Factors influencing treatment failure in HIV positive adult patients on first line antiretroviral therapy

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Abstract

Background: Risk factors for treatment failure in HIV positive adults have not been studied extensively in Zimbabwe.
Aim: To investigate socio-demographic, psychosocial and antiretroviral drug related factors as possible risk factors for treatment failure.
Objective: To compare the accuracy and reliability of CD4 count results in diagnosing treatment failure versus viral load results.
Design: A descriptive cross-sectional survey.
Setting: Harare Central Hospital adult opportunistic infections clinic.
Participants: One hundred and eighteen (118) HIV positive participants on 1st line antiretroviral therapy (any 1 of stavudine, tenofovir or zidovudine combined with lamivudine and nevirapine or efavirenz) for at least 1 year. Participants were conveniently sampled.
Main Outcome Measures: First line treatment failure as defined according to World Health Organisation (WHO) 2010 guidelines.
Results: Factors associated with higher odds of treatment failure were severe depression [OR 3.7; p-value 0.002; 95% CI 1.6-8.5] and discontinuing ART [OR 4.4; p-value 0.02; 95% CI 1.3-14.7]. Factors associated with lower odds of treatment failure were age =42 [OR 0.3; p-value 0.007; 95% CI 0.1-0.7], taking ART on time [OR 0.2; p-value 0.02; 95% CI 0.05-0.8], time on ART >4 years [OR 0.6; p-value 0.02; 95% CI 0.3-0.9] and female sex [OR 0.4; p-value 0.02; 95% CI 0.2-0.8]. There was statistically significant difference between CD4 count and viral load results in diagnosing treatment failure [OR 8.7; p-value 0.0005; 95% CI 3.6-21.2].
Conclusion: Severe depression and discontinuing ART predisposed to treatment failure. CD4 counts were not as reliable as viral load measurements in diagnosing treatment failure.

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Introduction

Highly active antiretroviral therapy (HAART) transformed a fatal condition into a chronic and manageable condition.[1] As a result, HIV related morbidity, mortality and orphans significantly reduced, and are expected to continue decreasing. However, treatment failure threatens to reverse the positive gains made in management of HIV infection in the past decades.[2] About 10-20% of adult patients on 1st line treatment are reported to be failing treatment, with higher figures (15-25%) being reported in sub-Sahara Africa.[3,4] First line antiretroviral therapy consists of 2 nucleotide reverse transcriptase inhibitors (NRTIs) and 1 non-nucleotide reverse transcriptase inhibitor (NNRTI]).[5]

Evidence shows that 1st line therapy offers the best chance of success in managing HIV infection, and the risk of developing subsequent treatment failure significantly increases after 1st line treatment failure.[6] Furthermore, salvage therapy is more expensive, is associated with higher pill burden and toxicities, and is more difficult to access in resource-limited settings (RLS), thereby increasing the risk of development of subsequent treatment failure.[7] It is therefore important to identify and address risk factors for treatment failure.

Studies looking into risk factors for treatment failure have been mainly conducted in developed nations, from which a lot of lessons can be drawn.[8,9] In these studies, sub-optimal adherence was reported to be the main cause of treatment failure, possibly leading to emergence and propagation of drug resistant HIV strains.[10] The main cited causes of sub-optimal adherence were side-effects to antiretroviral medicines, forgetting to take treatment, unresolved psychological factors, and having complex medication

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regimens, among others.[11] Inadequate drug exposure (pharmacological factors), viral factors (drug resistance) and the level of expression of the genes of drug metabolizing enzymes (pharmacogenetics) were also implicated in some studies.[12-14] Optimal adherence, leading to reduced cases of treatment failure, was seen in participants with less complex drug regimens, were not having side effects to their medications and regularly received adherence counselling.[11]

Even though these studies provide valuable lessons as to the cause of treatment failure, these results cannot be generalized to RLS due to differences in research subjects and research setting. There is, therefore, need to investigate the cause of treatment failure in RLS, where the disease burden is highest, and where there are limited treatment options after 1st line treatment failure. Strategies to identify the reason why patients are failing treatment early on, and addressing them, may lead to re-suppression, reduce development and propagation of drug-resistant HIV strains, and preclude the need to switch to salvage therapy.[15]

In line with the above, many studies have looked at the accuracy of cluster of differentiation 4 (CD4) count versus viral load monitoring in diagnosing treatment failure. While literature reveals that ART can be safely delivered without routine toxicity laboratory monitoring, CD4 count and viral load measurements are required to monitor disease extent and progression respectively.[16] However, there is a lot of individual immunological variation in response to HAART.[17] Some studies have also shown that immunological failure is a poor predictor of virological failure, and may result in unnecessary switching to 2nd line treatment.[18] Viral load monitoring is the gold standard in monitoring patients on ART, but is very expensive and complex.[19] However, with advances in biotechnology, costs of the equipment are becoming more and more affordable.

Objectives

This study sought to find out factors associated with treatment failure in HIV positive adult patients on antiretroviral therapy at Harare Central Hospital opportunistic infections clinic, and to find out if CD4 count monitoring is as reliable as viral load monitoring in diagnosing treatment failure.

The primary objective of this study was to identify factors associated with 1st line treatment failure, with focus on socio-demographic, psycho-social and antiretroviral drug (ARV) related factors.

A secondary objective was to compare the accuracy and reliability of CD4 count monitoring in diagnosing treatment failure versus viral load monitoring.

Materials and Methods

This was a descriptive cross-sectional survey of patients enrolled at Harare Central Hospital (HCH) adult opportunistic infections clinic in Harare, using an interviewer-based questionnaire in English or Shona. A pilot survey was conducted to test the questionnaire. Data was collected between 10 September 2012 and 8 November 2012. Participants were consecutively enrolled into the study after providing written and verbal informed consent. The inclusion criteria were as follows: HIV positive with documented HIV antibody test, 19 years of age, above and had taken 1st line ART for at least 1 year and were able to give informed consent. The exclusion criteria were as follows: pregnant or breastfeeding women and patients who were switched to 2nd line as a result of side effects to antiretroviral drugs in 1st line treatment.

Treatment failure was defined according to World Health Organisation (WHO) 2010 criteria by at least 1 of the following in a patient taking 2 NRTIs and 1 NNRTI for 1 year or more: 1) New WHO clinical stage 3 or 4 disease (with CD4 count <200 cells/mm^3 and viral load >400 copies/ml); 2) CD4 count of < 100 cells/mm^3 at 12 months of treatment OR a fall to baseline (nadir) or below baseline CD4 count OR a 50% fall from on-treatment peak value; 3) A viral load >5 000 copies/ml.[20]

The study protocol was approved by Joint Parirenyatwa Hospital College of Health Sciences Research Ethics Committee (JREC) and Harare Central Hospital Research Ethics Committee. All participants requiring medical attention and those diagnosed with treatment failure were referred to Harare Central Hospital opportunistic infections clinic and casualty for management.

Risk factors for treatment failure were assessed using univariate logistic regression. Co-variates assessed were: age, gender, marital status [married or single (widowed, never been married, divorced or separated)], place of residence, housing ownership (owned or rented), employment status (employed or unemployed), total monthly income, depression (a depression score =10 was considered mild depression while a score above 10 was considered severe depression), taking ART on time (that is, taking ART within 30 minutes of the prescribed time), time on ART, dosing schedule, switching of ARVs, WHO staging at initiation, adherence (optimal adherence [=95%] was defined as missing <3 doses in 30 days for patients on twice daily regimens and not missing a dose if on once daily regimens). Hospital Anxiety and Depression [HAD] Scale was used to assess depression, while questions on adherence were taken from Simplified Medication Adherence Questionnaire (SMAQ).[21-22] Data analysis was performed in Stata version 12.0.

Results

Patient characteristics: Table I below summarizes the socio-demographic, psychological and treatment characteristics of the participants. One hundred and eighteen (118) participants were interviewed. Mean

age was 42. Females made up 73% (n=86) of the sample size. There were 8 (7%) single men, compared to 60 (51%) single females. Thirty-eight (32%) participants were severely depressed (p-value 0.005). Forty-six percent of the sample was made up of unemployed women.

Table I: Socio-demographic, psychological and ARV characteristics of participants.

Variable (n=118)	Males (n=32)	Females (n=86)	p value
Age (years)			
< 42	8 (7%)	48 (41%)	0.003
= 42	24 (20%)	38 (32%)	
Marital status			
Single	8 (7%)	60 (51%)	<0.0005
Married	24 (20%)	26 (22%)	
Level of education			
Primary school	6 (5%)	33 (28%)	0.01
High school	17 (14%)	45 (38%)	
Tertiary level	9 (8%)	8 (7%)	
Place of residence			
High density	28 (24%)	74 (63%)	0.8
Medium density	4 (3%)	12 (10%)	
Housing ownership			
Other	13 (11%)	48 (41%)	0.1
Owned	19 (16%)	38 (32%)	
Employment status			
Unemployed	14 (12%)	54 (46%)	0.06
Employed	18 (15%)	32 (27%)	
Monthly income			
<200 USD	12 (10%)	56 (47%)	0.01
201-500 USD	11 (9%)	20 (17%)	
= 501 USD	9 (8%)	10 (8%)	
Depression			
Mild depression	28 (24%)	52 (44%)	0.005
Severe depression	4 (3%)	34 (29%)	
Take ART on time			
No	5 (4%)	6 (5%)	0.2
Yes	27 (23%)	80 (68%)	
Time on ART (years)			
1-2	12 (10%)	15 (13%)	0.07
2-4	9 (8%)	34 (29%)	
>4	11 (9%)	37 (31%)	

Figure I: Percentages of participants according to age group and treatment failure (n=118).

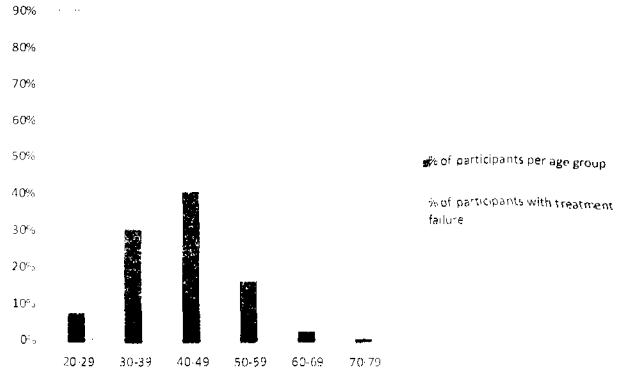

Figure 1 above shows the percentages of participants according to age group and treatment failure. Forty-seven (40%) participants were in treatment failure as defined by at least one of immunological, virological or clinical parameters. Optimal adherence (=95%) was reported in 97% of the participants. Eighty percent of participants aged 20-29 years were in treatment failure, even though this group constituted less than 10% of the sample.

Table II: Univariate logistic regression of treatment failure as defined by virological failure.

Variable	Odds ratio of Virological Failure	95 % CI	p value
Age (years)			
<42			
≥42	0.3	0.1 - 0.7	0.007
Gender			
Males			
Females	0.8	0.3 - 1.9	0.6
Marital status			
Single	1.8	0.8 - 4.1	0.1
Married			
Place of residence			
High density			
Medium density	0.7	0.2 - 2.4	0.6
Housing ownership			
Other	1.8	0.8 - 4.0	0.1
Owned			
Employment status			
Unemployed	0.7	0.3 - 1.5	0.4
Employed			
Monthly income			
<500 USD	1.1	0.6 - 1.8	0.8
≥500 USD			
Depression			
Mild depression	3.7	1.6 - 8.5	0.002
Severe depression			
Take ART on time			
No	0.2	0.05-0.8	0.02
Yes			
Time on ART (years)			
≤4	1.0	0.6 - 1.8	0.9
>4			
Discontinued ART			
No	4.4	1.3-14.7	0.02
Yes			
Dose schedule			
Once daily	1.1	0.3 - 3.2	0.9
Twice daily			
Initial WHO clinical stage			
Stage 1 and 2	1.0	0.7 - 1.7	0.7
Stage 3 and 4			
ARV switch			
No	0.7	0.3 1.6	0.4
Yes			
Number of times ARVs switched			
<2	0.8	0.5 - 1.3	0.3
≥2			
Co-medications			
No	0.7	0.3 - 1.8	0.5
Yes			

Tables II (above) and III (below) show univariate logistic regression analysis of treatment failure as defined by virological and immunological treatment failure respectively. Factors associated with higher odds of virological failure were severe depression [OR 3.7; p-value 0.002; 95% CI 1.6-8.5] and discontinuing

ART [OR 4.4; p-value 0.02; 95% CI 1.3-14.7]. Factors associated with lower odds of virological failure were age ≥42 [OR 0.3; p-value 0.007; 95% CI 0.1-0.7] and taking ART on time [OR 0.2; p-value 0.02; 95% CI 0.05-0.8]. The following factors were not associated with virological failure: gender, marital status, place of residence, housing ownership, occupation, monthly income, time on ART, dose schedule, co-medications, switching of ART, the number of times ART was switched and WHO staging at initiation.

Discontinuing ART was associated with higher odds of immunological treatment failure [OR 4.9; p-value 0.01; 95% CI 1.4-17.2]. Factors associated with lower odds of immunological failure were female sex [OR 0.4; p-value 0.02; 95% CI 0.2-0.8], taking ART on time [OR 0.2; p-value 0.01; 95% CI 0.04-0.7] and time on ART ≥4 years [OR 0.6; p-value 0.02; 95% CI 0.3-0.9]. The following co-variates were not associated with immunological treatment failure in univariate logistic regression analysis: age, marital status, place of residence, housing ownership, occupation, monthly income, depression, dose schedule co-medications, switching of ART, number of times ART was switched and WHO clinical stage at initiation.

There was statistically significant difference between CD4 count and viral load measurements in diagnosing treatment failure [OR 8.7; SE 3.9; p-value 0.0005; 95% CI 3.9-21.2].

Table III: Univariate logistic regression of treatment failure as defined immunologic failure.

Variable	Odds ratio of Immunologic Failure	95% CI	p value
Age (years)			
<42	0.5	0.3 - 1.2	0.1
≥42			
Gender			
Males	0.4	0.2 - 0.8	0.02
Females			
Marital status			
Single	1.0	0.5 - 2.2	0.9
Place of residence			
High density	2.0	0.7 - 5.8	0.2
Medium density			
Housing ownership			
Other	1.3	0.6 - 2.8	0.5
Owned			
Employment status			
Unemployed	0.8	0.4 - 1.6	0.5
Employed			
Monthly income			
<500 USD	1.0	0.6 - 1.6	0.9
≥500 USD			
Depression			
Mild depression	1.3	0.6 - 2.9	0.5
Severe depression			
Take ART on time			
No	0.2	0.04 - 0.7	0.01
Yes			
Time on ART (years)			
≤4	0.6	0.3 - 0.9	0.02
>4			
Discontinued ART			
No	4.9	1.4 - 17.2	0.01
Yes			
Dose schedule			
Once daily	0.4	0.2 - 1.2	0.1
Twice daily			
Initial WHO clinical stage			
Stage 1 and 2	0.7	0.5 - 1.2	0.3
Stage 3 and 4			
ARV switch			
No	0.9	0.4 - 2.1	0.8
Yes			
Number of times ARVs switched			
<2	1.2	0.7 - 2.0	0.4
≥2			
Co-medications			
No	1.8	0.7 - 4.5	0.2
Yes			

Discussion

There were more females in the study group. This finding is consistent with findings from other studies which showed that in public health care, there were more females in care than males.[23] Possible explanations could be that females have higher health seeking behaviour compared to males, men are more likely to seek care from private rather than public institutions as they are more financially empowered, or because there are more HIV infected females than males.[23-25]

High adherence rates in the study group correlate with results from a meta-analysis that showed that Africans have high adherence rates.[26] Optimal adherence (≥95%) was reported in 97% of the participants in this study, which is higher than that reported for developing countries (74.3%).[26-28] This finding is reassuring in the light of concerns raised that as patients remained on ART for longer periods, adherence rates could dwindle in Africa due to structural barriers, like distance travelled to health centres, few health centres, interruptions in supply chain and staff shortages, among others.[26] Therefore, despite the challenges faced in the health sector, adherence rates have remained high. However, self-reported adherence tends to over-estimate adherence.[28] More studies need to be conducted in rural settings were structural barriers predominate compared to urban settings where this current study was conducted, and in larger samples so as to evaluate this finding.

Discontinuing ART was associated with higher odds of both immunological and virological treatment failure. This is a result of on-going viral replication in the absence of ART, which results in decrease in CD4 cell count and increase in viral load.

Severe depression was associated with higher odds of virological treatment failure. This finding correlates with a study conducted in South Africa, and results of review of literature.[29-30] A possible reason is that patients with severe depression are less likely to adhere to treatment, and hence develop treatment failure. However, severe depression was not associated with higher odds of immunological treatment failure, a finding which could be a result of the study being inadequately powered to find the association.

Age ≥42 was associated with lower odds of virological failure, which correlates with a study by Shacham and colleagues. This finding was attributed to

increased maturity in patients above 40 years.[31] Another possible explanation is that people older than 40 could be on treatment for other conditions, such as diabetes mellitus and hypertension, for which good control relies on good adherence to treatment, especially when medication regimens are non-toxic and simplified.[32]

Taking ART on time was associated with lower odds of both immunological and virological treatment failure. This may be a result of achieving and maintaining steady state concentration and optimal therapeutic levels of antiretroviral drugs in the general circulation, and hence viral suppression is achieved and CD4 cell count increases.

Time on ART =4 years was associated with lower odds of immunological failure in this study. A possible explanation for this is that patients on ART for less than 4 years are more likely to forget taking their medication or take them wrongly due to inexperience when compared to those on ART for more than 4 years. This finding, however, contradicts findings from a study in India that showed adherence decreasing as time on ART increased because patients felt clinically better and developed treatment fatigue.[33]

Occupation, place of residence, housing ownership and total monthly income (all which assess patients' socio-economic status [SES]) had no association with both immunological and virological treatment failure in this study. This finding correlates with findings from a systematic review of literature that showed SES not being consistently associated with treatment failure in HIV infected patients.[34] However, according to some studies conducted in southern Africa, some occupations like cross-border traders and long distance truck drivers, among others, pose higher risk of defaulting ART leading to treatment failure in patients as they are highly mobile.[35] The difference between findings in this study and southern Africa studies might be explained by the sample size that might have been inadequate, and/or the under-representation of males in this study, resulting in low representation of occupations that are at risk of defaulting ART.

Marital status had no association with treatment failure in this study, which is contrary to findings from studies conducted in developed countries. This was attributed to married people and people in steady relationships offering each other moral and social support, and hence remind each other to take ART and score optimal adherence rates (treatment buddies).[36] The finding in the current study could be explained that immediate and extended family provided moral and social support for single participants. These could play the same role a spouse or partner would play in reminding patients to take their ART.[37] However, this finding needs to be evaluated in other studies because there was no information on disclosure in this study.

Dose schedule was not associated with treatment failure in the current study. This finding correlates with findings from a study conducted in 2003 which showed no difference in adherence between once and twice daily scheduling, which gave 95% medication adherence, compared to 3 times daily dosing, which reduced medication adherence to 60%[38]. In our study, there was no patient taking ART more than twice a day.

Switching ART and the number of times ART was switched did not have an association with treatment failure. This correlates with findings from a study conducted in Cote d'Ivoire which found that drug modification (which was defined as immediate substitution of the out of stock drug) did not result in treatment failure, whereas prolonged drug discontinuations doubled the risk of death.[39]

Female sex was associated with lower odds of immunological failure. This finding correlates with findings from a review article.[23] According to these studies, females are more likely to adhere to treatment compared to males. However, in this study female sex was not associated with lower odds of virological treatment failure, contrary to evidence, a finding which could also be attributed to inadequate sample size.[23]

In this study, CD4 counts and viral load measurements showed statistically significant difference in diagnosing treatment failure. This finding was supported by findings from older studies that showed 20% discordance between CD4 count and viral load criteria for diagnosing treatment failure, resulting in over-diagnosing treatment failure and unnecessary switch to 2nd line in RSL that do not measure viral loads routinely in public health care.[40] This finding is also supported by findings from a study in South Africa that showed that some patients exhibited CD4 increase in the presence of high viral loads. This is truer in adolescents and younger patients who have more robust immune systems, but might not remain true in older patients due to less robust immune systems.[41]

In this study, virological criteria showed that both discontinuing ART and severe depression had higher odds of treatment failure while immunologic criteria only showed discontinuing ART to have higher odds of treatment failure. This discrepancy could also be an indicator of the reduced accuracy of CD4 in diagnosing treatment failure, given that viral load monitoring is considered gold standard in diagnosing treatment failure.[40] There is therefore need for further studies to evaluate whether CD4 count is as reliable as viral load in diagnosing treatment failure in our setting.

Study limitations

This study had several limitations. Firstly, reliance on self-reported data might have resulted in recall and social desirability bias, and tendency to over-estimate adherence. Secondly, the study was conducted in one urban clinic, therefore results cannot be generalised outside the study setting. Thirdly, the cross-sectional nature of the study did not allow for assessment of incidences of treatment failure. Fourthly, convenient sampling might have resulted in under- or over-representation of certain populations.

Recommendations

With regard to our findings, we recommend that when patients are assessed for ART eligibility in opportunistic infections clinic at Harare Central Hospital, patients can also be screened for depression prior to ART initiation, and at regular intervals during the course of treatment. Successful management of HIV positive patients may require a holistic multi-disciplinary team approach with other departments, like psychiatry, clinical psychology, counselling and social services, for adequate care of depressed patients. Psycho-social functioning of patients is often neglected in clinical practise with dire consequences to patients' adherence and treatment outcome. Improving patients' psycho-social functioning could improve adherence, minimise resistance, maximise time on first line ART and hence reduce treatment failure. Longer stay on 1st line ART reduces the number of patients who are switched to 2nd line ART as a result of 1st line treatment failure. Other measures to improve adherence include modifying a regimen to fit the patients' lifestyle, and early substitution of toxic drugs.

Defaulting ART was associated with higher odds of treatment failure in this study. As such, we recommend that there be timely follow-up of patients that are lost-to-follow-up, and encourage retention in care. Novel techniques such as Short Message Services (SMS) could prove useful in such instances, since they are affordable and do not require special training of health personnel.

We also recommend that viral load monitoring be made available routinely to every patient, and not only when indicated as cheaper technology is emerging. Reliance on CD4 and clinical criteria alone may result in delayed diagnosis of treatment failure, with dire consequences. Routine virological monitoring on every patient could help alert health care workers of patients at risk of treatment failure. If appropriate, measures to halt viral replication, like intensive adherence counselling, could be introduced much earlier and viral replication stopped. This not only precludes the need for 2nd line treatment in patients who re-suppress, but saves the patients from developing opportunistic infections, with implications at patient, family, economic and public health levels.

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