Predictors of HIV Antiretroviral Treatment Failure among Patients Attending a Semi - Urban HIV Clinic–Kenya, 2012: Can Social Support Help?

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ABSTRACT

Background: HIV antiretroviral treatment [ART] failure increases morbidity and mortality. In Kenya, use of treatment supporter, HIV serostatus disclosure, and support groups are believed to reduce the risk of treatment failure by improving adherence.

Methods: We conducted a case-control study to identify factors associated with clinical or immunologic indicators of treatment failures. Cases and controls were adult patients attending a semi-urban HIV clinic who initiated ART at least six months prior to the study. Cases were patients who had a] a decline in CD4 count [below baseline or 30% from highest value since ART initiation] or b] unimproved CD4 counts or c] a World Health Organization [WHO] stage III or IV opportunistic infection. Controls did not meet either immunologic or clinical criteria for treatment failure. Information was obtained through face-to-face interviews medical chart reviews.

Results: We enrolled 52 cases and 104 controls. Twenty-eight [53%] cases and 71 [70%] controls were women, and median age was 44 years [range: 38-50 years] among cases and 43 years [range: 38-49 years] among controls. Discontinued ART for 2 weeks or more [adjusted odds ratio [AOR] 8.9, 95% confidence interval [CI] 1.4-57.4] and alcohol use [AOR 7.2, 95% CI 1.1-45.5] were found to significantly increase the risk of ART failure. Compared to men who discontinued ART for less than 2 weeks, women who discontinued ART for less than 2 weeks had reduced risk [AOR 0.4, 95% CI 0.2-0.9] while those who

discontinued for two weeks or more had a greater risk [AOR 12.97, 95% CI 1.5-111.8] of developing ART failure. Social support factors were not associated with treatment failure.

<u>Conclusions</u>: Discontinuing ART and alcohol use were identified to be modifiable factors associated with clinical or immunologic criteria of ART failure. Interventions with proven efficacy at reducing alcohol use and increasing continuous ART should be implemented.

Key words: Antiretroviral treatment failure, HIV, AIDS, adherence, alcohol, Kenya

Introduction

HIV disease stands out as one of the most profound public health concerns in the world. By end of 2012, there were an estimated 35.3 million HIV-infected adults and children, 25 million of whom were living in Sub Saharan Africa [1]. Kenya has been severely impacted by HIV. In 2012, there were 1.2 million HIV-infected Kenyans aged 15-64 years, accounting for 5.6% of this population [2]. The Kenyan Ministry of Health is the main provider of antiretroviral therapy [ART] for the Kenyan HIV-infected population which has been available at no cost to treatment eligible persons since 2006. By end of 2012, there were over 600,000 Kenyan adults living with HIV who were receiving ART [3].

ART has been shown to decrease HIV-related morbidity and mortality [4-5] and, by reducing circulating virus in treated persons, decrease sexual transmission of HIV [6-7]. However, to be effective, ART must be taken consistently. Poor adherence to ART can lead to the development of drug resistance and the need to change to what is often a more expensive and toxic regimen [8]. Transmission of drug resistant HIV has also been documented [9] which adversely impacts initial treatment. Adherence to ART is therefore important to the health of the HIV- infected individual and to the public as a whole. To increase adherence among those on ART and consequently minimize the need to change to second or third line regimen, the Kenya Ministry of Health recommends that patients receive education and counselling prior to initiating ART that includes information on the importance of adherence [10]. In addition, as part of the psychosocial support all patients are encouraged to identify a treatment supporter, to disclose their HIV status to family members and/or sexual partners, and to join peer support groups [10]. The use of psychosocial support for persons on ART has been recommended to patients because these factors have been shown to be positively related to the physical and mental well-

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being of persons with chronic diseases[11] and is a coping strategy used by people living with HIV[12]. A number of interventions to increase ART adherence, including the use of a treatment supporter, have been tested and found to be efficacious in many, but not all settings,[13]. How these interventions translate from research settings into improved adherence and reduced treatment failure in standard care environments is less clear. We conducted a case-control study to determine the association between socio-demographic, behavioral, and social support factors and ART failure among patients receiving ongoing care at Rift Valley Provincial General Hospital, a semi-urban level 5 referral hospital in Kenya.

Methods

Study design, subjects and setting

The study was conducted in May to July 2012 at the Rift Valley Provincial Hospital which is located in Nakuru County, Kenya. On average 90 to 120 HIV-infected persons are managed at the HIV outpatient clinic each day. During the study period, patients with a CD4 count of less than 350 cells/mm3, a World Health Organization [WHO] clinical stage III or IV or HIV, co-infection with tuberculosis or with hepatitis B virus,[10] were eligible for ART. Stabilized patients on ART were monitored clinically every two to three months and immunologically through CD4 counts measured every six months. As per national policy, viral load testing is not routinely done but is instead limited to confirm the need to change regimens in patients identified to have clinical and/or immunological signs of ART failure,[10].

The study population included patients aged 18 years and older at the time of data collection who had been enrolled at the HIV outpatient clinic and receiving ART for at least six months. A case was recruited if they had a decline in CD4 count [below baseline or 30% from highest value since ART initiation], unimproved CD4 counts from baseline, or a WHO stage III or IV opportunistic illness. A control was recruited if all aforementioned signs were absent. Patients were excluded from the study if they did not meet the eligibility criteria, did not give consent, or were too sick to participate [as determined by the triage nurse].

A total of 156 study participants were recruited with two controls enrolled for every case. Sample size was calculated using the Fleiss formula [1981] and with assumptions made from a study conducted in an urban clinic in Uganda that investigated poor adherence as a predictor of ART failure [14-Gregory et al., 2007]. At the start of the data collection, the clinicians at the HIV outpatient clinic were re-trained on the criteria outlined in the national ART guidelines for identification and diagnosis of ART failure,[10]. In addition they were instructed on the study

objectives, subject eligibility criteria and data collection methods. The clinicians identified the patients who met any one of clinic-immunological criteria of ART failure as stipulated in the ART treatment guidelines,[10] and referred them to the study team who confirmed that the patients met at least one of the immunological or clinical criteria for ART failure. For every case identified, the next two patients who were seen by the clinician and did not fit the case definition of ART failure were recruited as controls. If either cases or controls refused participation, the next eligible patient was recruited until the sample size was met.

Measurements

On enrolment into the study, a standard questionnaire was administered to each study participant that collected socio-demographic, behavioral, and social support factors thought to be associated with treatment failure. The medical records of participants were reviewed to obtain data on CD4 count at ART initiation, and the dates of clinic enrollment and ART initiation.

Statistical analysis

Crude odds ratios [OR] with 95% confidence intervals [CI] were used to measure differences between cases and controls. Stratified and multivariate analysis was done to assess for effect modification and confounding. To evaluate for effect modification stratum specific OR were compared to assess if the range of associations was wide enough to be meaningful and represent normal sampling variation. Variables that had a p value of 0.1 or less in the bivariate analysis were included in the multivariate logistic regression model. In addition, interaction variables were created between the duration of non-adherence to ART and sex and these were also included in the model. Step wise backward elimination method was used to develop the final model. Statistical analysis was conducted using Epi Info version 3.5.1 [CDC, Atlanta, GA] and Stata [College Station, TX].

Ethical considerations

Ethical clearance was obtained from the ethical review committees of the Kenya Medical Research Institute and the Rift Valley Provincial General Hospital.

Results

A total of 156 patients; 52 cases and 104 controls were recruited into the study. Cases and controls were demographically similar [Table 1]. Most of the study population were women, aged 35 to 44 years, had completed primary or secondary school, were currently married, and had some employment.

Table 1: Characteristics of patients who met and did not meet clinical or immunologic criteria for ART failure, Rift Valley Provincial General Hospital, Kenya, 2012.

Characteristic	Total N [%]	ART failure Yes N [%]	No N [%]	Crude OR [95% CI]	P value
Total study participants	156 [100]	52 [33]	104 [67]		
Demographic factors					
Sex					
Male	59 [38]	25 [48]	34 [33]	1.9 [1.0–3.8]	0.09
Female	97 [62]	27 [52]	70 [67]	Referent	
Age group [years]					
25 - 34	17 [11]	8 [15]	9 [9]	2.4[0.8-7.2]	0.2
35 - 44	71 [46]	19 [37]	52 [50]	Referent	
45 - 54	50 [32]	16 [31]	34 [33]	1.3[0.6-2.8]	0.7
> 55	18 [12]	9 [17]	9 [9]	2.7[0.9-7.9]	0.1
Highest education level					
None	9 [6]	4 [8]	5 [5]	1.6[0.3-8.4]	0.4
Primary	65 [42]	23 [44]	42 [40]	1.1[0.5-2.4]	0.9
Secondary	67 [43]	22 [42]	45 [43]	Referent	
Post-secondary	15 [10]	3 [6]	12 [12]	0.5[0.1-2.2]	0.3
Marital status					
Currently married	90 [58]	31 [60]	59 [57]	Referent	
Separated/divorced	16 [10]	7 [13]	9 [9]	1.4[0.5-4.4]	0.7
Never married/cohabited	14 [9]	4 [8]	10 [10]	0.8[0.2-2.9]	0.8
Widowed	36 [23]	10 [19]	26 [25]	0.7[0.3-1.7]	0.6
Employment status					
Employed	42 [27]	16 [31]	26 [25]	1.4[0.7-3.1]	0.5
Irregular employment	86 [55]	26 [50]	60 [58]	Referent	
Unemployed	28 [18]	10 [19]	18 [17]	1.2[0.5-3.2]	0.8

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The time from HIV diagnosis to entry into care and the time to ART initiation did not differ significantly between cases and controls [Table 2a,b].

Table 2a: Care and treatment, behavioral, and social support factors associated with treatment failure, Rift Valley Provincial General Hospital, Kenya, 2012

Characteristic	Total N=156	ART Failure Yes N=52	No N=104	Crude Odds Ratio [95%CI*]	P value
	N [%]	N [%]	N [%]		
Care and treatment factors					
Period between HIV diagnosis and enrolment into HIV clinic					
Less than 12 months	123[79]	44[85]	79[76]	Referent	
12 months or more	33[21]	8 [15]	25[24]	1.7[0.7-4.2]	0.2
Period between enrolment into HIV clinic and start of ART					
Less than 12 months	137[89]	44[85]	93[89]	Referent	
12 months or more	19[11]	8[15]	11[11]	0.65[0.2-1.7]	0.4
CD4 count at ART initiation					
Less than or equal to 150 cells/mm^3	72[54]	28[67]	44[48]	2.1[1.0-4.7]	0.07
More than 150 cells/mm^3	61[46]	14[33]	47[52]	Referent	
Behavioral factors					
Longest duration off ART					
0 days	122[78]	34[65]	88[85]	Referent	
1 – 14 days	15[10]	4[8]	11[10]	0.9[0.2-3.5]	0.6
More than 14 days	19[12]	14[27]	5[5]	7.2[2.4-21.7]	0.0002

Table 2b: Care and treatment, behavioral, and social support factors associated with treatment failure, Rift Valley Provincial General Hospital, Kenya, 2012.

		ART Failure			
Characteristic	Total N=156	Yes N=52	No N=104	Crude Odds Ratio [95%CI*]	P value
	N [%]	N [%]	N [%]		
Alcohol use in past three months					
Yes	14 [9]	9 [17]	5 [5]	4.1[1.2-16.5]	0.01
No	142 [91]	43 [83]	99 [95]	Referent	
History of use of substances other than alcohol while on ART					
Yes	11[7]	8 [15]	3 [3]	6.1[1.4-37]	0.007
No	145 [93]	44 [85]	101 [97]	Referent	
Social support factors					
Disclosure of HIV status					
Yes	127[81]	45[87]	82[79]	Referent	
No	29[19]	7[13]	22[21]	1.7[0.7-4.3]	0.3
Has a treatment supporter					
Yes	83 [53]	26 [50]	57 [55]	0.8[0.4-1.6]	0.7
No	73 [47]	26 [50]	47 [45]	Referent	
Member of a support group					
Yes	16 [10]	8 [16]	8 [8]	2.3[0.8-6.4]	0.2
No	137 [90]	42 [84]	95 [92]	Referent	

*Confidence interval

In the bivariate analysis we found four factors that were associated with increased risk for treatment failure: non-adherence to ART for two weeks or more [OR 7.2, 95% CI 2.4-21.7], alcohol consumption in the past three months [OR 4.1, 95% CI 1.2-16.5], and use of illicit substances other than alcohol [OR 1.4 95% CI 1.4-37] [Table 2]. A CD4 count of 150 cells/mm^{3}at ART initiation was more frequent among patients failing treatment but the difference between the cases and controls was of borderline significance [p=0.07]. Though not shown in the table, patients failing ART had a lower median CD4 cell count at ART initiation than controls [104 cells/mm^{3}and 154 cells/mm^3, respectively, p=0.05]. Having a treatment supporter, belonging to a support group or non-disclosure of HIV status were not significantly associated with ART failure.

In the multivariate analysis, having discontinued ART for 2 weeks or more and alcohol use were found to significantly increase the risk of ART failure [Table 3].

Table 3.Multivariate analysis of predictors of treatment failure.

	ART Failure			
Variable	Yes N [%]	No N [%]	Adjusted Odds Ratio	95% Confidence Intervals
Alcohol use in past three months	9 [17]	5[5]	7.2	1.1-45.5
Discontinued ART for 2 weeks or more	14 [27]	5 [5]	8.9	1.4-57.4
Discontinued ART period and sex				
Male and discontinued ART for less than 2 weeks	20[80]	30[88]	Referent	Referent
Male and discontinued ART for 2 weeks or more	5[20]	4[12]	1.49	0.34-6.61
Female and discontinued ART for less than 2 weeks	18[67]	69[99]	0.41	0.19-0.89
Female and discontinued ART for 2 weeks or more	9[33]	1[1]	12.97	1.50-111.75

Significant interaction between sex and the duration of non-adherence was found. Compared to men who discontinued ART for less than 2 weeks, women who discontinued ART for less than 2 weeks had lower risk of developing failure while those who discontinued for more than 2 weeks had a greater risk

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of developing ART failure. Comparison between men who discontinued ART for less than 2 weeks and those that discontinued for more than 2 weeks indicated that the latter group had a greater risk of developing ART failure but this was statistically not significant.

Discussion

In an HIV clinic located in a referral hospital in semi-urban part of Kenya, patients on ART were more likely to fail if they had a recent history of alcohol use or had discontinued ART for 2 weeks or more. The association between discontinuation of ART and clinical deterioration is expected and understood to be a direct effect on continued immune destruction in the absence of ART. In contrast, the association between alcohol and clinical or immunologic markers of treatment failure is likely to be an indirect effect most likely on compliance with treatment regimens. Previous studies have demonstrated an association between alcohol use and inadequate adherence,[15-17].As such, to optimize adherence, and thereby improve clinical outcomes and reduce the risk of transmission of resistant strains, factors that directly and indirectly affect adherence must be addressed. Use of alcohol and other mood altering substances is not routinely ascertained in ART clinics but given its association with poor adherence, as well as other adverse health outcomes, health care providers in

ART clinics in Kenya should routinely inquire about substance use as part of routine clinical monitoring.

An unexpected finding was the modifying effect of sex on discontinuation of ART and treatment failure. Among subjects for whom the duration off ART was under 14 days most of whom had not missed any days of treatment] females were found to have a lower risk of developing ART failure compared to men. However, females who discontinued ART for more than 2 weeks were thirteen times more likely to develop failure as compared to men who had discontinued for less than 2 weeks. Relative to men who had missed ART for less than two weeks, men who missed ART for two weeks or more had slightly higher odds of treatment failure but this was not statistically significant. Although health behaviors have been shown to differ between men and women, the magnitude of increased risk among women who had discontinued treatment compared to men who had discontinued treatment merits further examination.

In this study, participating in a support group, having a treatment supporter or history of having disclosed one's status to someone were found to have no effect on ART failure. Functional social support that involves emotional and practical support has been shown to be more strongly associated with ART adherence than with structural support which involves how one lives and whether on is in a

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relationship or not,[17]. In a study carried out in Tanzania,[18], to determine predictors of virological failure, history of disclosure of one's HIV status was found to be protective. The first step in acquiring social support is disclosure of one's HIV status. Although the majority of the participants in our study indicated that they had disclosed their status, it is possible that the disclosure in most cases was not made to persons who could provide support for HIV treatment. In addition, it is possible that persons who were aware of participants' serostatus were not aware that they were receiving ART. As part of the interview, participants who acknowledged that they had a treatment supporter were asked to name that individual. It was noted that, patients usually gave the name of their next of kin, some of whom resided very far from the patients. As such, the degree of daily support for medication adherence was not likely to have been received from these supporters. Although belonging to a peer support group has been shown to be part of the forms of functional support,[19], we did not find that membership in a support group reduced the risk of ART failure. Though not captured systematically, the participants who had joined groups mentioned that the number of group members varied, meetings were scheduled infrequently and irregularly and lacked a structured format. Unfortunately our study only ascertained the presence of absence of these social support factors

and did not systematically collect information on the quality or quantity of support received. Additional investigation that obtains detailed information on these factors and their relationship to adherence and treatment failure might identify a benefit of social support. Alternatively, it is possible that such factors, in the real world context in which our study was conducted, do not reduce the risk of treatment failure.

The findings from this study are subject to several limitations. First, we had limited access to HIV viral load testing since the National Treatment Guidelines at the time prescribed targeted rather than routine viral load testing and therefore definition of treatment failure was done using clinical and immunologic criteria which has low positive predictive value,[20-24]. Thus, some of the cases may not have had high viral loads. This could explain why some factors did not differ between cases and controls. Second, adherence to ART was measured through self-reports. This would likely over-estimate adherence. This possibility was minimized because the study interview was administered by independent researchers rather than the routine clinical staff, a method shown to increase the reliability of self-reported data,[25]. Third, patients who were too ill to participate were excluded and there is the very real possibility that such patients were failing therapy. As such, our findings might not be representative of patients with severe treatment failure but are likely to

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provide important information among patients with early or mild symptoms of treatment failure.

However, the strength of our study is that the data come from a typical clinic in a semi-urban area in Kenya and as such, present findings that are likely to be reflective in many similar settings where viral load testing is not routinely performed. Based on our findings, we recommend that clinicians be encouraged to identify patients whose use of alcohol interferes with optimal health care behavior so that interventions to reduce alcohol use can be implemented. In the absence of additional information of a protective effect of social support against treatment failure, we recommend that proven strategies of increasing adherence, such as the use of text messaging as part of reminding the patients, continued counseling, family and psychological therapy,[26] be implemented in combination bearing in mind what will work best for a particular patient. Health care workers, people living with HIV and the public as a whole need to be educated on the importance of treatment adherence and its impact on reducing HIV-related morbidity and mortality and the opportunity for HIV-infected persons to lead healthy and productive lives.

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