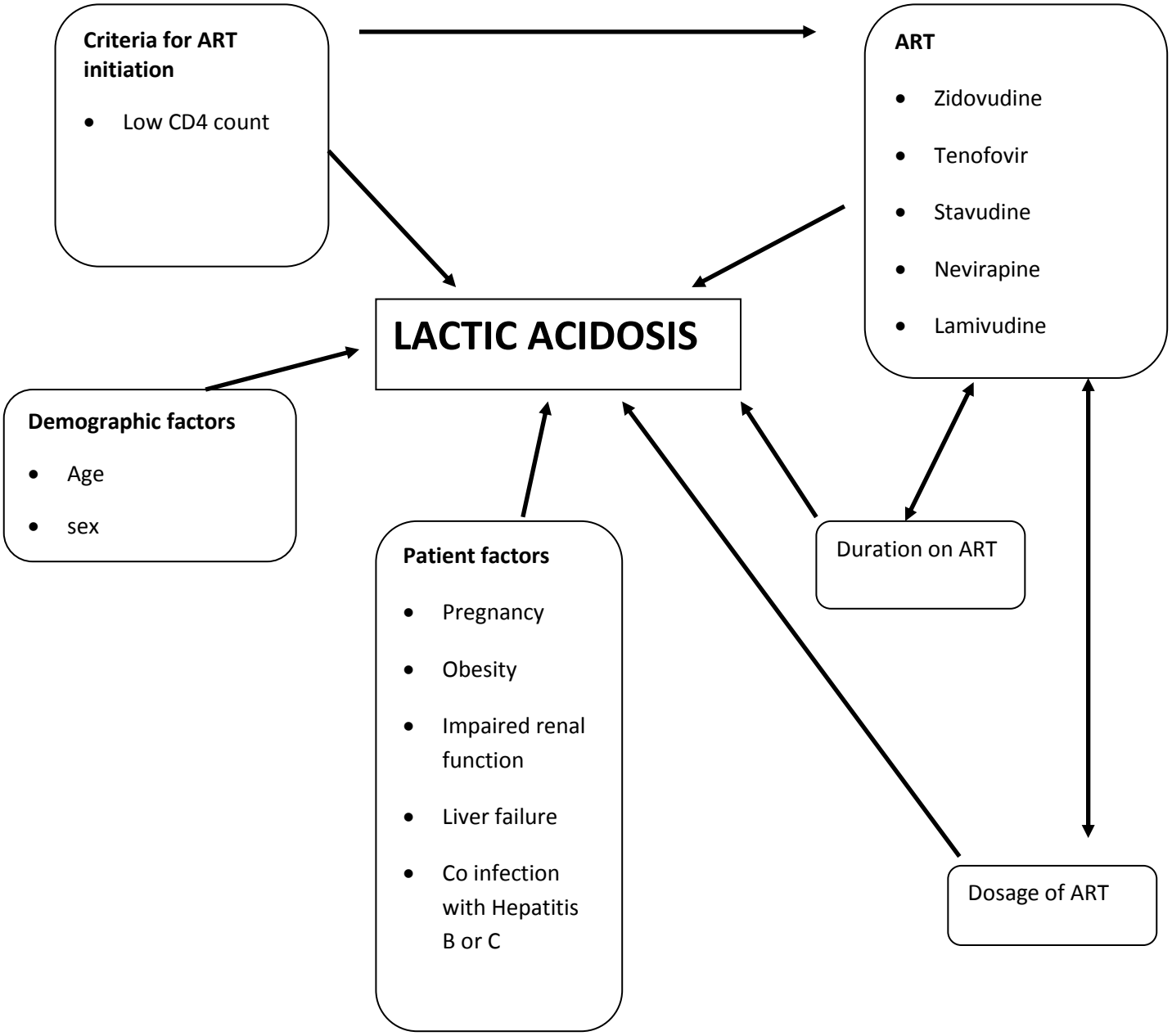
[45]. Stavudine or stavudine based compounds because of its low cost and widespread availability was still widely used in first-line therapy in developing countries [45].

CD4 count at ART initiation was also reported as one of the main factors that predisposed HIV patients on ART in developing lactic acidosis. Sheng et al (2004) reported that the median CD4+ lymphocyte count at the initial diagnosis of HIV infection and at the onset of lactic acidosis was 38 cells/ µL (range, 4 to 103 cells/µ L) and 108 cells/ µL (range, 79 to 224 cells/ µ L), respectively, and Desakorn et al (2011) reported a similar median CD4 cell count of 23 (8-94) cells/µL at baseline before ART initiation [46, 47]. A reduced risk of having lactic acidosis was seen by Phan et al (2012) for patients initiating ART with a baseline CD4 count >200 cells/µL [48].

Bolhaar and Karstaedt (2007) and Currier (2007) reported a higher chance of developing lactic acidosis in females when compared to their male counter parts [33, 40]. Currier though showed that lactic acidosis occurred among obese women with a median weight of 81 kg and postulated that genetic predisposition and the tendency of women to have hepatic steatosis were the most likely reasons for this gender disparity [47]. Similarly Wester et al revealed that females having a higher baseline BMI were predictive for the development of hyperlactatemia and lactic acidosis [33]. Other factors that predisposed HIV patients on ART to develop lactic acidosis and hyperlactatemia included impaired renal clearance, pregnancy and co-infection with hepatitis B or C [50.51,52,53].

Lactic acidosis is a life threatening condition in HIV patients on ART. Several researches have been conducted in different parts of the world and have shown the prevalence and factors causing lactic acidosis in HIV patients, but few or none have been recorded to show the burden of the disease in Zimbabwe.

Figure1: Conceptual framework: Factors leading to lactic acidosis in patients on ART



Study justification

Malunga's study showed that Harare City had patients on stavudine based regimens that were developing lactic acidosis but the magnitude or factors associated with the problem were not known. The number of patients that need to be changed from stavudine based regimens in Harare City is an issue of public health importance in the HIV/AIDS program particularly on issues of adverse reactions and making informed decisions. Life threatening adverse reactions from ART such as lactic acidosis cannot be ignored if optimal benefits are to be obtained.

Research questions

1. What is the burden of lactic acidosis in Harare City?

2. What are the factors associated with lactic acidosis in Harare City?

OBJECTIVES

Broad objective:

To assess the burden of lactic acidosis and factors associated with its occurrence among HIV patients on ART in Harare City

Specific objectives:

- To determine prevalence of lactic acidosis in HIV patients on ART in Harare City – 2012
- To determine factors associated with lactic acidosis in HIV patients on ART in Harare City – 2012

METHODS

Study Design

An analytic cross sectional study was carried out.

Study settings

Wilkins Hospital and Beatrice Road Infectious Disease Hospital Opportunistic Infection clinics constituted the study sites.

Study Population

HIV positive patients on ART presenting Wilkins Hospital and Beatrice Road Infectious Disease Hospital Opportunistic Infection clinics.

Study participants

HIV positive patients, on ART for at least four months presenting at Wilkins Hospital and Beatrice Road Infectious Disease Hospital Opportunistic Infection clinics.

A lactic acidosis study participant was defined as any HIV positive patient on ART for at least four months, tested during the time of study and had lactate levels above 5mmols/L.

A non lactic acidosis study participant was an HIV positive patient on ART for at least 4months, tested during the time of study and had lactate levels below 2.5mmols/L.

A patient with hyperlactatemia was defined as any HIV positive patient on ART for at least four months, tested during the time of study and had lactate levels between 2.5 and 5mmols/L.

Exclusion criteria

All HIV patients not on ART and all HIV patients on ART but less than 12 years.

Sampling procedure

Study participants were purposively sampled.

Sample size

Sample size was calculated using Epi-Info stat cal at 95% CI. Based on Marceau *et al*'s cross sectional study in 2003; an expected frequency of 1.8% in unexposed group and the percent disease among exposed of 24.8% was used to calculate a sample size of 250[54]. A total of 250 patients and nineteen health workers participated in the study.

Data collection technique

Interviewer administered questionnaires were used to assess for factors associated with lactic acidosis and health worker knowledge on lactic acidosis. Patient opportunistic infection card and opportunistic infection registers were reviewed for patient information. Blood was collected from study participants and was analysed for serum lactate levels.

Sample collection

After an overnight fast and being at rest for two hours, 5ml of arteriole blood was collected after explaining to the patient not to clench their hand. Tourniquet use was discouraged. Clenching hands and applying a tourniquet could raise levels of lactic acid from the hand muscles. Sodium fluoride or potassium oxalate was used as the anticoagulant of choice. The samples were chilled by packing on ice, and sent to the laboratory where plasma was separated within fifteen minutes of collection. Samples were analyzed within thirty minutes of collection. When samples could not be analysed within thirty minutes of collection the plasma was refrigerated for twenty four hours or frozen for one month.

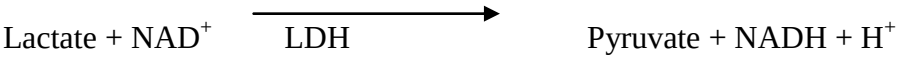
Sample analysis

The sclera E and Roche Cobras 3 chemistry analyzers were used in the analysis of plasma separated from the sodium fluoride or potassium oxalate anticoagulated sample. The method used in the in the analysis of lactate was a modification of the Marbach and Weil method which employed the oxidation of lactate to pyruvate.

Principle of test procedure

Rabbit muscle lactate dehydrogenase (LDH) catalysed the oxidation of lactate to pyruvate with simultaneous reduction of nicodinamide adenine dinucleotide (NAD). One mole of NAD was converted to one mole of NADH for each mole (equivalent) of lactate present. The absorbance due to NADH was directly proportional to the lactate concentration and was measured using a

two filter end point at 340 – 383nm. Hydrazine was used to trap the pyruvate as it formed thereby driving the reaction to completion.



Pretesting

A two-stage pretest of the study questionnaires and lactate level analysis was conducted. The questionnaire and lactate analysis procedure were initially given to other laboratory personnel soliciting comments to assess their validity and consistency. For lactate analysis, laboratory personnel from CIMAS and Lancet laboratories were consulted.

Ten opportunistic clinic patients participated in the interviewer administered reviewed questionnaire and based on the combined feedback from the OIC patients, a final version of the questionnaire was obtained. Ten samples were analysed – 5 at BRIDH and 5 at WIDH using the reviewed lactate method and the same samples were sent to Premier medical laboratory and UZUCSF laboratory with complimentary analyzers – inter-laboratory comparison was used to access for precision. All analyzers had been validated for accuracy.

PERMISSION

Permission to conduct the study was sought from the Health Studies Office and the director of health services of Harare City.

ETHICAL CONSIDERATIONS

Ethical approval was granted by the Medical Research Council of Zimbabwe (MRCZ) and Joint Research Ethics Committee (JREC). Participant consent was given after the aim, discomforts and benefits and their freedom to refuse without any consequences arising from their refusal or right to participate had been explained. Confidentiality of responses was assured. All data collected remained anonymous as no names were written on the questionnaires. The questionnaires were kept in a locked cabinet. Patients were asked to remit their phone numbers and patients with high lactate levels were contacted to report to opportunistic infectious clinic and managed according to the Harare City guidelines.

DATA ANALYSIS

Epi-info version 3.5.1 was used to generate frequencies, prevalence odds ratio (POR) and 95% confidence intervals (CI). Stratified analysis and logistic regression were used to control for confounding.

RESULTS

Demographic information

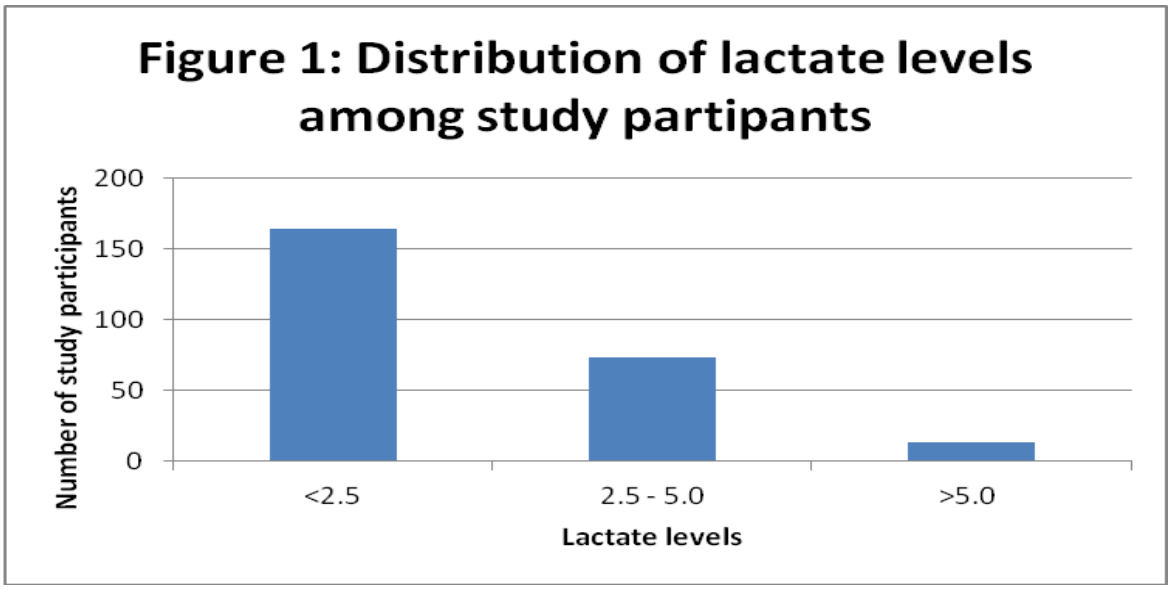
Beatrice road infectious disease hospital and Wilkins infectious disease hospital's opportunistic infection clinics constituted the study sites. A total of 250 patients; 54% (136) from BRIDH and 45.6% (114) from WIDH, on antiretroviral therapy (ART) for more than four months participated in the study. Majority were females 67% (170). The median age of the respondents was 37 years (Q_1:26, Q_3:45) and median years on ART was 2.1 years (Q_1:1, Q_3:3.2). The body mass index (BMI) was 18.7 kg/m^2 (Q1: 16.4, Q3: 23.7). Table I summarizes demographic information on study participants.

Table I: Socio- demographic characteristics of study participants from BRIDH and WIDH OIC in Harare City -2012

Variable		**Frequency (n=250)**	**p- value**
Sex	Females	168 (67)	0.22
	Males	82 (33)	
Median age = 37years (Q_1:26, Q_3:45)			
Median years on ART = 2.1 (Q_1:1, Q_3:3.2).			
(BMI) =18.7 kg/m^2 (Q1: 16.4, Q3: 23.7)			

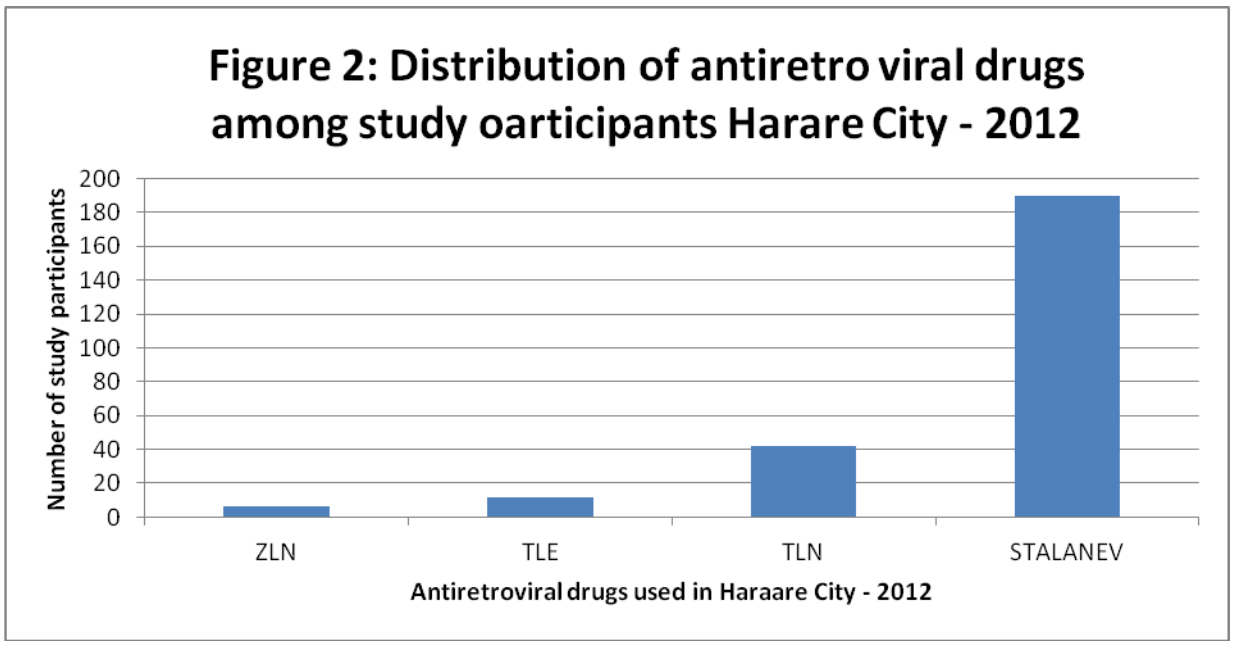
Lactate levels among study participants

Majority of the patients 65.6 % (164) had serum lactate levels of < 2.5 mmols/l, 29.2% (73) had levels between 2.5 and 4.9mmols /l. and 5.2% (13) had levels of > 5mmols /l. Figure 1 summarizes the distribution of serum lactate levels in the study participants.



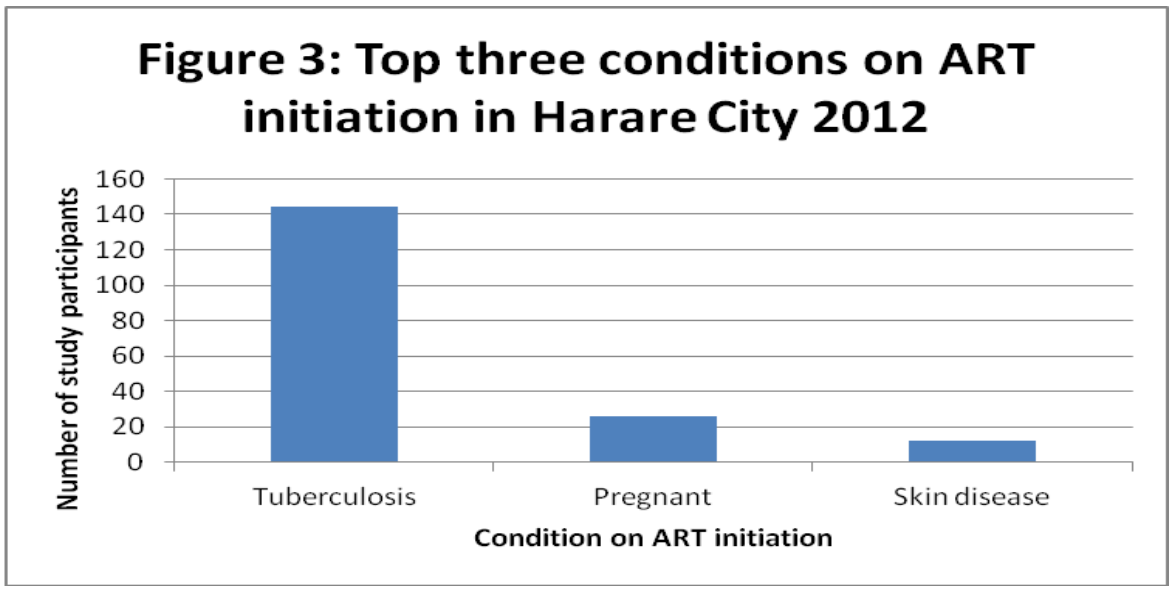
Drug combinations among study participants

Different drug combinations were recorded from the study participants. A total of four combinations were noted namely: Zidovudine, lamivudine, neverapine (ZLN); tenofovir, lamivudine, efevirenz (TLE); tenofovir, lamivudine, neverapine (TLN) and stavudine, lamivudine, neverapine (stalanev). ZLN was found in 2,4% (6), TLE in 4.8% (12), TLN in 16.8% (42) and stalanev in 76%(190) of the respondents. Figure 2 summarizes the distribution of the antiretroviral drug combinations among the study participants.

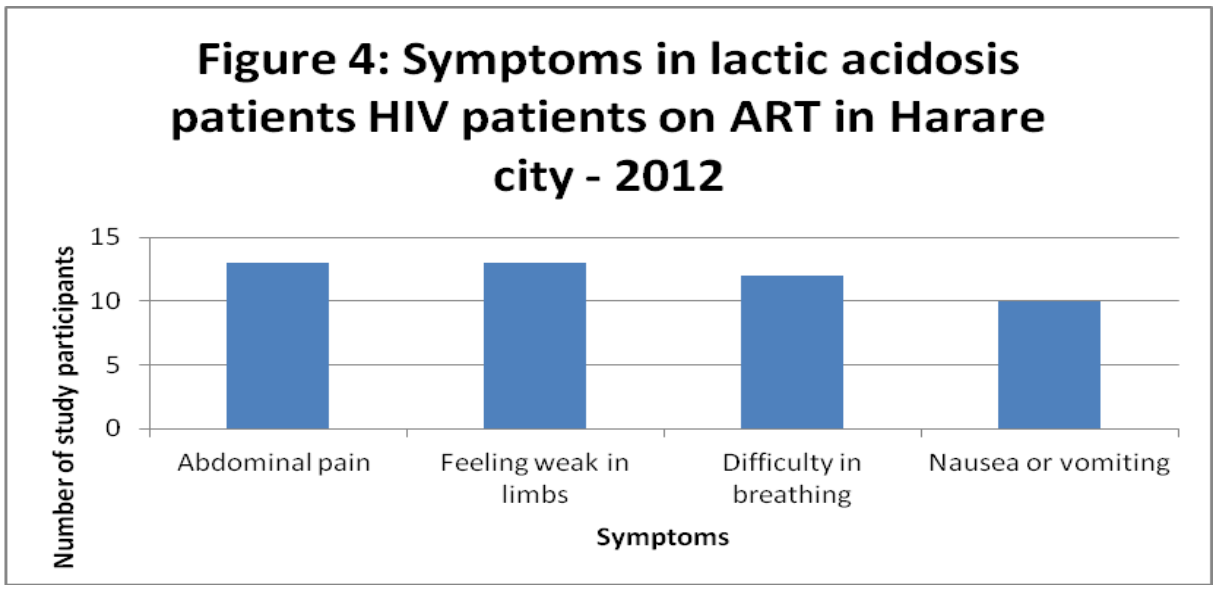


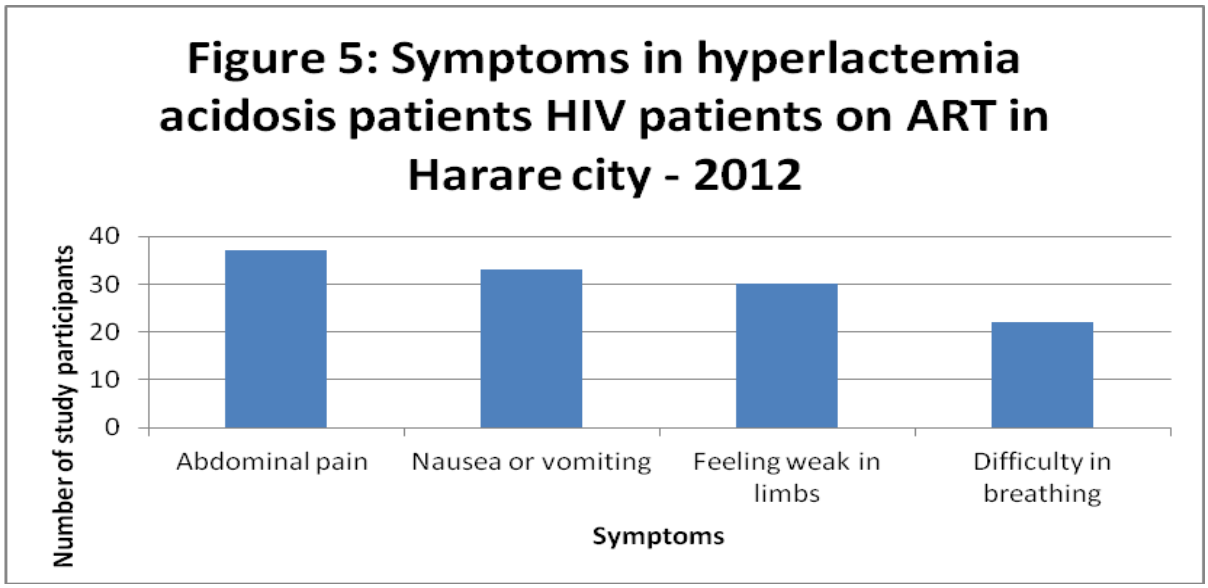
Descriptive statistics among study participants

Respondents were initiated on ART when presenting with different conditions. Majority of the patients had tuberculosis 57.6%(144), 11.4% (26) were pregnant and 4.8% (12) had skin disease. Figure 3 summarizes the top three conditions that respondents had on ART initiation.



All lactic acidosis patients presented with abdominal pain and feeling weak in the limbs whilst 92.3% (12) had difficulty in breathing and 76.9% (10) had nausea or vomiting. Hyperlactemia patients presented with nausea or vomiting 45.2% (33), abdominal pain 50.7% (37) difficulty in breathing 30.1% (22), weakness in the limbs 41.1% (30) and 39.7% (29) did not have any complaints. Figures 4 and 5 summarises the common symptoms in HIV patients on ART with lactic acidosis and hyperlactatemia.





Checking from the opportunistic infection card none of the participants had a history of renal or liver problems during the time of study and only one participant was co-infected with Hepatitis B virus.

On ART initiation the respondents had a median of 100 CD_4 cells/µl (Q_1:75.5; Q_3: 128)

Analytic studies

Factors associated with lactic acidosis in HIV patients on ART

Two risk factors were found and associated with developing lactic acidosis in HIV patients who have been on ART for at least four months namely: having a CD4 count of less than 100 cells/µl (OR: 6.1; p: 0.03), and being on stalanev (OR: 4.4; p: 0.025). Table II summarises factors associated with lactic acidosis in HIV patients on ART in Harare City - 2012

Table II: Factors associated with lactic acidosis in HIV patients on ART in Harare City - 2012

Factors			**Lactic acidosis case (n=13)**	**Normal case (n=247)**	**OR**	**P-value**
Sex	Male		6	76	1.8	0.29
	Female		7	161		
Cd4 count	≤100	Yes	10	84	6.1	0.003
		No	3	153		
Antiretroviral therapy	On Stalanev	Yes	13	177	4.4	0.025
		No	1	60		

Factors associated with hyperlactatemia in HIV patients on ART

No factors were found associated with developing hyperlactatemia in HIV patients on ART for more than four months. Having none of the four major symptoms; abdominal pain (OR: 0.17; p: < 0.01), feeling weak in the limbs whilst (OR: 0.23; p: < 0.01), difficulty in breathing (OR: 0.12; p: < 0.01), and nausea or vomiting (OR: 0.13; p: < 0.01), was found to be protective against hyperlactatemia in HIV patients on ART. Table III summarises factors associated with hyperlactatemia in HIV patients on ART in Harare City – 2012

Table III: Factors associated with hyperlactatemia in HIV patients on ART in Harare City - 2012

Factors			**Lactemia (n=73)**	**Normal case (n=164)**	**OR**	**P-value**
Sex	Males		24	52	0.95	0.86
	Females		49	112		
Antihero-viral therapy	On Stalanev	No	14	46	0.6	0.12
		Yes	59	118		

Logistic regression

A stepwise logistic regression was conducted. All factors associated with lactic acidosis were added to the model one after another until all possible variables were finished. One factor was found to be independently associated with lactic acidosis in HIV patients on ART for more than four months; CD4 of less than 100cells/μL. This factor remained statistically significant after completing the analysis (OR: 4.9; CI: 1.3-18.3).

Health worker knowledge

A total of 19 health workers from opportunistic infection clinics of BRIDH and WIDH participated in the study. Majority were females 78.9% (15). The median age of the respondents was 34years (Q_1:28, Q_3:38) and median years in OI clinic was 8 (Q_1:7, Q_3:9). Table IV summarises the socio- demographic characteristics of health workers from BRIDH and WIDH OIC in Harare City -2012.

Table IV: Socio- demographic characteristics of health workers from BRIDH and WIDH OIC in Harare City -2012

Designation	**Frequency**	
	No.	%
SRN	5	26.3
SCN	4	21.1
PCC	10	52.6
Median age: 34years (Q_1:28, Q_3:38)		
Median years in OI clinic 8 (Q_1:7, Q_3:9).		

A few 2(10.5%) of the health workers knew what lactic acidosis was and 5 (26.3%) knew that antiretroviral drugs caused lactic acidosis. Only 3 (15.8%) knew the symptoms of lactic acidosis. When the responses on knowledge on lactic acidosis were aggregated on a Likert scale of 1-10 where 0-4 was poor, 5-6 was fair and 7-10 was good, 15/19 respondents had a poor score of 5-6 out of 10. Knowledge on the ART associated lactic acidosis was below 50% on all objectives. Eight (42.1%) of the study participants, only state register nurses and state certified nurses, were trained in HIV ART.

DISCUSSION

The percentage of HIV adolescents and adults not on stavudine or stalanev –a stavudine based therapy; in Harare City was 24% which is actually higher than the national 2011 target of 20%. Harare City seems to be doing well in line with the 2010 World Health Organization recommendation for transitioning patients to less toxic regimens. The City though still has a big challenge of transitioning 76% of its HIV patients on ART from stavudine based therapy as it does not have enough capacity in terms of human resources and initiating sites as well as enough of the drugs such as tenolum.

Though several drug combinations of ART were being used in Harare City, only stalanev, a stavudine based regimen, was found to be associated with developing lactic acidosis. Similar associations between stavudine based regimens and the development of lactic acidosis have been reported in several studies [40, 41]. This finding on stavudine is contrary to reports by Murphy et al (2003) and Butt (2003) that have shown that didanosine was also associated with HIV patients on ART developing lactic acidosis [54, 55]. Zidovudine was also found associated with developing lactic acidosis in HIV patients [56, 57].

Patients on ART for more than four months, presenting at BRIDH and WIDH's OIC had an unnoted high prevalence of lactic acidosis (5.2%) and hyperlatactemia (29.2%). Some studies, Calza et al (2005) for example, have reported a similar prevalence of hyperlactatemia in HIV-infected patients on ART of between 15% and 35%.[25] Other studies though, like Datta et al

(2001) and Moyle et al (2001), have reported lower prevalences of hyperlactatemia in outpatients on ART of around 9–16% [31,58]. Datta et al (2001) and Moyle et al (2001) also reported a prevalence of 2% hyperlactatemia among untreated patients postulating that the hyperlactatemia among HIV patients on ART may be a consequence of the therapy [31, 58].

All lactic acidosis patients presented with at least one of the four major symptoms but had not been suspected of lactic acidosis. Failure to notice this life threatening condition syndromically, in lactic acidosis patients, may be attributed to the non training of primary care counselors on the adverse effects of antiretroviral therapy. Furthermore little knowledge by the majority of the health workers on the symptoms of lactic acidosis may indicate that HIV patients were not being routinely screened syndromically for lactic acidosis.

Even though having symptoms, namely nausea or vomiting, abdominal pain, weakness in limbs and difficulty in breathing, was a major indicator of lactic acidosis in patients on ART about 50% of the hyperlactataemia patients could not be identified by symptoms or were asymptomatic. This, having symptomatic and asymptomatic hyperlactatemia has also been reported in other studies [25, 37]. Since this was a cross sectional study the information generated could not show whether hyperlactatemia preceded lactic acidosis. Some other studies though have shown that hyper-lactemia could not predict development of lactic acidosis as the onset of lactic acidosis was abrupt, without preceding elevation of lactate levels [36]. This study therefore would recommend routine syndromic screening for lactic acidosis in HIV patients but would refrain from syndromic screening for hyperlactatemia.

This research has also shown that a low nadir CD4 count of ≤ 100 cells /µl before the inception of NRTI therapy increased the chance of having lactic acidosis. This, association of having lactic acidosis in HIV patients on ART and low CD4 count, is consistent with findings reported by Boennet et al and Coglan et al, although they both reported a nadir CD4+ count of ≤ 200 cells/ µl [59, 60]. HIV patients with CD4 counts of ≤ 100 cells/µl before the inception of ART may therefore need to have their lactate level monitored after ART initiation.

The strength of the research included the unalterable exposure to stalanev overtime thereby allowing temporal relationship to be established between stalanev and lactic acidosis, and providing estimates of prevalence of all factors measured. Despite these strengths, the research had potential limitations one of which was the non availability of blood gas analyzers to assess pH in the study participants. As such lactate levels were used as proxy indicators of acidosis. Another limitation was the use of literature that was more than ten years old. Most studies on antiretroviral therapy were conducted in the early years when ART was established and with new ART regulations such as the phasing out of stavudine would explain the use of old literature.

Conclusion

In Harare lactic acidosis remained a problem in HIV patients on ART. The problem of having the disease was highest in patients on stavudine based therapy and had a low nadir CD4 count on

ART initiation. The problem though was low in patients not complaining of abdominal pain, difficulty in breathing, nausea or vomiting and feeling weak in the limbs.

Although lactic acidosis was a problem in Harare it may reflect similar challenges in other areas with HIV patients on ART. It maybe therefore important to stop stavudine based therapy or to routinely screen for lactic acidosis in HIV patients who had a CD4 count of less than 100 cells /µl on ART initiation in areas where stavudine replacement was still a challenge.

Recommendations

We recommend mandatory training of all OIC staff on lactic acidosis especially syndromic screening of lactic acidosis such that patients suffering from the adverse reaction would be identified and removed the from the drug. Replacement of stavudine should be continued but at a higher rate in order to reduce the number of patients with or will have lactic acidosis. There is also need to periodically screen for plasma lactate levels in patients who had low (<100cells/µl) CD4 counts on ART initiation. Further analytic studies would be of benefit in showing the temporal relationship between stavudine and lactic acidosis.

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Appendix 1: Data collection tools

Questionnaire for HIV patients on ART presenting at Harare City OICs

1.Questionnaire No……

2. Name of Hospital …….

Demographic Data

3. Sex: Male *murume*…….Female *mukadzi*……..

4. Age *makore ekubarwa*……..

Patient factors

5. May we know if you are pregnant *tingada kuziva kana makazvitakura* YES *hongu*..... NO *kwete*.....

6. What is your weight and height (Obesity) *huremu huye kureba kwenyu kwakadini* check on patient card or measure .....kgs, ...m

8. Have you ever had Kidney problems (Impaired renal function*) makamborwara kana kuti munotambura neitsvo here* check on card YES.....NO.....

9.Have you ever had liver problems (Impaired liver function) *makamborwara kana kuti munotambura nechitaka chenyu here* check on card YES.....NO.....

10.Have you ever had Hepatitis (Co infection with Hepatitis B or C) *makamborwara kana kuti munotambura nehepatitisi here* check on card YES.....NO.....

11.Are you suffering from the following *munombonzwa zvinotevera here*

12.Nausea/vomiting *kuda kurutsa kana kutorutsa* YES…….. NO…….

13.Abdominal pain *kurwadziwa nemudumbu* Yes……. No……

14.Difficulty breathing *kutambura pakufema* YES …….. NO……..

15.Severe weakening of muscles in the legs and arms *kuneta neta mumakumbo nemumaoko* Yes …… No…….

16.Others *zvimwe* ……

Criteria for ART initiation

12.What were you suffering from when you were initiated on ART check on card *mungaziva zvamainzwa apo makatanga kupiwa mapitsi emuchirongwa cheshuramatongo* ..... Opportunistic infections (list) check on card .....

.....

.....

13.WHO stage check on card .....

14.CD4 count check on card .....

15.TB check on card.....

15.Other .....

17. NRTIs

Zidovudine YES..... NO.....

Tenofovir YES..... NO.....

Stavudine YES..... NO.....

Nevirapine YES..... NO.....

Lamivudine YES..... NO.....

18. Dosage of NRTI .....

Others specify

.....

19. How long have you been on ART check on card *mavanenhamboi muri muchirongwa* years *makore*.....? months *mwedzi* .....

20. Laboratory results

lactate levels…… mmol/l

Health worker knowledge

1. Questionnaire No…… Name of Hospital …….

Socio- Demographic Data

2. Sex

Male……Female……..

3. Age……..

4. Designation ……..

5. Number of years in service ……

6. Number of years in OI clinic ……

7. Trained in HIV ART therapy

    a. YES……. NO…….

    b. when……

Knowledge on HIV lactic acidosis

8. what is lactic acidosis (correct def) YES…… NO……..
9. what causes lactic acidosis in HIV patients

   ……

10. what are the symptoms of lactic acidosis
    a. Nausea/vomiting YES ☐ NO ☐
    b. abdominal pain Yes ☐ No ☐
    c. difficulty breathing YES ☐ NO ☐
    d. severe weakening of muscles in the legs and arms Ye☐ No ☐
    e. others ……

Appendix 2: Consent Forms

Project title: Factors associated with lactic acidosis in HIV patients on ART - Harare city

Name of researcher: Emmaculate Choto

Designation: MPH student at the college of health Sciences Zimbabwe

Phone number: 077263363

Project description: This project involves a questionnaire on HIV management in Harare City and analysis of lactate levels from a blood sample. Approximately two tea-spoonfuls (4ml) of blood will be collected once during the study and the researcher will ask you questions. Lactate results and your answers will be used in the study.

Purpose of research: The aim of this research is to gain a better understanding of the disease - lactic acidosis and to identify the magnitude of the problem in patients on ART in Harare city so as to improve patient's quality of life. The information obtained from the study will help in the management of patients on ART and may also be used in decision making in the future.

Procedure: If you are to participate in this study, blood will be drawn from your arm and you will be asked questions on the questionnaire? Any significant findings from your blood test and these questions will be brought to the attention of the director of Health services and the health team in OI clinics. The OI team will notify you immediately if the results indicates you need treatment or during your normal routine visits if they do not. You will be managed according to the City health guidelines. The blood collected will be kept refrigerated for a week and then discarded according to city health guidelines.

Discomforts and risks: There is no risk of your answers being known by anyone else except the usual medical staff and myself. The forms you will fill for your participation in this project are kept in a locked office. There is no risk to you on collection of the blood sample but little discomfort will be felt during sample collection.

Potential benefits: there is a direct benefit to you in this study as any significant findings during this study is communicated to the health team in OI clinics who can use them to improve on management of the disease. There is also an indirect benefit for present and future HIV infected patients as the findings from this study could be used in further management of their disease.

Study withdrawal: You may choose not to participate or withdraw from the study anytime without loss of benefits entitled to you as a patient.

Problems or Questions: If you have questions about this study now or in the future please ask, call Ms Choto on 0772 263 363 or contact her on BRIDH laboratory ,City Health department, Box 596, number 369 Simon Mazorodze Road Harare. If you have any questions about your rights as a research participant please call the director of city of Harare on 04-791631 Xt 2240,MRCZ on 04- 791792 or JREC on 04-708140

Participant Informed Consent

I have read the above Explanatory Statement. I agree to take part in the above research project. I am willing to allow the researcher to ask me questions and draw blood to be tested for lactate levels.

I understand that any information I provide and from my blood test is confidential, and that no information that could lead to the identification of any individual will be disclosed in any reports on the project.

I also understand that my participation is voluntary, that I can choose not to participate in the project, and that I can withdraw freely from the project.

Name: ..... (please print)

Signature:.....Date: .....

Chibvumirano

Musoro wetsvakiridzo: tsvakiridzo yezvikonzero zveLactic acidosis kuvanhu vane utachiwana hweshuramatongo (HIV) muguta reHarare

Zita remuongorori kana musori: Emmaculate Choto **Run hare** 0772263363

Basa remuongorori kana musori: Mudzidzi weMPH paCollege of Health Sciences

Tsanangudzo yetsvakiridzo: Mutsvakiridzo iyi tinenge tichitarisa zvikonzero zvinoita kuti munhu aneHutachiwana hweshuramatongo (HIV) aite lactic acidosis muguta reHarare uye tinoda kuona huwandu hwechirwere ichi. Tinobvunza mibvunzo uye tinovheneka ropa. Panoongororwa ropa panodikanwa zvimirimita zvinokwana zvina zveropa kana kuti zvipunu zviviri zvatoisisa tsvigiri patinonwa putugadzike. Tinokumbira kuzoshandisa mhinduro dzenyu uye zvichabuda pakuvhenekwa kweropa renyu mukuwana ruzivo rwakapetwa maererano nechirwere ichi.

Chinangwa chetsvakiridzo: Chinangwa chetsvakiridzo ndechekuda kunzwisisa zvinoitika apo munhu akabatwa nechirwere cheshuramatongo pamwe nelactic acidosis uye kuona kuti chirwere ichi chakawandasei muguta reHarare. Tinodavira kuti zvinowanikwa mutsvakiridzo iyi zvichabetsera pakukurudzira kugara noutano hwakanaka pamurwere uye pakurapwa kwevarwere vanehutachiwana nelactic acidosis. Tinodavira ruzivo urwu ruchawanikwa ruchabatsirawozve vanamazvikokota veutano apovanenge vachironga nezveutano hwevanhu varipachirongwa uye vakabatwa ne lactic acidosis.

Nzira dzichashandiswa: Kana mukapinda mutsvakiridzo iyi muchabvunzwa mibvunzo inoenderana nelactic acidosis uye muchatorwa ropa riniongororwa kuti mune lactic acidosis here.

Zvichawanikwa pachavhenekwa ropa renyu uye pakuongororwa kwemhinduro dzenyu tinodavira kuti zvichabatsira pakurapwa kwenyu nevagari vemuno. Zvichaudzwa kudare rinoona nezveutano muhurumende, kuvakuru veutano imo muguta reHarare uyezve kuvadzidzisi vangu. Panobuda maresults enyu elactic acidosis vashandi veku OI vachakuudzai, nukuchimbidzika kana maonekwa muchida rubatsiro kana musina zvamawanikwa munozoudzwa apo munowanzouya kuzowonekwa .Tichatevedza gwara rekurapwa reguta reHarare apo muchange morapwa. Ropa ratichatora ticharichengeta kwevhiki, tozobva torirasa tichitevedza nzira dzinoshandiswa neCity of Harare.

Matambudziko kana zvibinga mupini: Zvinenge zvabuda mukuongororwa kweropa uye kwemhinduro dzenyu mutsvakiridzo iyi zvichachengetedzwa zvikuru zvokuti hatibvumiri munhu ani-nani kuzviona (kusiya kwevashandi vemuchipatara vanoshanda basa irori neni badzi) uye tichazvivharira mukabati inokiyiwa. Hamuna matambudziko amunowana pachatorwa ropa renyu. Mutsvakiridzo iyi hatikurwadzisei panhengo dzemuviri wenyu asi muchangodzwa kuti tobvu apotichatora ropa.

Zvamunokwanisa kuwana kubva mutsvakirodzo: Mutsvakiridzo iyi tinokwanisa kuwana zvinobatsira pakurapwa kwenyu kana vanhu veguta rino reHarare. Zvinobatsirawozve pakuronga matanho akanaka ekurapa chirwere ichi panguva ino neramangwana.

Kubuda mutsvakiridzo: Munokwanisa kuita sarudzo yekupinda kana kubuda mutsvakiridzo chero nguva yamunoda musingarasikirwe nezvamanga muchawana muhurongwa uhwu.

Mibvunzo kana zvinonetsa: Tinokumbirawo kuti kana minemibvunzo mutibvunze uye kana pane zvamunenge muchida kuzobvunza pamberi mundibate parunhare rwunoti-0772263363 kana kunyora kukero inoti BRIDH laboratory ,City Health department, Box 596 Harare kana

kusvika pa369 Simon Mazorodze road. Kana panezvamungada kuziva nezvekodzero dzenyu maererano nezvetsvakiridzo iyi munokwanisa kubata mukuru weutanao muguta re Harare parunhare rwunoti 04 791631 Xt 2240, MRCZ pa 04-791 792 kana JREC nhamba dzinoti 04-708140

Mvumo

Ndaverenga gwaro retsvakiridzo. Ndinofarira kupinda mutsvakirdzo iyi. Ndichapa kumuongororo mvumo yekushandisa zvichawanikwa pakuvhenekwa kweropa rangu uye pamhinduro idzo ndichapa panguva yetsvakiridzo.

Ndanzwisisa kuti panezvandichataura uye pane zvichawanikwa mutsvakiridzo iyi, hapana munhu unozozviziva sezvo muongorori nevamwe vake vachavimbika kubata miromo yavo uyezve havazoburitsi zita rangu pachena apo vanonyora magwaro avo.

Ndanzwisisawo kuti kupinda mutsvakiridzo iyi hazvimanikidzwe, uye kuti ndinokwanisa kusapinda muurongwa uhwu pasina zvibingidzo.

Zita rangu) _____

Runyoro rwangu) _____

Parental Consent Form

Project title: Factors associated with lactic acidosis in HIV patients on ART - Harare city

Name of researcher: Emmaculate Choto

Designation: MPH student at the college of health Sciences Zimbabwe

Phone number: 0772 263363

Project description: This project involves a questionnaire on HIV management in Harare City and analysis of lactate levels from a blood sample. Approximately two tea-spoonfuls (4ml) of blood will be collected once during the study and the researcher will ask questions. Lactate results and your answers will be used in the study.

Purpose of research: You are being asked to allow your child to participate in a research study of lactic acidosis in HIV patients on ART. The purpose of the study is to gain a better understanding of the disease - lactic acidosis and to identify the magnitude of the problem in patients on ART in Harare city so as to improve patient's quality of life. Your child was selected as a possible participant in this study because he/she is HIV positive and has been on ART for more than 3moths. The number of participants is 250 and they are all coming from City of Harare.

Procedure: If you decide to allow your child to participate in this study, blood will be drawn from your child's arm and questions on the questionnaire will be asked? Any significant findings from the blood test and these questions will be brought to the attention of the director of Health services and the health team in OI clinics. The OI team will notify you immediately if the results indicates that the child needs treatment or during the child's normal routine visits if they

do not. Your child will be managed according to the City health guidelines. The blood collected will be kept refrigerated for a week and then discarded according to city health guidelines.

Discomforts and risks: There is no risk of the answers being known by anyone else except the usual medical staff and myself. The forms filled during your child's participation in this study will be kept in a locked office. There is no risk to your child on the collection of the blood sample but little discomfort will be felt during sample collection.

Potential benefits: there is a direct benefit to your child in this study as any significant findings during this study is communicated to the health team in OI clinics who can use them to improve on management of the disease. There is also an indirect benefit for present and future HIV infected patients as the findings from this study could be used in further management of their disease.

Voluntary participation: Participation in this study is voluntary. If you decide not to allow your child to participate in this study, your decision will not affect your or your child's future relations with this institution, its personnel, and associated hospitals **of Harare City.** If you decide to allow your child to participate, you and your child are free to withdraw your consent and assent and discontinue participation at any time without penalty.

Problems or Questions: If you have questions about this study now or in the future please ask, call Ms Choto on 0772 263 363 or contact her on BRIDH laboratory ,City Health department, Box 596, number 369 Simon Mazorodze Road Harare. If you have any questions about your rights as a research participant please call the director of city of Harare on 04-791631 Xt 2240,MRCZ on 04- 791792 or JREC on 04-708140

AUTHORIZATION

You are making a decision whether or not to allow your child to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to allow your child to participate.

The date you sign this document to enroll your child in this study, that is, today's date, MUST fall between the dates indicated on the approval stamp affixed to each page. These dates indicate that this form is valid when you enroll your child in the study but do not reflect how long your child may participate in the study. Each page of this Informed Consent Form is stamped to indicate the form's validity as approved by the MRCZ.

_____ _____

Name of Parent (please print) Date

_____ _____

Signature of Parent or legally authorized representative Time

_____

Relationship to the Participant

_____

Signature of Witness Signature of Research Staff

(*Optional*)

For children 13 years old to 17 years old

My participation in this research study is voluntary. I have read and understood the above information, asked any questions which I may have and have agreed to participate. I will be given a copy of this form to keep.

_____

Name of Participant

_____

Signature of Participant

For children between the ages of 12 - 13

I have discussed this clinical research study with the child using language which is understandable and appropriate. I believe I have fully informed this participant of the nature of the study and its possible risks and benefits. I believe the participant understood this explanation and assented to participate in this study.

Researcher Name ……

Researcher signature

…….

Witness name ……..

Witness signature ……

Chibvumirano chinobva kuvabereki

Musoro wetsvakiridzo: tsvakiridzo yezvikonzero zveLactic acidosis kuvanhu vane utachiwana hweshuramatongo (HIV) muguta reHarare

Zita remuongorori kana musori: Emmaculate Choto **Runhare** 0772263363

Basa remuongorori kana musori: Mudzidzi weMPH paCollege of Health Sciences

Tsanangudzo yetsvakiridzo: Mutsvakiridzo iyi tinenge tichitarisa zvikonzero zvinoita kuti munhu aneHutachiwana hweshuramatongo (HIV) aite lactic acidosis muguta reHarare uye tinoda kuona huwandu hwechirwere ichi. Tinobvunza mibvunzo uye tinovheneka ropa. Panoongororwa ropa panodikanwa zvimirimita zvinokwana zvina zveropa kana kuti zvipunu zviviri zvatoisisa tsvigiri patinonwa putugadzike. Tinokumbira kuzoshandisa mhinduro dzenyu uye zvichabuda pakuvhenekwa kweropa renyu mukuwana ruzivo rwakapetwa maererano nechirwere ichi.

Chinangwa chetsvakiridzo: Tirikukumbira kuti mwana wenyu apinde mutsvakiridzo lactic acidosis muvanh u vane utachiwana hweHIV uye vachinwa mishonga yacho. Chinangwa ndechekuda kunzwisisa zvinoitika apo munhu akabatwa nechirwere cheshuramatongo pamwe nelactic acidosis uye kuona kuti chirwere ichi chakawandasei muguta reHarare. Mwana wenyu tamusarudza nokuti ane chirwere cheshuramatongo uye anwa mishonga yechirwere ichi pamwedzi inopfuura mitatu. Vanhu vachapinda mutsvakiridzo iyi vanokwana mazana maviri nemakumi mashanu uye vose vanenge vachibva muguta reHarare

Nzira dzichashandiswa: Kana mukabvumira mwana wenyu kupinda mutsvakiridzo iyi tichatora ropa paruoko rwemwana wenyu uye tichabvunza mibvunzoe. Zvichawanikwa pachavhenekwa ropa remwana uye pakuongororwa kwemhinduro dzenyu tinodavira kuti zvichabatsira pakurapwa kwenyu nevagari vemuno. Zvichaudzwa kudare rinoona nezveutano muhurumende, kuvakuru veutano imo muguta reHarare uyezve kuvadzidzisi vangu. Panobuda maresults elactic acidosis vashandi veku OI vachakuudzai, nokuchimbidzika kana maonekwa muchida rubatsiro kana musina zvamawanikwa munozoudzwa apo mwana anowanzouya kuzowonekwa .Tichatevedza gwara rekurapwa reguta reHarare apo mwana achangeorapwa. Ropa ratichatora ticharichengeta kwevhiki, tozobva torirasa tichitevedza nzira dzinoshandiswa neguta reHarare.

Matambudziko kana zvibinga mupini: Zvinenge zvabuda mukuongororwa kweropa remwana uye mhinduro dzenyu mutsvakiridzo iyi zvichachengetedzwa zvikuru zvokuti hatibvumiri munhu ani-nani kuzviona (kusiya kwevashandi vemuchipatara vanoshanda basa irori neni badzi) uye tichazvivharira mukabati inokiyiwa. Mwana haana matambudziko anowana pachatorwa ropa rake. Mutsvakiridzo iyi hatikurwadzise mwana panhengo dzemuviri weke asi achangodzwa kuti tobvu apotichatora ropa.

Zvamunokwanisa kuwana kubva mutsvakirodzo: Mutsvakiridzo iyi tinokwanisa kuwana zvinobatsira pakurapwa kwemwana kana vanhu veguta rino reHarare. Zvinobatsirawozve pakuronga matanho akanaka ekurapa chirwere ichi panguva ino neramangwana.

Kubuda mutsvakiridzo: Mukabvumira mwana kupinda mutsvakiridzo iyi munokwanisa kuita sarudzo yekupinda kana kubuda mutsvakiridzo chero nguva yamunoda musingarasikirwe nezvamanga muchawana muhurongwa uhwu.

Mibvunzo kana zvinonetsa: Tinokumbirawo kuti kana minemibvunzo mutibvunze uye kana pane zvamunenge muchida kuzobvunza pamberi mundibate parunhare rwunoti-0772263363 kana kunyora kukero inoti BRIDH laboratory ,City Health department, Box 596 Harare kana kusvika pa369 Simon Mazorodze road. Kana panezvamungada kuziva nezvekodzero dzenyu maererano nezvetsvakiridzo iyi munokwanisa kubata mukuru weutanao muguta re Harare parunhare rwunoti 04 791631 Xt 2240, MRCZ pa 04-791 792 kana JREC nhamba dzinoti 04-708140

Mvumo

Muri kuzotaura zvichaitika maererano nekuti mwana wenyu apinde kana kusapinda mutsvakiridzo. Runyoro rhenium rwunoreva kuti manzwisisa nezve tsvakiridzo uye mabvuma kuti mwana apinde mutsvakirdzo iyi.

Musi wamunoisa runyoro rwenyu mwana anobva apinda mutsvakiridzo, zvichireva zuva ranhasi.

Zita remubereki…….. Zuva ……..

Runyoro rwemubereki…… Nguva…….

Ukama huripakati penyu no mwana ……..

Zita remunhu anpo uchapupu……..

Runyoro rwemunhu anopa uchapupu……

Kuvana vane makore 13 kusvika 17

Ndapinda mutsvakiridzo iyi nokuda kwangu. Ndaverenga ndikanzwisisa magwaro ari pamusoro pendima ino, ndabvunza mibvunzo ndikada zvangu kupinda mutsvakiridzo. Ndichapuwawo gwaro rakafanana nerandichanyora kuti ndigozvichengetera.

Zita rangu…….

Runyoro rwangu…….