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Original Article

Rate and predictors of HIV virological failure among adults on first-line antiretroviral treatment in Dar Es Salaam, Tanzania

Florence George Samizi[1,2], Onna Duuma Panga[3], Senga Sembuche Malugu[4], Catherine Gale Gitige[5], Elia John Mmbaga[2,6]

[1] Mwananyamala Regional Referral Hospital, Dar es Salaam, Tanzania
[2] Department of Epidemiology and Biostatistics, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
[3] Geita Regional Health Management Team, Geita, Tanzania
[4] Ministry of Health, Community Development, Gender, Elderly and Children, Dodoma, Tanzania
[5] Kibong'oto Infectious Diseases Hospital, Kilimanjaro, Tanzania
[6] Department of Community Medicine and Global Health, University of Oslo, Oslo, Norway

Abstract

Introduction: Monitoring resistance to first line Antiretroviral therapy (ART) is crucial in preventing accumulation of viral mutations following the implementation of the World Health Organization "treat all" initiative. We estimated the rate and predictors of virological treatment failure among adults living with HIV/AIDS in Dar es Salaam, Tanzania.

Methodology: A retrospective cohort study involving adults aged 18 and above receiving first line ART in Dar as Salaam between 2016 and 2018 were recruited using multistage random sampling. Clinical and laboratory data were extracted from Care and Treatment Clinic database-2 (CTC2) followed by participant's interviews. Adjusted Cox-regression modelling was used to determine independent predictors of treatment failure.

Results: A total of 340 participants with mean age of 37 were recruited. Overall, 10.59% had virological failure and the rate of failure was 5.24 (95% CI:3.72; 7.27) per 100 person-months at risk with a median failure time of 18 months. Independent predictors of treatment failure were being a male (Adjusted hazard ratio (aHR) 2.78, 95%CI:1.16;6.63), having used treatment for less than two years (aHR, 12.48, 95%CI:3.64-22.71) and co-infection with Tuberculosis (aHR 2.1, 95%CI: 1.0;5.9).

Conclusions: HIV virological failure occurs early during treatment in this population. Male clients, co-infected with Tuberculosis were at higher risk of ART failure within two years of treatment. Substantial stride has been made towards the achievement of the last UNAIDS 90 goal but tailored counseling and close monitoring of HIV/TB co-infected male clients following ART initiation could accelerate efforts to close the gap. Further studies on pre-treatment drug resistance mutations are called for.

Key words: First line antiretroviral drugs; HIV; virological failure; predictors; Tanzania.

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Introduction

The Universal HIV "treat all" programme initiated in 2015 by the World Health Organization (WHO) has been effective in increasing the number of infected individual on antiretroviral treatment (ART) worldwide (from 19.4 million in 2016 to 21.7 million people at the end of 2017 [1, 2]. A recent HIV impact survey in Tanzania indicated that 1,432,001 people were living with HIV/AIDS and of these, 61% were aware of their HIV status. Of those aware of their HIV status, 94% of them were on treatment with the proportion of viral load suppression estimated to be 87% [3]. These results suggest that Tanzania has made remarkable progress towards the achievement of the second and third ambitious UNAIDS goals (90% of those who knew their HIV status are on treatment and 90% of those on treatment have suppressed viral load) [4]. Despite these promising results virological monitoring of people who are on ART is critical and highly recommended to ensure effective response, detect treatment failure and possible drug resistance(9). Failure to systematically monitor first line ART resistance have been reported to results into accumulation of viral mutations [5-8]. Previous studies conducted in sub Saharan Africa including Uganda, South Africa and Tanzania, have reported rates of treatment failures among adults on first line ART to be 11%, 15% and 14.9%, respectively [9-14]. A multicenter cohort study in Ethiopia involving

874 HIV infected individual on first-line ART reported treatment failure rates of 23.3% and 33.9% at 6 and 12 months [15]. In 2015 Tanzania adopted the WHO "treat all" recommendation with establishment of routing viral load monitoring [1]. A study conducted in 2017 to evaluate pre-treatment and acquired HIV drug resistance mutations in Dar es Salaam city indicated a 30% pre-treatment drug resistance mutation in ART naïve clients [16]. Effective routine HIV viral load monitoring to timely detect treatment failure and potential drug resistance were strongly recommended in the country [12,17]. Moreover, understanding the rate and predictors of ART treatment failure is of paramount in informing failure cascade and timing for switching to second line treatment [18,19]. This study therefore seeks to estimate the rate and predictors of first line ART failure following the introduction of routine viral load monitoring in Tanzania.

Methodology

Study design

This was a retrospective cohort study of all adults living with HIV/AIDS (PLHIV) on first line ART attending care and treatment clinics (CTC) in Dar es Salaam, Tanzania. The study recruited all participants who were on ART during the period January 2016 to December 2018 in the selected HIV CTC in the city.

Study setting and population

The study was conducted in Dar es Salaam metropolitan city of Tanzania with a population of 5,495,569 and HIV prevalence of 4.3% among adults aged 15-49 [3]. The region has a total of five administrative municipalities with 116 CTCs. Recent survey indicated that 55% of people living with HIV/AIDS in the city were not aware of their status and only 43% of those who were aware of their status were on ART [3]. The region had a total of 11064 clients on ART and of these 10,743 (97%) clients were on first line ART treatment. All PLHIV aged 18 and above who were on first line ART for at least 6 months as of January 2016 with at least two viral load results were eligible for inclusion in the study. Participants were excluded if they were too sick to be interviewed or were mentally ill.

Sample size calculation

Sample size was calculated based on the Kelsey formula for qualitative (binary) outcome (treatment failure/no treatment failure) [20]. Estimates of treatment failure of 30% among exposed group and 15% among unexposed group were used [14]. With an estimated 10% non-response rate, 80% statistical power and two tailed alpha level of 95%, a total of 340 patients on treatment for at least 6 months were required.

Sampling procedures

All five municipalities of Dar es Salaam city were involved in this study. Multistage sampling procedure was used where 10 facilities (2 from each municipal) were systematically selected from a list of high-volume CTC obtained from each municipal. High volume facility was defined as a facility with 500 or more clients on ART. The number of participants selected from each facility was based on the number of clients in each of the selected facility. In each facility, computer generated random numbers were used to select participants to participate in the study. CTC2 cards of all the selected random numbers were identified, and data was extracted from the CTC database accordingly.

Data sources and data collection

Baseline and follow up socio-demographic, clinical and laboratory data were extracted from each study participant's medical records. Treatment failure was defined as having last two consecutive high viral load results less than 1000 copies/ml [1]. All participants recruited were contacted and invited for a face-to-face interview using structured questionnaire during their next clinic visits. The interview collected additional information of relevance in the assessment of predictors of treatment failure that are not usually recorded in the CTC2 card such as distance from the facility, marital status, education level; behavioral data such as food and alcohol consumption and reported data on adherence to ART. Adherence was assessed using 8-items Morisky scale [21].

Data analysis

Categorical variables were summarized using frequency distributions while continuous variables were summarised using mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Kaplan Meier method was used to estimate time to treatment failure. Participant person time started from the date of treatment initiation until 31 December 2018. Differences in the rate of treatment failure between different groups were examine using Log - Rank test. Cox-regression modelling was used to determine predictors of treatment failure. All predictors with p-value ≤ 0.2 in bivariate analyses were entered into a multivariable Cox- regression models to identify independent predictors for treatment failure. Two models were run one with age, CD4 count and distance

from the facility set as continuous predictors and the second with the same variables set as categorical predictors. Time varying variables in the analysis were all measured at baseline. The best parsimonious model was based on the lowest Akaike Information Criterion. All analyses were two-tailed, and significance level was set at 5%.

Ethical consideration

The protocol for this study was reviewed and approved by the Ethical Review committee of the Muhimbili University of Health and Allied Science, Tanzania with reference number DA.287/298.0/D34 dated 24 January 2018. Permission to conduct the study was sought from the city, municipal and health facility administrative authorities. All participate granted written informed consent before any interview.

Table 1. Distribution of socio-demographics characteristics of the study participants.

Variables	n (%)
Age group (years)	
18-24	34 (10.00)
25-30	59 (17.35)
31-39	101 (29.71)
40 and above	146 (42.94)
Gender	
Male	109 (32.06)
Female	231 (67.94)
Education	
None/Primary	192 (56.50)
Secondary/College/University	148 (43.50)
Marital status	
Married/cohabiting	170 (50.00)
Single	129 (37.90)
Widowed/ separated	41 (12.10)
Municipality of origin	
Kinondoni	99 (29.11)
Ubungo	73 (21.47)
Ilala	57 (16.76)
Temeke	86 (25.30)
Kigamboni	25 (7.36)
Occupation	
Employed	99 (29.11)
Unemployed	241 (70.88)
Means of transport	
Public	305 (89.81)
Private	11 (3.13)
Walking	24 (7.06)
Distance to health facility (in km)	
< 5	196 (57.58)
≥ 5	144 (42.42)
Frequency of food per day (meals)	
1-2	15 (4.32)
More than 2	325 (95.68)
Do you take alcohol	
Yes	227 (66.82)
No	113 (33.18)

Results

A total of 340 eligible participants receiving ART were randomly selected proportional to the number of those eligible in each of the included facility. The mean age of the study participants was 37 (Standard deviation 10). Two third of the participants (67.9%, N = 231) were female, (42.9%, N = 146) were aged above 40 with half (56.5%, N = 192) reporting to have either not attended school or competed primary school. Moreover, half (N = 179) of the participants were married or cohabiting and nearly three quarter (70.8%) were unemployed. Use of public transportation, alcohol consumption and having more than two meals per day were common (Tables 1). Half (55.9%, N = 190) of the participants were on ART for more than two years with median treatment time of 2.3 years (IQR 0.8-3.8). The median CD4 count was 351 cells/ ml (IQR 285-1402). A total of 175 (51.5%) participants were in the WHO clinical stage 3 and majority (96.5%) on TDF/3TC/EFV ART combination. TB co-infection rate in this population was 7.1% with drug adherence (good-medium) proportion of 41.59% (Table 2).

Table 2. Distribution of clinical characteristics of the study participants.

Variables	n (%)
Time on ART	
6 months to 2 years	150 (44.1)
More than two years	190 (55.9)
Initial CD4	
Less 350	136 (49.8)
350+	137 (50.2)
WHO HIV clinical stage	
Stage 1	60 (17.6)
Stage 2	92 (27.1)
Stage 3	175 (51.5)
Stage 4	13 (3.8)
ART regime used	
TDF/3TC/EFV	328 (96.5)
AZT/3TC/NVP/EFV/DTG/ETC	12 (3.5)
TB co-infection	
Yes	24 (7.1)
No	316 (92.9)
Adherence*	
Good	20 (6.02)
Medium	121 (35.57)
Poor	199 (58.41)

*Adherence based on Morisky scale.

Table 3. Rate of Virological failure by socio-demographic, clinical and facility characteristics, Dar es salaam Tanzania.

Variable	ART Virological failure			95%CI
	Follow up time (months)	Cases	Rate per100	
Age group (years)				
18-24	250.97	13	5.18	3.01-8.92
25-30	187.17	10	5.34	2.88-9.92
31-40	113.50	6	5.29	2.37-11.77
Above 40	134.00	7	5.19	2.48-10.89
Gender				
Male	230.73	14	6.06	3.59-10.24
Female	455.67	22	4.83	3.18-7.33
Education				
None/Primary	436.53	21	4.81	3.14-7.38
Secondary /College/ university	249.87	15	6.00	3.62-9.96
Marital status				
Married/cohabiting	226.20	11	4.86	2.69-8.78
Single	418.77	23	5.49	3.65-8.27
Widowed/ separated	41.43	2	4.82	1.21-19.30
Residence				
Kinondoni MC	60.10	3	4.94	1.59-15.32
Ubungo MC	163.13	9	5.52	2.87-10.60
Ilala MC	159.30	9	5.69	2.94-10.86
Temeke MC	233.10	11	4.72	2.61-8.86
Kigamboni MC	70.17	4	5.70	2.14-15.19
Occupation				
Employed	110.53	7	6.33	1.87-18.13
Unemployed	575.87	29	5.04	2.77-9.57
Means of transport				
Public	616.43	32	5.19	3.67-7.34
Private	21.50	1	4.65	0.65-33.02
Walking	48.47	3	6.19	1.90-19.19
Time on ART				
6 months to 2 years	141.47	11	7.78	4.31-14.04
More than two years	544.93	25	4.59	3.09-6.79
Distance to health facility (km)				
< 5	395.20	22	5.57	3.67-8.45
≥ 5	291.20	14	4.81	2.85-8.11
Adherence				
Good	41.33	2	4.84	1.21-19.35
Medium	244.17	12	4.92	2.79-8.65
Poor	400.90	22	5.49	3.61-8.33
Initial CD4				
Less 350	350.70	19	5.42	3.46-8.49
350+	228.83	11	4.81	2.66-8.56
Do you take alcohol				
Yes	227.77	12	5.27	2.99-9.28
No	458.63	24	5.23	3.50-7.80
Frequency of food per day (meals)				
1-2	29.63	2	6.75	1.96-12.23
More than 2	656.77	34	5.18	2.36-8.11
WHO HIV clinical stage				
Stage 1	93.33	5	5.36	2.23-12.87
Stage 2	28.33	2	7.06	1.7-28.22
Stage 3	513.87	27	5.25	3.60-7.66
Stage 4	50.87	2	3.93	0.98-15.72
TB co-infection				
Yes	168.53	11	6.53	3.61-11.79
No	517.87	25	4.83	3.26-7.14
ART regime used				
TDF/3TC/EFV	636.73	33	5.18	3.38-7.29
AZT/3TC/NVP/EFV/DTG/ETC	49.67	3	6.04	1.94-18.73

Rate of first line ART failure among adults living with HIV/AIDS

Of the 340 participants recruited, 36 (10.59%) had first line ART virological treatment failure. The overall rate of treatment failure was 5.24 (95% CI = 3.72-7.27) per 100 person-months. The median viral load among those who experienced virological failure was 1800copies per ml as compared to 500 copies/ml among those who experienced successful viral suppression. The median failure time was 18 months and this was higher among male, single, those with less than 350 CD4 count and those who were on ART for less than two years. Treatment failure was higher among those with poor adherence or TB co infection (Table 3).

Independent predictors of first line ART failure

Results of crude and adjusted cox regression modeling of predictors of ART failure are presented in Table 4. Being a male client was associated with almost three times (aHR,2.78,95%CI 1.16;6.63) higher rate of failure as compared to female clients. Being on treatment for less than two years was associated with 12 times higher rates of first line ART failure (aHR 12.48, 95%CI: 3.64; 22.71) as compared to those who were on treatment for more than two years. Moreover, co-infection with tuberculosis was associated with twice the rate of ART treatment failure (aHR 2.1, 95%CI: 1.0;5.9) as compared to those without TB co-infection.

Discussion

This study provides crucial data on the rate and predictors of first line ART virological failure in an urban population in Tanzania to inform strategy to achieve the UNAIDS third 90 goal. The overall treatment failure was 10.59% with a median failure time of 18 months. The rate of treatment failure was comparable to an estimate of 14.9% published earlier in the city from a cohort involving 2,403 adults [14]. Similar estimates have also been published in Ethiopia (11.5% and 14.7%), Lesotho (8.8%) and South Africa (9.9%) [9,19,22,23]. However, our estimate was lower compared to an estimate of 16% from a systematic review in sub Saharan Africa, 17% in Cameroon, 26% in Northern Ethiopia and 41.3% in rural Gabon [10, 24, 25]. Similar to what was reported in Addis Ababa Ethiopia, the urban nature of our study site and well established health system and follow up mechanism may have contributed to the relatively lower estimates in our study compared to average estimate for the whole of sub Saharan Africa [26]. The medium time to first line ART failure was 18 months which is consistence to those published from Ethiopia (17.5 months) and South Africa (16 months) but lower than estimates from Northern Ethiopia [23, 27]. Moreover, our study indicated that clients who have been on treatment for less than 2 years were more likely to experience treatment failure than those who have been on treatment for more than 2 years. These findings have also been reported in studies conducted in Ethiopia and South Africa [28, 29]. The earlier treatment failure might be due to higher level of pre-treatment drug resistance mutations which has recently been reported to be high in the city (30%) [16]. Moreover, these results may be attributed to early treatment related factors which includes side effects, use of unfavorable taste brand, complication and/or interaction with existing treatment of opportunistic infection and/or missing opportunity for adherence counselling due to shortage of staffs [30]. The rate of treatment failure was higher among men than female in this study population corroborating findings from elsewhere in Africa and beyond [10,31-33]. Men have been reported to have low HIV testing rate resulting into late diagnosis consequently having low CD4 count and severe disease stage. Moreover, occupational nature of men, societal demands in African context, high level of alcohol consumption and low clinic attendance for ART refill could results into poor adherence, high rate of TB co-infection and early drop out [10,11,23,33]. Men have also been reported to have poor HIV status disclosure, which is of paramount in treatment support and adherence [34, 35]. Opportunistic infection particularly Tuberculosis have been associated with treatment complications and/or virological failure [11,29,36]. Tanzania uses an intensive six months Rifampicin-based TB treatment regimen (2 months of Rifampicin, Isoniazid and Ethambutol) and 4 months of Rifampicin and Isoniazid). Studies have shown that Rifampicin- based regimen may interact with ART particularly Nevirapine based ART resulting into subtherapeutic blood levels and possible virologic failure [37,38]. HIV infected individual co-infected with tuberculosis in this study were twice more likely to experience treatment failure that those without tuberculosis. Studies have shown that HIV/TB co-infected individual are more likely to have lower CD4 count, higher HIV disease clinical stage and poor treatment outcomes [39, 40]. Moreover, increased pill burden has also been attributed to drug-drug interaction that also affect safety, adherence and response [41]. The results presented in this paper should be interpreted in light of the following limitations. Firstly, we selected individuals who were still attending CTC clinics who may have good access to treatment and hence less virological failure.

Table 4. Adjusted cox regression analysis of independent predictors of first line ART virological failure among adults in Dar es Salaam, Tanzania.

Variable	cHR(95%C1)	aHR(95%C1)	p-value
Age group (years)			
18-24	1.15 (0.45-2.94)		
25-30	1.03 (0.38-2.79)		
31-39	1.27 (0.41-3.93)		
40 and above	1		
Gender			
Male	1.77 (0.88-3.59)	2.78 (1.16-6.63)	0.02
Female	1	1	1
Education			
None/Primary	0.58 (0.29-1.18)	0.68 (0.43-2.00)	0.57
Secondary/college	1	1	1
Marital status			
Married/cohabiting	1		
Single	1.33 (0.63-2.82)		
Widowed/ separated	1.07 (0.23-4.99)		
Municipal of residence			
Kinondoni	1		
Ubungo	1.76 (0.45-6.81)		
Ilala	1.95 (0.51-7.51)		
Temeke	0.94 (0.25-3.51)		
Kigamboni	1.72 (0.37-8.03)		
Occupation			
Unemployed	1	1	1
Employed	0.67 (0.45-6.97)	0.59 (0.38-8.13)	0.89
Means of transport			
Private	1		
Public	1.03 (0.13-7.68)		
Walking	1.69 (0.17-16.39)		
Distance to health facility (km)			
< 5	1	1	1
≥ 5	0.76 (0.38-2.49)	0.76 (0.38-2.51)	0.45
Do you take alcohol			
Yes	1		
No	0.92 (0.42-6.17)		
WHO HIV clinical HIV			
Stage 1	1	1	
Stage 2	1.50 (0.29-0.78)	0.69 (0.46-47.37)	0.19
Stage 3	0.82 (0.31-2.17)	0.62 (0.10-25.30)	0.73
Stage 4	0.21 (0.02-1.92)	0.54 (0.43-29.08)	0.24
ART regime used			
TDF/3TC/EFV	1		
AZT/3TC/NVP/EFV/DTG/ETC	1.89 (0.55-6.43)		
TB co-infection			
Yes	1.93 (0.92-4.06)	2.1 (1.0-5.9)	0.03
No	1	1	1
Initial CD4			
Less than 350	1.24 (0.57-2.69)		
350+	1		
Adherence			
Good	1		
Medium	1.35 (0.29-6.21)		
Poor	1.57 (0.35-6.98)		
Time on ART			
6 months to 2 years	4.89 (2.09-21.44)	12.48 (3.64-22.71)	0.00
More than two years	1	1	1

However, the potential role of pre-treatment drug resistance strain which may not be affected by adherence or access to ART may offset this limitation. Secondly, collection of behavioral data such as those related to food habits, alcohol consumption and self-reported adherence may suffer from desirability bias. Thirdly, given that this was a secondary data analysis of existing surveillance we did not collect detailed information about the use of other drugs that either may have interaction with ART or those causing immunosuppression.

Conclusions

HIV virological treatment failure occurs early during ART treatment, and associated with multiple factors, including potential for pre-treatment drug resistance viral mutation. Tanzania has made a significant stride in achieving the last UNAIDS 90. Enhancing care and strategic counseling and follow up for HIV infected men and those with HIV/TB co-infection could reduce first line ART failure. More studies on drug resistance viral mutations are called for.

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Authors' contributions

FGS, collected, analyzed the data, interpreted the results, and wrote the first draft of the manuscript, ODP, SSM, and CG interpreted the results and critically revised the manuscript, EJM, designed the study, analyzed the data, interpreted the results, and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Corresponding author

Prof. Elia John Mmbaga. MD, PhD
Department of Community Medicine and Global Health,
P.O.Box 1130, Blindern,0318, Oslo
Tel: +4747728384
Fax: +47 22850590
E-mail: ejmmbaga@medisin.uio.no

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