

Research Article

Factors Associated with Human Immunodeficiency Virus First Line Treatment Failure in Zvishavane District, Zimbabwe, 2014

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Abstract

Introduction: Globally, first line HIV treatment failure remains a challenge, particularly in resource constrained settings. Midlands Province 2013 data showed that Zvishavane district had the highest prevalence of first line treatment failure at 16% against a national average of 1%. First line ART failure comes with poor treatment outcomes. We conducted a study to determine factors associated with first line HIV treatment failure in Zvishavane district.

Methods: A 1:1 unmatched case control study was conducted. A case was an HIV positive patient who was on first line ART for >6 months in Zvishavane district and was switched to second line ART regimen because of treatment failure in 2013/2014. A control was an HIV patient in Zvishavane district who had been on first line ART for >6 months and had not failed first line ART. Pretested interviewer administered questionnaires were used to collect data from randomly selected participants. Logistic regression analysis was conducted.

Results: A total of 246 participants, 123 cases and 123 controls, were recruited. Independent risk factors were poor adherence (<80% adherence) to ART [AOR=5.14, 95%CI (2.75-9.62)], drug stock outs [AOR=3.02, 95%CI (1.20-6.98)], baseline CD4 count of <50 cells/mm³ [AOR=3.25, 95%CI (1.47-7.16)] and baseline WHO Stage 3 or 4 [AOR=1.95, 95%CI (1.05-3.61)]. Drug stock outs were a significant determinant of poor ART adherence [OR=3.09, 95%CI (1.83-5.21)].

Conclusion: Low baseline CD4 count and WHO stage 3 or 4 at ART initiation is associated with treatment failure. Improving adherence and avoiding ART drug stock outs may reduce treatment failure.

Keywords: First line treatment failure; Zvishavane district

Introduction

Human Immunodeficiency Virus (HIV) is a lentivirus that causes acquired immunodeficiency syndrome, a condition in humans in which progressive failure of the immune system allows life threatening opportunistic infections [1]. Globally 35.3 million (32.2 million-38.8 million) people were living with HIV at the end of 2013 [2]. Approximately, 0.8% of adults aged 15-49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions [2]. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults living with HIV, and accounting for 70.8% of the people living with HIV worldwide [2]. Zimbabwe has experienced a decreasing trend in HIV prevalence from 26.7% in 2002 to 13.1 % in 2013 [3].

Human Immunodeficiency Virus (HIV) treatment failure can be defined by clinical, immunologic or virologic measures. Virologically, HIV treatment failure is a repeated HIV Ribonucleic acid (HIV RNA) values above the lower limit of detection of a sensitive assay (usually 50 copies per mL) [4]. The World Health Organization (WHO) guidelines define treatment failure virologically as viral load

persistently (at least 2 results) above 5000 copies/mL. This is despite the patient taking antiretroviral therapy regimen. The implication would be that the medication is no longer effective to suppress viral replication in a patient.

The success of antiretroviral treatment is defined more specifically by viral suppression [4]. Therefore the standard of care should be to maintain an RNA level of below the limit of detection (generally <50 copies/mL). Based on this specific criterion, HIV RNA levels that are >50 copies/mL mean that Antiretroviral Therapy (ART) regimen is failing to suppress viral load; hence the patient can be diagnosed with HIV treatment failure. Zimbabwe National Opportunistic Infections/Antiretroviral Therapy (OI/ART) program does not routinely measure viral load in patients and uses clinical and immunological measures for patient monitoring and diagnosis [5].

Some measures which can be adopted to prevent or reduce HIV treatment failure include perfect adhering to ART. According to De Beaudrap P et al in 2013 in Senegal; if a patient fails first line ART, the risk of that patient failing subsequent ART or developing HIV DR significantly increases [6]. Detecting virologic failure and intervening appropriately reduces mortality from HIV infection. Furthermore,

early detection of virologic failure is an important HIV treatment cost reduction mechanism. The reduction in cost can be realized, for instance, through avoiding second line drugs which are more expensive than first line drugs.

A systematic review of the epidemiology of ART failure on a global scale by Gereti AM et al in 2007 noted that reported prevalence surveys showed inter-region and intra-region variability in part because of methodological differences [7]. Despite this variability, a collaborative study and meta-analysis of global trends of ART treatment failure in 2012 by Gupta RK, et al found a significant increase in prevalence of treatment failure over time since ART rollout especially in regions of sub-Saharan Africa [8].

Hammers S, et al in 2008 conducted a study on six sub-Saharan African countries and determined 5.5% prevalence of HIV first line treatment failure [9]. A cross sectional study to determine the prevalence of HIV-1 treatment failure among reproductive aged women in Durban, Kwazulu Natal province, South Africa, was conducted by Horn S et al [10]. Of the 1073 valuable women, 37% (n=400) had HIV treatment failure.

Zimbabwe has experienced a decreasing trend in HIV prevalence from 26.7% in 2002 to 13.1% in 2013 [3]. While the prevalence of adult HIV is well documented; in contrary, the prevalence of HIV treatment failure is not well known at national level. In 2010, the National Drug and Therapeutics Advisory Committee (NDTAC) estimated that the percentage of patients who switched to HIV second line treatment was 1% [5]. As a proxy to HIV first line treatment failure; the 2009-2011 national HIV Drug resistance (HIV DR) survey reported an overall HIV DR prevalence of 6.3% [11].

Zvishavane district experienced an increasing trend of Sexually Transmitted Infections (STIs) cases from 66 per 1000 population in 2002 to 97 per 1000 population in 2005 [12]. According to the provincial health information STIs data, the district still records increasing trend of STIs and as of 2013, the rate is at 113 cases per 1000 population. In 2013 alone, the district recorded 4881 new STI cases, 35% (n=1721) of which were HIV positive cases.

According to the provincial health information, the district has the highest prevalence of HIV first line treatment failure. The district is one of the 12 sentinel sites for the surveillance of HIV-1 drug resistance in Zimbabwe [11]. An operational research, through genotyping, to determine the prevalence of HIV 1 drug resistance (HIV-1 DR) among all sentinel sites showed that the district had the highest prevalence of HIV-1 DR in Zimbabwe at 12.8% [11]. The district monitors HIV treatment failure using clinical and immunological measures [5]. However, it takes virologic measures irregularly.

Zvishavane district had the highest prevalence of HIV treatment failure at 16% (n=183). This is well above the regional prevalence of 5.5% [9]. According to the 2013 Zimbabwe HIV Drug Resistance Early Warning Indicators (EWIs) survey report, Zvishavane district was the least performer to EWI 1 on “on time pill pick up” [2]. Against a target of 90%, the district recorded 63% and 50% for adults and pediatrics respectively. While the district achieved 86%, which is above national target, on EWI 2 on retention in care, it fell short of national target on EWI 3 on pharmacy stock outs. Zvishavane is

one of the 12 sentinel sites for monitoring HIV DR and recorded the highest prevalence of HIV DR at 12.7% [11]. We, therefore seek to find out possible factors which could be contributing to HIV first line treatment failure in Zvishavane district.

Materials

A 1:1 unmatched case control study was conducted on HIV positive patients who had received ART in Zvishavane district for a period of at least 6 months. A case was an HIV patient who was on first line ART for at least 6 months in Zvishavane district and switched to second line ART regimen because of treatment failure during the 2013/2014 period. A control was an HIV patient in Zvishavane district who was on first line ART, had been on first line ART for at least 6 months and had not failed first line ART. Patients' files in health facilities in Zvishavane district and notes (cards) were reviewed in the study. Permission to conduct the study was obtained from the Provincial Medical Director (PMD), Midlands, Zvishavane District Medical Officer (DMO), Health Studies Office (HSO), Medical Research Council of Zimbabwe (MRCZ/B/702) and Joint Research Ethics Committee (JREC/199/14). Written informed consent was obtained from study participants. Consent of parents or legal guardians for those participants that could not legally consent (<18 years) was obtained. Confidentiality was maintained throughout the study. Participation was voluntary and there were no financial gains for participating in the study.

A total of 246 participants of all educational levels (none, primary, secondary and tertiary), 123 cases and 123 controls, was recruited into the study. Cases were randomly recruited from OI/ART register into the study using the lottery method. Names of participants were

Table 1: Socio-demographic characteristics of study participants, Zvishavane district, Zimbabwe, 2014.

Variable	Category	Cases n=123 (%)	Controls n=123 (%)	P value
Sex	Males	70 (57)	61 (50)	0.25
	Females	53 (43)	62 (50)	
Age in years	<13	4 (3)	4 (3)	
	13-19	14 (12)	9 (8)	
	20-29	43 (35)	39 (31)	
	30-39	32 (26)	43 (35)	
	>39	30 (34)	28 (23)	
Median age in years		30 (Q ₁ =22, Q ₃ =39)	32 (Q ₁ =25, Q ₃ =38)	0.68
Marital status	Single	44 (36)	18 (15)	0.16
	Married	47 (38)	58 (47)	
	Divorced	16 (13)	35 (28)	
	Widow	16 (13)	12 (10)	
Place of residence	Urban	82 (67)	79 (64)	0.41
	Rural	35 (28)	41 (33)	
	Outside Zimbabwe	6 (5)	3 (3)	
Highest level of Education	None	3 (2)	1 (1)	0.31
	Primary	27 (22)	26 (21)	
	Secondary	88 (72)	81 (66)	
	Tertiary	5 (4)	15 (12)	
Religion	Orthodox	37 (30)	30 (24)	0.53
	Pentecostal	39 (32)	56 (45)	
	Traditional	19 (15)	13 (11)	
	Muslim	1 (1)	1 (1)	
	None	27 (22)	23 (19)	
Employment Status	Formally employed	43 (35)	71 (58)	0.03
	Informally employed	29 (24)	17 (14)	
	employed	51 (41)	35 (28)	
	Unemployed			

written on pieces of paper and blindly picked by the researcher until the required sample size was reached. A pre-tested interviewer administered, semi-structured questionnaire and checklists were used to collect data from cases and controls. Epi info version 5.3.1 was used for data analysis. Stratified analysis was done to control for confounding and effect modification. Forward stepwise logistic regression analysis was done to determine independent factors associated first line HIV treatment failure.

Results

Descriptive epidemiology

A total of 123 cases and 123 controls were recruited into the study. (Table 1) illustrates socio-demographic characteristics of study participants. Cases and controls were statistically comparable in terms of socio-demographic characteristics except on employment where cases were more likely to be unemployed.

Analytic epidemiology

Significant risk factors: (Table 2) illustrates risk factors

associated with first line HIV treatment failure in Zvishavane district. Significant risk factors associated with first line HIV treatment failure were baseline CD4 Count of <100 cells/mm³ (OR=2.82, CI 1.68-4.74), long patient waiting time (OR=2.49, CI 1.48-4.19) and drinking alcohol (OR=2.05, CI=1.08-3.90). Significant protective factors were disclosure of HIV status (OR=0.34, CI 0.14-0.80), receiving at least one individual counseling on ART (OR=0.35, CI 0.18-0.69), having previously undergone Prevention of Mother to Child Transmission (PMTCT) (OR=0.41 CI 0.17-0.96).

Independent risk factors: (Table 3) shows independent risk factors for first line HIV treatment failure in Zvishavane district. Independent risk factors associated with first line HIV treatment failure were poor adherence to ART (<80% adherence) (AOR=5.14, CI 2.75-9.62), drug stock outs (AOR=3.02, CI 1.20-6.98), CD4 Count of <50 cells/mm³ (AOR=3.25, CI 1.47-7.16) and baseline WHO Stage 3 or 4 (AOR=1.95, CI 1.05-3.61).

Discussion

Gereti AM et al in 2007 showed that reported prevalence of

Table 2: Factors Associated with 1st Line HIV Treatment Failure, Zvishavane District, Zimbabwe, 2014.

Factor		Cases n=123 (%)	Controls n=123 (%)	Odds Ratio 95% CI	P value
Poor adherence (<80 adherence)	Yes	96 (78)	42 (34)	6.86[*]	<0.05
	No	27 (22)	81 (66)	3.89-12.09	
Baseline CD4 Count of <50 cells/mm ³	Yes	43 (35)	15 (12)	3.87[*]	<0.05
	No	80 (65)	108 (88)	2.01-7.45	
Drug Stock outs	Yes	70 (57)	33 (27)	3.60[*]	<0.05
	No	53 (43)	90 (73)	2.11-6.15	
Clinical WHO Stage 3 or 4 at ART initiation	Yes	82 (67)	50 (59)	2.92[*]	<0.05
	No	41 (33)	73 (41)	1.74-4.91	
Long patient waiting Time	Yes	66 (54)	39 (32)	2.49[*]	<0.05
	No	57 (46)	84 (68)	1.48-4.19	
Baseline CD4 Count of <100 cells/mm ³	Yes	81 (67)	51 (41)	2.82[*]	<0.05
	No	42 (33)	72 (59)	1.68-4.74	
Drinking alcohol	Yes	32 (26)	18 (15)	2.05[*]	0.03
	No	91 (74)	105 (85)	1.08-3.90	
Lack of privacy at facility	Yes	2 (2)	1 (2)	2.02	0.56
	No	121 (98)	122 (98)	0.18-22.54	
Smoking	Yes	21 (17)	12 (10)	1.90	0.09
	No	102 (83)	111 (90)	0.89-4.07	
Duration of Treatment of >3 Years on ART	Yes	39 (32)	27 (22)	1.65	0.08
	No	84 (68)	96 (78)	0.94-2.94	
Initiated at a private institution	Yes	17 (14)	11 (9)	1.63	0.23
	No	106 (86)	112 (91)	0.73-3.65	
No money for consultation	Yes	3 (2)	2 (2)	1.51	0.65
	No	120 (98)	121 (98)	0.25-9.21	
No money for transport	Yes	23 (19)	17 (14)	1.46	0.28
	No	100 (81)	108 (86)	0.74-2.89	
Presence of co-morbidities	Yes	68 (55)	59 (48)	1.34	0.25
	No	55 (45)	64 (52)	0.81-2.21	
Experiencing drug side effects	Yes	68 (55)	59 (48)	1.34	0.25
	No	55 (45)	64 (52)	0.81-2.21	
Have sex with at least 2 people per month	Yes	13 (13)	10 (10)	1.33	0.52
	No	86 (87)	88 (90)	0.55-3.20	
Taking ART before initiation by a doctor	Yes	10 (8)	8 (6)	1.27	0.63
	No	113 (92)	115 (94)	0.48-3.34	
Sexually active	Yes	100 (81)	98 (80)	1.11	0.75
	No	23 (19)	25 (20)	0.59-2.08	
Busy schedule at attend OI/ART Clinics	Yes	16 (13)	15 (12)	1.08	0.85
	No	107 (87)	108 (88)	0.51-2.29	
Disclosure of HIV status	Yes	102 (83)	115 (93)	0.34[*]	0.01
	No	21 (17)	8 (7)	0.14-0.80	
≥ 1 individual counseling on ART adherence	Yes	90 (73)	109 (89)	0.35[*]	<0.05
	No	33 (27)	14 (11)	0.18-0.69	
Having previously undergone PMTCT	Yes	10 (17)	22 (33)	0.41[*]	0.04
	No	49 (83)	44 (67)	0.17-0.96	
Having a sexual partner on ART	Yes	68 (67)	77 (79)	0.56	0.08
	No	33 (33)	21 (21)	0.30-1.06	
Practice safer sex	Yes	74 (73)	76 (77)	0.80	0.49
	No	28 (27)	23 (23)	0.42-1.51	

Table 3: Independent Risk Factors Associated with First Line HIV Treatment Failure, Zvishavane District, Zimbabwe, 2014.

Variable	Adjusted OR	95% C.I	P-value
Poor adherence (<80% adherence) to ART	5.14	(2.75-9.62)	<0.05
CD4 Count of <50 cells/mm ³	3.25	(1.47-7.16)	<0.05
Drug stock outs	3.02	(1.20-6.98)	<0.05
Baseline WHO Stage 3 or 4	1.95	(1.05-3.61)	0.03

ART failure on a global scale is varied both inter-regionally and intra-regionally partly due methodological differences and lack of a standardized international definition [7]. According to this systematic review, while highest prevalence continues to be observed in North America and Western Europe and areas of South America, ART failure is emerging sub-Saharan African. In fact, a collaborative study and meta-analysis of global trends of ART treatment failure in 2012 by Gupta RK, et al found a significant increase in prevalence of treatment failure over time since ART roll out in regions of sub-Saharan Africa particularly in East and Southern Africa from 2001 to 2011 [8].

In accordance with the Zimbabwe national OI/ART program, the case definition for HIV treatment failure was a CD4 count fall to below pre-therapy baseline or a 50% fall from the treatment peak value (if known) or CD4 count levels persistently (at least 2 results) below 100cells/mm³ [6]. Clinically, HIV treatment failure was when there was a new or recurrent WHO stage 4 conditions in a patient who had been on ART for at least 6 months [6]. Factors associated with HIV treatment failure are as varied as is the prevalence and particularly multi-factorial as was demonstrated in this study.

Poor adherence to ART was an independent risk factor associated with first line HIV treatment failure in Zvishavane district. Similar findings were reported by Charles et al in Kenya [13]. Drug stock outs significantly predicted poor ART adherence in Zvishavane district. Patients defaulted treatment when drugs were out of stock because they could afford to buy them from the private sector. Stocking drugs above required minimum levels could be one opportunity for improving adherence and reducing ART failure.

Besides predicting poor adherence, drug stock outs were an independent determinant of first line HIV treatment failure in Zvishavane district. Worrisomely, this district had the least performance in Midlands Province on EWI 1 on “on time pill pick up” [2]. This means that besides not buying ART medicines when they were out of stock, patients could not take them timely when they were in stock. Such behavior could explain both non adherence and treatment failure in the district. Poor adherence could lead to insufficient suppression of viral load by ART and hence treatment failure.

This study demonstrated that CD4 count of <50 cells/mm³ and baseline WHO Stage 3 or 4 were independent risk factors for first line HIV treatment failure in Zvishavane district. Chimbetete C and Tshimanga M had similar findings at Newlands clinic in Harare [14]. If an HIV positive patient is commenced on ART at baseline WHO stage 3 or 4 and /when CD4 is low, viral load may not be successfully suppressed leading to HIV treatment failure. For better treatment outcomes, interventions should focus on detecting and treating HIV before it advances.

Drinking alcohol was a significant risk factor for HIV treatment failure in Zvishavane district. Some patients who failed first line HIV treatment in Zvishavane district took alcohol. This is plausible since alcohol compromises effectiveness of medication. This can therefore partly explain treatment failure in this district. Instituting strategies to discourage this behavior may potentially provide an opportunity for reducing treatment failure.

Males were more likely to fail first line treatment though it was not statistically significant in this study. Other studies have shown significant associations and concluded that men have poor health seeking behaviors [14,15,16]. The difference could, however, be partly attributed to improved ART adherence and more males than females who were recruited in the latter studies. Improving health seeking behaviors of men in this district could also provide an opportunity for reducing HIV treatment failure.

This study demonstrated that PMTCT is protective of treatment failure. Pregnant mothers are tested for HIV during ante-natal care visits. This offers them an opportunity for early detection and treatment of HIV before risk factors; for instance viral load, CD4 count and clinical WHO stages, have worsened. Therefore, PMTCT programs should be regarded as one additional strategy to reduce HIV treatment failure by public health practitioners.

Long patient waiting time was a significant risk factor for first line HIV treatment failure in Zvishavane district. According to Miller et al in South Africa, long patient waiting time was a significant institutional factor for treatment failure [17]. OI/ART clinics are done twice per week on specific dates in respective ART initiating sites/facilities in Zvishavane district. The district has over 1000 patients on ART, a number that overwhelms health staff leading to long patient waiting times for reviews and resupplies. Patients therefore do not come or delay to come for resupply which causes them to miss their doses.

Disclosure of HIV status was a significant protective factor for first line HIV treatment failure in Zvishavane district. According to Ramadhani HO et al in 2007, disclosure of HIV status to family members and others was protective against virologic failure in Tanzania [18]. Disclosure of HIV status by patients could be of benefit to them through support that follows from those to whom disclosure could have been made. Lack of support may lead to poor adherence and consequently HIV treatment failure. This means that encouraging disclosure among patients on ART should be an integral part of HIV management to reduce failure.

Having a sexual treatment partner was protective though not statistically significant. Though not significant, this could mean that partners encourage each other to adhere to ART. Sexual partners should be encouraged to disclose their HIV status and support each other to reduce failure of ART in Zvishavane district.

Having at least one individual counseling session on ART at ART commencement was a significant protective factor for first line HIV treatment failure in this study. While this indicates that institutions are providing this service, it means counseling is effective in reducing HIV treatment failure in Zvishavane district. Consistent findings were made by Chimbetete C and Tshimanga M in Harare [14]. This could indicate that if people are provided with counseling, adherence

to ART could improve thereby reducing HIV treatment failure.

Contrary to finding by Cleopas C and Tshimanga M at Newlands clinic in Harare of Zimbabwe, being initiated on ART by a private doctor was not a significant risk factor for HIV treatment in Zvishavane district [14]. Private practitioners could be not having enough time for adherence counseling to ART patients owing to their model of business (profit making) which limits them in terms of how much time they can spend with each patient. However, the difference noted in the two studies could be accounted for by differences in study settings. There are few private health care services in Zvishavane district relative to Harare and few ART patients utilize them.

There was a significant difference in terms of employment status between patients who failed first line treatment and those who did not. Those who failed first line treatment were more likely to be unemployed relative to those who did not. This could mean that those who are not employed could be having challenges accessing ART in case of drug stock outs. OI/ART programs should prioritize these vulnerable people when drug stocking levels are below required minimum stocking levels.

Summatively, the development of HIV-1 treatment failure is not only a global clinical and public health concern but also a threat to ART expansion efforts in countries that use ART particularly in Zimbabwe (Zvishavane district). This means that effort should be directed towards reducing it for better treatment outcomes. Preventing HIV first line treatment failure (virologic failure) is important for minimizing if not preventing disease progression and avoiding the development of antiretroviral resistance i.e. wild strains of Human Immunodeficiency Virus Drug Resistance (HIV DR) [4].

The study was able to examine multiple etiologic factors for first line HIV treatment failure in Zvishavane district. It was conducted on patients of all age groups making the results generalizable to other populations.

Controls that failed first line HIV treatment but not yet diagnosed could have been recruited into the study thereby reducing the strengths of associations. This was reduced by recruiting controls that had been on ART for at least 6 months and were not diagnosed with first line HIV treatment failure. There was a possibility for recall bias which relates to differences in ways exposure information was remembered or reported by cases that were diagnosed with first line HIV treatment failure, and by controls that were not. Cases could have more likely reported more exposures than controls thereby overestimating the strengths of associations. There was a potential for cases to overestimate or underestimate their adherence levels. This could have threatened internal validity of this study. Ascertainment of exposure, where possible, was done through checking medical records. This study assessed reported adherence.

There are areas that were beyond the scope of this study and were therefore not answered. We suggest a process-outcome evaluation on the AIDS and TB program in Zvishavane district to explain poor performance outcomes of the program.

Conclusion

First line HIV treatment failure affected all age groups in Zvishavane district. Multiple etiological factors were associated with

first line HIV treatment failure in Zvishavane district. Poor adherence, drug stock outs, CD4 Count of <50 cells/mm³ and baseline WHO Stage 3 or 4 were demonstrated to be independent risk factors for HIV first line treatment failure in the district. Providing counseling, disclosing HIV status and receiving PMTCT were significantly protective in Zvishavane district. Results of the study provided guidance to AIDS/TB program managers to reduce first line HIV treatment failure in Zvishavane district.

Public Health Actions

As result of this study, the district hospital is now sees OI/ART patients on every working day of the week. Health education on benefits of disclosure and avoiding drinking alcohol is being given. Strategies for early detection and treatment of HIV taken included road side shows where patients were tested and managed.

Authors' Contributions

TM: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. GS: conception, design, data collection, analysis, interpretation and reviewing of several drafts of the manuscript for important intellectual content. GNT: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. MT: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. DB: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. MC: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. All authors read and approved the final manuscript.

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