Chapter

Gender Differences in Human Immunodeficiency Virus (HIV) Disease Progression and Treatment Outcomes

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Abstract

Several interventions have been implemented for control and prevention of HIV, including provision of Antiretroviral Therapy (ART). A major concern is how this investment can effectively reduce morbidity and mortality due to HIV given the existence of various factors that contribute to treatment failure. The purpose of this chapter is to elaborate the role of gender on HIV Disease progression and treatment outcomes. Demographic, epidemiological, clinical, immunological, treatment information as well as blood from HIV infected patients were collected. Epidemiological analyses, using standard phylogenetic and statistical tests were done. A follow-up of patients who were initiated on ART for 1 year enabled description of the gender differences in HIV disease progression and treatment outcome. After 1 year of follow up on ART, more females survived, and more females had undetectable viral load compared to males. However, women lost their initial immunological advantage as they presented with lower immunological recovery after 1 year of therapy. Socio-demographic factors do have an impact on disease progression during ART in HIV-1 infected patients. We recommend that more cohorts of patients be continuously followed up to understand the differences on ART outcome between males and females.

Keywords: gender differences, HIV, disease progression, treatment outcomes, Tanzania

1. Introduction

The epidemic of the Acquired Immune Deficiency Syndrome (AIDS) was first recognized as a clinical entity in 1981 [1]. HIV-1 was identified as the causative agent for AIDS in 1983 [2]. Globally, 37.9 million people were living with HIV, with 1.7 million new infections and 770,000 people having died of AIDS in 2018. Sub-Saharan Africa is the most severely affected by HIV infection in which 1 in every 20 adults (4.9%) are living with HIV [3].

HIV may be classified into types, groups and subtypes based on genetic similarities. There are two types of HIV: HIV-1 and HIV-2. Both types can be transmitted by sexual contact, blood contact, and vertical from mother to child [4]. HIV-1 is the predominant type worldwide with high genetic diversity due to extremely high

mutation and recombination rates and high cell turnover [5]. The strains of HIV-1 can be classified into four groups: the "major" group M, the "outlier" group O and two new groups, N and P, representing the four separate introductions of simian immunodeficiency virus into humans [6]. The majority (more than 90%) of HIV-1 infections are caused by HIV-1 group M strains. Within group M there are nine genetically distinct subtypes (or clades) of HIV-1. These are subtypes A, B, C, D, F, G, H, J and K [7].

1.1 Gender differences in HIV disease progression

HIV disease progression and clinical manifestations of diseases may differ between women and men because of biological and socioeconomic factors [8]. The progression of AIDS reflects the chronic nature of the disease, the hallmark of which is a gradual deterioration of the host immune system. Previous investigations found different rates of HIV disease progression and of virological and immunological response to antiretroviral therapy (ART) among HIV-infected women compared with men [9]. The rate of increase in viral load over time is presumably greater for women than men given that women and men progress to AIDS and death at similar rates [10]. Baseline clinical and immunologic status was found to be predictors of HIV related mortality and morbidity in HIV outcome studies conducted in both high income and low-income countries. In the same studies, Men were found to have a significant higher rate of loss to follow-up and ART non-adherence [11]. More evidence suggests that HIV positive men have worse treatment outcomes than their women counterparts in Africa [12]. One study found that humans show strong sex differences in immunity to infection and autoimmunity, suggesting sex hormones modulate immune responses [13]. Similarly, evaluation of the gender difference in the outcome of other viral diseases like the COVID-19, revealed a higher mortality rate of male patients as compared with female patients, suggesting the protective role of estrogen [14].

Some studies have documented the differences in clinical progression of HIV between women and men due to hormones and age at the time of HIV infection [15], some studies suggesting that the differences in immunological responses to ART and mortality risk are due to biologic differences between men and women. The hormonal fluctuations in ovulating females, may affect immune function, and thus can cause variation on viral loads in women, where HIV RNA levels can decrease to a median of 0.16 log10 from the time of early follicular to the mid-luteal phase [10]. Studies involving male-to-female transsexuals have shown decrease in CCR5 expression when female hormones are administered.

Women living with HIV have limited access to care and treatment in several countries, most of who belong to ethnic or racial minorities, despite having better treatment outcomes and higher enrolment to ART care when compared to men [12]. However, women may delay ART initiation because of social obligations, pregnancy and socioeconomic factors [16].

1.2 Problem statement

Highly Active Antiretroviral Therapy (HAART) for treatment of HIV infection has improved the lives of HIV infected people by reducing the morbidity and mortality in patients receiving treatment. This has transformed a chronic fatal infectious disease into a manageable chronic infectious disease. Despite the use of HAART, numerous reports indicate failure of therapy due to lack of potency of some drugs or drug combinations, insufficient drug adherence and transmission of drug resistant virus. In a number of patients, HAART is not sufficiently effective

thus results into virological, clinical and immunological decay [17]. The success of HAART in HIV infected patients may be influenced by other host factors; however, there is no enough information with combined assessment of a variety of factors that can influence treatment efficacy in clinical routine practice. One of the poorly understood factors that may influence disease progression and treatment response is gender. Men and women are affected differently with HIV and women's immune systems may respond differently to the virus because of hormonal influence. Women may also experience stronger side effects when using ARV drugs, such as central nervous system and gastrointestinal symptoms, which could then lower their ARV adherence [18]. Survival of HIV infected patient from the point of HIV diagnosis to AIDS within a comparable clinical care setting is affected mostly by the time of HIV diagnosis (WHO stage I and II), and other differences like age, gender, race and behavioral factors may also play a role on survival [19]. Also the differential use of ARV drugs for purely social economic reasons may lead to survival disadvantages for women [10].

Some patients, especially males diagnosed with HIV in developing countries, are not always successfully linked to onward treatment services, resulting in delays on initiating ART, or prophylaxis for opportunistic infections. Delayed presentation to care and treatment, and late HIV diagnosis, can result into late initiation of ART which affects adherence to treatment and results into poor prognosis in a disadvantageous group in the society [20]. More studies will be of benefit to explore the possibility of initiating ART at lower viral loads in women, especially during the early stages of infection.

1.3 Rationale of the study

As the use of ARV drugs in resource-limited countries increases, it is important to understand the effect of several factors on disease progression and outcome of ART. Combined analyses of various factors are scarce. Several studies except trials on specific regimens, have addressed aspects such as baseline clinical characteristics and adherence as predictors of treatment success. For limited resource settings, where ARV drugs are not sufficient for all patients, it would be cost effective to issue the drugs to patients who will ultimately adhere to the therapy. Cheap alternative methods are needed, to help in guiding therapy, especially in this era where the use of ARV has become widespread. If not controlled, emergence of HIV drug resistance will further complicate the epidemiology and transmission patterns of HIV especially during the time when ARV resources are limited. Various studies came up with different results on the survival difference between male and female HIV patients, and some of the differences were a result of inadequate medical care rather than biological differences. Some of the differences were related to the time to development of AIDS and opportunistic infections, viral load, ARV drug resistance and CD4 counts over time of observation. HIV disease progression can be determined by viral and host factors and sex differences in immune modulation. The purpose of this study was to assess the socio-demographic and virological factors predicting HIV disease progression among HIV patients in Dar es Salaam, Tanzania.

2. Methods

We conducted a cohort study in which we followed up HIV-infected ARV naïve patients for 1 year. We enrolled ARV naïve, HIV infected patients who were due to initiate ART, if they were 18 years and above, with available medical records from

previous year. All patients were enrolled after providing written informed consent. We used a structured questionnaire to collect social demographic variables and anthropometric information, while patient record files and CTC database were used to collect data with respect to HIV diagnosis, clinical and ARV treatment information.

We categorized patients according to the clinical and performance scales of the staging system for HIV-1 patients [21]. The differences on these variables were assessed between males and females. All patients were followed up for a period of 1 year after starting treatment where treatment outcome was evaluated after 12 months from the time of initiation of therapy.

Ethical clearance to conduct the study was obtained from the National Institute for Medical Research in Tanzania and permission was seek from Hospital administration. All patient identifying information was de-linked from the collected data.

We collected blood in EDTA collection tubes, CD4 level was estimated using Becton Dickinson FACSCalibur, and viral load using TaqMan Viral-Load Assay COBAS® AmpliPrep.

Whole blood was separated by centrifugation at 4000 revolutions per minute for 20 minutes at −15°C, and plasma aliquoted and stored for testing. HIV RNA was extracted from plasma using Qiagen QIAamp Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. cDNA synthesis was performed using SS III RT-PCR System (Life Technologies, USA) according to the manufacturer's instructions with the primers PrtM-F1 and RT-R1. Nested PCR was performed from obtained RT-PCR product, using primers Prt-F2 and RT-R2. The QIA quick PCR purification kit (Qiagen, Hilden, Germany) was used to purify the nested PCR products and quantified by agarose gel visualization. The ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction kit was used for sequencing together with the following primers PRT-F2, RT-R2, SeqF3 (35V), SeqR3 (90v1), SeqF4 (36V) and SeqR4 (AV44). Sequences were aligned using Clustal X [22], manually edited with BioEdit [23].

Data were analyzed using Epi Info version 3.5.1 and STATA 11. Clinical progression was assessed by comparing clinical characteristics at hospital registration, baseline and at the time of the study, taking into account the change in clinical characteristics over time. Median percentage weight gain was adjusted for amount of time on treatment. Gender differences were assessed using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical data. Descriptive analysis was done for the basic demographic, clinical and immunological characteristics of patients as well as continuous variables like CD4 counts, age, plasma viral load levels and BMI for both males and females. Survival distributions for male and female patients were estimated using the Kaplan-Meier method. Patients who were lost to follow up were censored at the date when they were last seen. Patients who were still alive on the date when the study ended were censored on this date. Survival times were expressed in days. Cox's proportional hazards regression models were used to assess the associations between patient characteristics and outcomes. All other variables were included in multivariable models to assess their impact on the association between gender and outcomes.

3. Results

3.1 Sociodemographic characteristics

In a study of 234 patients recruited to initiate ARVs in Tanzania, 164 (70%) of them were females and 70 (30%) were males, with a refusal rate of 6 and 25%,

respectively. Significantly more males had attended secondary schools than females; had a higher income and a better knowledge of ARV use (**Table 1**). There was no significant difference in median age (36 years), alcohol intake and use of traditional medicine and use of intravenous drugs (**Table 1**). Significantly more males tested for HIV following a chronic illness, in contrast to females who tested without signs of AIDS. Consequently, the disease stage at HIV diagnosis was significantly more advanced in males: more males had CD4 count <100 cells/ml at baseline; they had a significantly lower Body Mass Index and higher mean Log10 viral load (males 5.5; females 5.1) (**Table 1**).

3.2 Treatment response and disease progression

The prevalence of adherence to ART as measured by consistence in keeping appointment was not different between females (62.8%) and males (62.9%)

Characteristics	**Females (N = 164)**	**Males (N = 70)**	**P value**
Categorical variables	**N (%)**	**N (%)**	
Primary level education	156 (95.1)	59 (84.3)	**0.005**
Above 100 US Dollar monthly income	57 (34.8)	43 (61.4)	**0.0002**
Having relative to remind to take medication	133 (81.1)	59 (843)	095
Alcohol intake	33 (20.1)	18 (25.7)	04
Use of traditional medicine	97 (592)	45 (652)	05
History of intravenous drug abuse	8 (4.9)	7(10)	02
Knowledge on ARV use and side effects	10 (6.9)	14 (20)	**0.005**
HIV testing due to chronic illness	105 (64)	55 (78.6)	**0.04**
Starting treatment with in 1 year of HIV diagnosis	130 (793)	55 (78.6)	0.96
Presence of 2 or more opportunistic infections	75 (45.7)	37 (519)	03
WHO staging at initiation of therapy			
Stage I	16 (9.8)	5 (7.1)	0.6
Stage II	49 (29.9)	16 (22.9)	0.3
Stage III	82 (50.0)	34 (48.6)	0.8
Stage IV	17(10.4)	15 (21.4)	**0.04**
CD4 < 100 cells/μl at ART initiation	50 (333)*	31 (47.0)*	**0.05**
Continuous variables	**Median (IQR)**	**Median (IQR)**	**P value**
Age (Years)	35 (30.5–43.5)	37 (33.5–42.0)	0.38
CD4 (cells/μl) at ART initiation	149 (6–148; 75–218)	102 (3–221; 47–184)	**0.02**
Continuous variables	**Mean (SD)**	**Mean (SD)**	**P value**
BMI at initiation of therapy	22 (5)	20 (4)	**0.002**
Log 10 viral load (RNA copies/ml) at initiation of therapy	5.1 (1.3)	5.5 (1.1)	**0.05**

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Table 1.
Baseline characteristics of 234 HIV-1 infected naïve patients, Dar es Salaam 2010.

(**Table 2**). After 1 year of treatment with ART, the virological response was significantly better in females than in males (females 69%; males 45% with undetectable viral load) but the mean CD4 increase was significantly higher in males (230 cells/ml) than females (202 cells/ml) (**Table 3**).

The BMI was still significantly higher in females (24.5) compared to males (22.5), but the percentage increase of BMI was not significantly different. Also, more females (61.6%) survived than males (50%) with more deaths occurring in males. The unadjusted relative hazard for death for males at 1 year of ART was 1.94 with a confidence interval of 0.91 to 4.11, p = 0.08 (**Figure 1**). Cox proportional hazards (of a model containing social demographic variables) showed no significant difference in the survival rate after 1 year on treatment between males and females (relative hazard 1.02, 95% CI 0.75, 1.38). The reported opportunistic infections during 1 year of follow up were not significantly different (**Figure 2**).

3.3 Genotyping of patients with detectable viral load

A total of 67 patients were found to have detectable viral load at enrolment (females 43 (64%); Males 24 (36%)) during 1 year of treatment. Among which, 31 females and 29 males (60 total), were alive after 1 year of follow up. The status of 7 could not be confirmed after 1 year of treatment, as they were either died or Loss to follow up. The main subtypes identified were C 18 (27%), A 14 (21%) and D 13 (19%) (**Figure 3**). There was no significance difference on subtype distribution between males and Females.

3.3.1 Nucleoside reverse transcriptase inhibitors (NRTI) resistance mutations

A total of 6 (9%) patients had detected NRTI resistance mutations, 4 females and 2 males, among which 3 were alive after 1 year of therapy. There was no significance difference between males and females with regard to NRTI resistance mutations. Two of the patients had both NRTI and Protease Inhibitor (PI) resistance mutations. One patient-initiated treatment at WHO stage IV, four at WHO stage III and one at WHO stage II of disease staging. All patients started treatment with CD4 below 100 cells/μl and Viral Load above 5000 copies/ml.

3.3.2 Non nucleoside reverse transcriptase inhibitors (NNRTI) resistance mutations

A total of 2 (3%) patients had detected NNRTI resistance mutations, all females and were alive after 1 year of therapy. One patient-initiated treatment at WHO stage

Characteristics	Females (N = 164)	Males (N = 70)	P value
	N (%)	N (%)	
Death	21 (12.8)	14 (20)	0.2
Alive	101 (61.6)	35 (50.0)	0.1
Lost to follow up	42 (25.6)	21 (30.0)	0.5
Missed appointments	103 (62.8)	44 (62.9)	0.99

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Table 2.
One year outcomes of 234 HIV infected patients after starting ART from September 2010 to August 2011.

Characteristics	Females (N = 101)	Males (N = 53)	P value
Percentage with undetectable viral load	70 (69%)	24 (45%)	**0.003**
Continuous variables	**Median (IQR)**	**Median (IQR)**	
CD4 (cells/μl) count after 1 year	312 (252–413)	321 (110–480)	0.6
Continuous variables	**Mean (SD)**	**Mean (SD)**	
Percentage BMI increase (from Baseline)	10.5 (14.2)	9.8 (17.5)	0.3
BMI after 1 year	24.5 (4.8)	22.5 (4.1)	**0.02**
Percentage weight gain	10.4(14.3)	9.3 (17.3)	0.2
CD4 (cells/μl) increase from baseline	202 (516; 35–163)	230 (272; 86–181)	**0.05**

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Table 3.
Progression of patients 1 year on ART, Dar es Salaam.

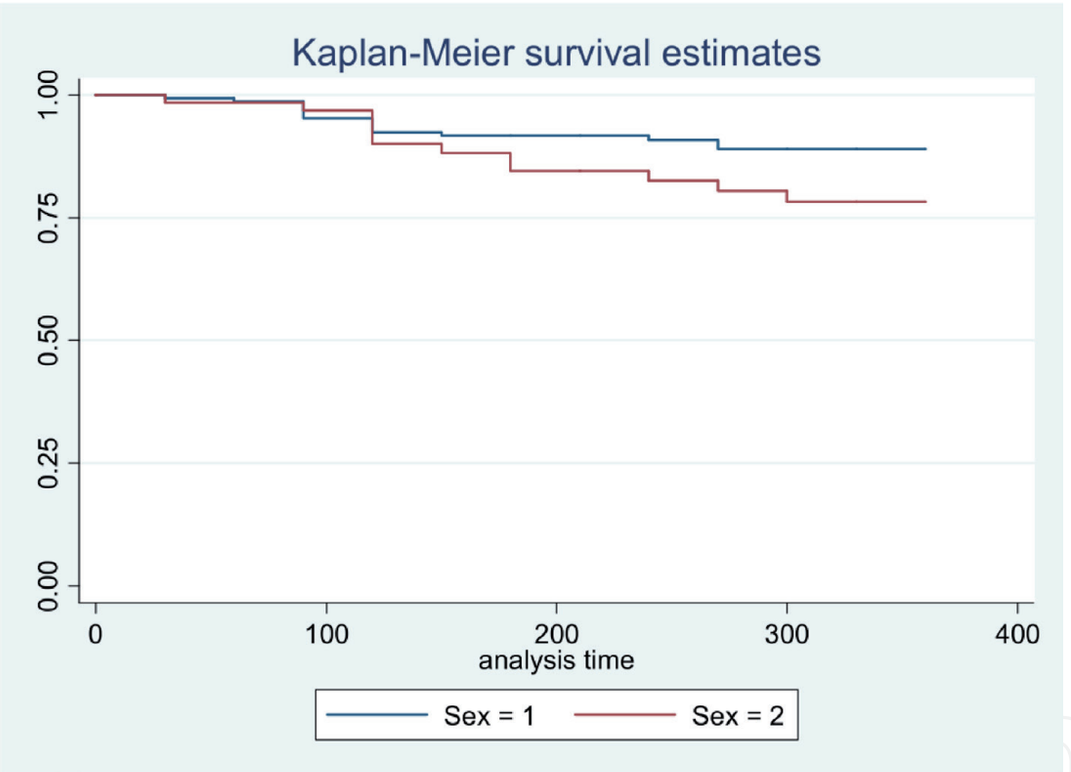

Figure 1.
Kaplan-Meier survival curves on time to death for 234 patients, Dar es Salaam (reproduced with permission from [24]).

III and one at WHO stage II of disease staging. All patients started treatment with CD4 below 100 cells/μl and Viral Load above 5000 copies/ml.

3.3.3 Protease inhibitors (PI) resistance mutations

There was no patient with PI major resistance mutations. A total of 15 (22%) patients had detected PI minor resistance mutations, 6 females and 9 males, among which 6 were alive after 1 year of therapy. There was no significance difference between males and females with regard to PI minor resistance mutations. One patient-initiated treatment at WHO stage IV, nine at WHO stage III and five at WHO stage II of disease staging. Eight patients started treatment with CD4 below 100 cells/μl and all with Viral Load above 5000 copies/ml.

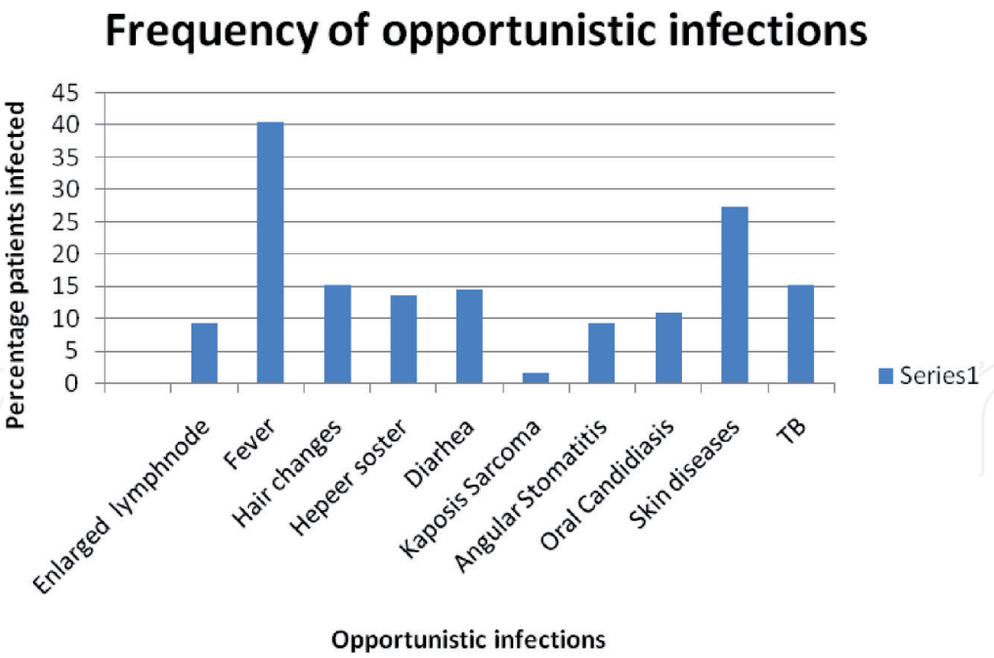

Figure 2.
Observed opportunistic infection during 1 year of follow up (reproduced with permission from [24]).

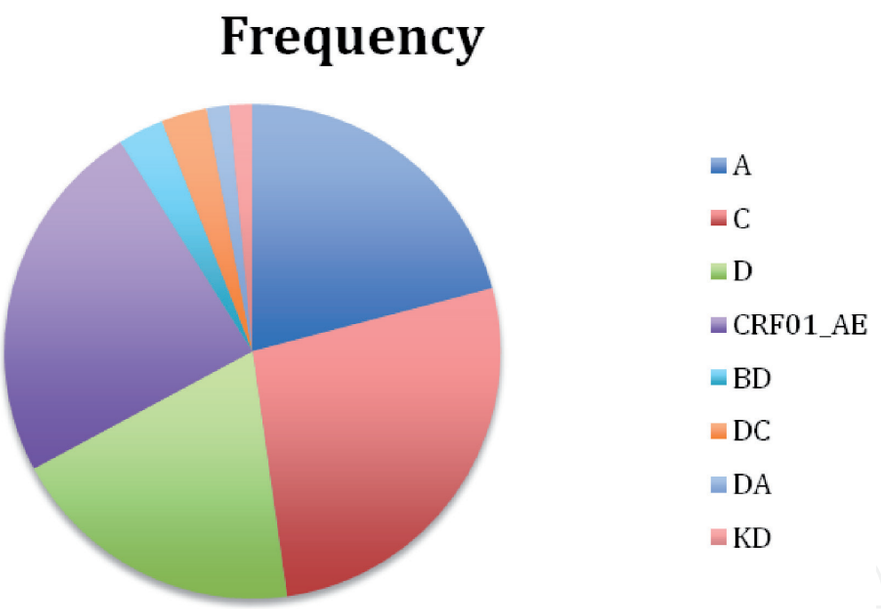

Figure 3.
Subtype distribution of the detected sequences [24].

4. Discussion

Our analysis of gender difference found significant clinical and social-demographic variations between females and males on HIV disease progression after 1 year of treatment. Overall, females were found to start CTC with higher CD4 count and BMI, and lower viral loads than males. Similar findings were reported by other studies, which found that women had higher CD4 cell count at ART initiation than men [9].

There was no statistical significant difference in survival between males and females in our study population after 1 year of follow up; this is in contrast with the findings of another study which found better survival among females and less disease progression among females after 3 years follow up [25]. The difference could be

due to a shorter follow up (1 year) in our study compared to 3 years. Despite the fact that more males died, the ones who survived were found to have higher mean CD4 increase than females and more females had undetectable plasma viral load. Our findings are similar to a study, which found a significant better survival of female HIV-1 infected patients on HAART compared to male patients [10].

The fact that women did not fare worse than men is encouraging considering that females were found to be less educated with lower monthly income. This is consistent with the current data available in Tanzania where males earn more than females and are more educated [12]. However, males delayed reporting to care, with an advanced disease. Several studies have also indicated differences in health seeking behavior, between men and women, where more women were reporting to health facilities earlier [26]. This could be a result of differences in social responsibilities giving women more entry points to HIV services, like during pregnancy. However, we did not have similar results in this study.

The most common reason for HIV testing was presence of AIDS related symptoms, rather than voluntary testing, especially for males, and this denied the patients time for care at CTC. Despite the fact that both groups had delayed registering for care at CTC, 66% of males understood more about the use of ARVs than females. Immune Reconstitution Inflammatory Syndrome (IRIS) was associated with poor response to HIV patients initiated ART with low CD4 [26], which could also have happened to some of the patients in this cohort, as also observed in another study that CD4 cell count at ART initiation was a strong predictor of mortality [27].

Significant number of patients was using alternative medicines, illicit drugs and alcohol prior to starting ARVs, more observed among males than females. The use of alternative medicines and alcohol could contribute to the delay in seeking health care and late presentation to the care and treatment centers with advanced disease and also predispose the patients to poor adherence and poor prognosis [28]. However, there was no significant difference on ART adherence as measured by consistency in keeping appointment. There was also no significant difference in development of ARV drug resistance mutations. Excessive alcohol consumption can exacerbate immunosuppression, enhance the toxicity of ARV on liver cells and accelerating liver damage and may also depress the immune system leading to increased multiplication of the virus in mononuclear cells [29]. A significant number of patients reported use of injection-based illicit drugs in the past and present, this could have implications on ARV adherence and disease progression. Several studies have associated the use of illicit drugs with non-adherence to ART and poor prognosis. People who inject drugs (PWID) are also challenged with poor social and economic conditions, mental illnesses, which may affect their access and adherence to ART [30].

Women had a lower median viral load at initiation of therapy compared to men, despite the fact that there was no much difference on the period of illness before starting ART between the two groups. However, after 1 year of treatment, more females had undetectable plasma viral load and lower mean CD4 cell increase than males. This will need further evaluation, as this may need redefining the time to initiate ART in the two groups. Further studies are needed to understand the benefits of initiating ART, earlier with lower viral loads. This is because the absolute viral load seems to confer different risks for AIDS between men and women, which is not the case with relative viral loads [10]. Because HIV related morbidity is influenced by both viral and host factors, sex differences in immune modulation will likely play instrumental roles in determining the course of disease. Despite an observed high number of both males and females patients presenting with opportunistic infections; females reported more fever and oral candidiasis than males. The reason could be late presentation to CTC and thus could not benefit from the

care and treatment services like prophylaxis against opportunistic infections. This may predispose the patients to poor prognosis and poor adherence after starting treatment [31]. Patients receiving HIV diagnosis late in the course of infection are usually more severely immune compromised and are more likely to present with co-morbidities like tuberculosis, which may be part of the immune reconstitution syndrome.

Consistent with our previous report, the most prevalent subtypes were A, C and D, and recombinants [32]. Our study found no contradiction to previous studies that found no association between subtype and therapy response, although our sample size was too small to conclude that [33].

Of concern was the detection of resistance to the first line ARV in Tanzania, in individuals who have been on treatment for only 1 year. This ARV resistance pattern was not limited to a particular subtype or gender. We observed minor PI mutations, which could be naturally occurring polymorphisms with no clinical significance. Interestingly, similar resistance mutations in the protease inhibitor genes were also observed in two different studies in Tanzania [34, 35].

5. Conclusion

We assessed the gender differences on HIV disease progression and outcomes after 1 year of ART among HIV infected patients and whether this potential difference is influenced by social, virological and immunological differences among patients starting ART. We observed some differences in clinical disease progression between males and females before starting ART and after 1 year of treatment. Male HIV patients delay seeking care and enter into treatment at a more advanced stage of HIV infection, which predisposed them to increased mortality. We also observed social factors that can affect future ART success in these patients. We recommend continuous follow up of this and other cohort of patients to understand responses to ART and the differences between males and females, together with advocating early HIV diagnosis and treatment to males. The observed gender difference between males and females will need further evaluation, as there may be a need to redefine the time to initiate ART in the two groups. The possibility of initiating ART at lower viral loads in women, especially during the early stages of infection merits further study. We recommend continuous follow up of this and more cohort of patients to understand responses to ART and the differences between males and females, together with advocating early HIV diagnosis and treatment to males.

It is important to monitor the viral response to patients on ART for early detection of treatment failure, together with understanding the ARV resistance pattern to ART Naïve patients and ART experienced patients. ARV resistance monitoring will help avoid unnecessary costs on use of ineffective treatment. The observed mutations within the pol region are of considerable concern because they may increase the development and spread of ARV resistant strains.

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