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Prevalence and Predictors of Immunological Treatment Failure among HIV Infected Adults on the First-line Antiretroviral Therapy in Mbeya Region, Tanzania

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ABSTRACT

Background: Immunological treatment failure (ITF) is a common challenge among HIV-infected patients on first-line ART in resource-limited settings. This study aimed to determine the magnitude of ITF and its predictors among adult HIV-infected patients on ART in Mbeya Region, Tanzania.

Methods: This was a cross sectional, retrospective study which analyzed data of HIV-infected patients (≥ 15years) on ART. Data were collected from patients enrolled at health facilities in Mbeya region from January 2010 to June 2016. Data were obtained from the HIV care and treatment clinic (CTC) electronic database and patients' CTC - 2 cards and were analyzed to determine the factors influencing the ITF.

Results and discussion: A total of 2,565 patients' records were reviewed and followed retrospectively for median duration of 24.5[13.6-43.6] months. Of these 64.4% (1653/2,565) were female and the median age was 41 (IQR: 35-48) years. The median baseline CD4 count was 194 (IQR: 92-344) cells/µl. ITF was reported in 42.8% (1237/2,565) patients. There was a significant association between ITF and baseline CD4 of ≥ 350cell/µl (OR = 7.2, 95%CI = 5.7 – 9.2, $p < 0.001$), increased age (OR = 1.01, 95% CI =1.002 – 1.020], $p = 0.012$), being the patient from district council designated hospital (OR = 1.2, 95%CI =1.1 – 1.5, $p = 0.008$), hemoglobin < 8g/dL (OR = 1.4, 95%CI 1.1 – 1.8, $p = 0.017$), longer duration from HIV diagnosis to ART initiation (OR = 1.9, 95% CI = 1.2 – 3.0, p = 0.006) and Zidovudine (AZT) based regimen (OR = 1.3, 95%CI = 1.1-16, $p = 0.010$).

Conclusion: There was a high prevalence of immunological treatment failure. Significant predictors of ITF were age, baseline CD4 of ≥ 350cell/µl, being patient from district hospital, anaemia, longer duration from HIV diagnosis to ART initiation and AZT-based ART regimen. Health care providers should be guided to focus on predictors of immunological failure so that they do early switching to second line ART.

KEYWORDS

Prevalence of Immunological Failure; Treatment Failure; ART; Mbeya; Tanzania.

BACKGROUND

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) continues to be a major global public health issue, having claimed more than 34 million lives so far and continues to cost the lives of so many individuals in the country and worldwide [1]. Even though HIV/AIDS is both pandemic and endemic, Sub-Saharan Africa (SSA) suffers the most with more than 25 million people living with HIV/AIDS (PLHA) in 2014 [1].

In Tanzania, it is estimated that 1.4 million people were living with HIV in the year 2013 alone making an estimated prevalence of 5.1% [2]. Across the country, HIV prevalence varies between regions with some regions reporting an HIV prevalence of around 1.5% (Manyara) and others as high as 14.8% (Njombe) [2]. Mbeya region is also one of the hardest-hit region with the prevalence of 9.0% [2].

Antiretroviral therapy (ART) has shown to delay progression to AIDS, resulting in a greater and more sustained virologic and immunologic response and improve survival [3]. It refers to the lifelong use of a combination of three or more antiretroviral (ARV) drugs for treating HIV infection.

The number of people receiving antiretroviral treatment (ART) has increased dramatically in recent years, particularly in resource-poor countries. As of March 2015, 15 million PLHA were receiving (ART) globally and 13.5 million of these people were in low- and middle- income countries [4]. In Tanzania, the Ministry of Health, Community Development, Gender, Elderly and Children is coordinating a nationwide HIV care and treatment programme since 2004, aiming at providing Antiretroviral medicines to PLHA. By September 2014, a cumulative number on HIV care was 1,486,162 while a total of 589,431 were on ART. For those who are not eligible, they are closely monitored at 1209 health facilities that are providing Care and Treatment services in the whole country [5].

Monitoring of ART among HIV infected patients is a pivotal strategy in ensuring specific management of patients. Much as the standard recommended system is ideally supposed to be a combination of clinical, immunological and virological parameters, the latter has remained hypothetical in developing countries. This is due to logistical and financial constraints. As a matter of fact, monitoring in these settings is largely based on clinical and immunological markers [5-7] but for the purpose of this study, only immunologic criteria were used.

The Tanzanian 2015 National Guidelines for the Clinical Management of HIV and AIDS defined immunological treatment failure (ITF) as CD4 count <50% of peak value or <pre-treatment levels, or persistently <100 cells/mm^3 [8]. This resembles the WHO 2010 Antiretroviral Therapy for HIV Infection in Adults and Adolescents guidelines [7]. Both WHO and National guidelines were revised in 2013 and 2015 respectively to remove the criterion of a 50% drop [5,6].

In developed countries, data is generally missing on prevalence and predictors of immunologic treatment failure as they use virological criteria to define treatment failure [6]. In low and middle income countries, particularly sub-Saharan Africa, reported prevalence show inter-region and intra-region variability but usually above 10% [9-11]. Moreover, there is an increase in prevalence of treatment failure over time since ART roll-out [12]. In a study from South India, 40 of 1,443 patients (14%) experienced first-line treatment failure at a mean of 14 months [13] while the study from Uganda reported the prevalence of 11% among 1,133 patients after a median follow-up time of 22 months [14].

In Tanzania, reported prevalence of immunological treatment failure ranged from 7% to 57% [15-17]. In short, these studies show that different settings have different levels of immunologic failures.

Factors associated with HIV treatment failure are varied, as is the prevalence. Documented factors associated with immunological treatment failure include poor adherence, low baseline CD4 cells count, low baseline hemoglobin count, low baseline weight, initiation in lower level facilities, non-disclosure of HIV status, HIV/TB co-infection and having an ambulatory functional status at baseline [9-11,15,16,18,19]. Other factors include WHO stage 3 and 4, longer duration on ART, Higher baseline CD4 cells count, history of changing care and treatment clinics (CTC) and lack of treatment supporter [17,20]

Prior ARV exposure, high baseline plasma viral load, certain ART regimen combinations and primary infection with drug resistant strains of HIV also pose a serious threat to the sustained success of ART [21].

Despite the fact that Mbeya is one of the hardest-hit region with HIV/AIDS [22], the magnitude and factors associated with ITF has not yet been studied. Therefore, this study assessed retrospectively immunological treatment failure among patients on ART treated in two hospitals in Mbeya region. The results herein will be crucial for the respective hospital authorities as well as policy makers in ensuring sustainability of this monitoring strategy and favorable patients' outcomes.

METHODOLOGY

Study Area

This study was conducted at two HIV Care and Treatment Clinics (CTCs) in Mbeya region, Southern Highland Zone of Tanzania. These hospitals are Mbeya Regional Referral Hospital and Mbalizi Council Designated Hospital. ART initiation in these facilities is in accordance with guidelines from the National AIDS Control Program [5]. First-line treatment comprised Tenofovir (TDF), Zidovudine (AZT) or Abacavir (ABC), combined with Lamivudine (3TC), and either Nevirapine (NVP) or Efavirenz (EFV). Regimen of choice is subject to availability, with use of a generic fixed-dose combination of TDF, 3TC and EFV (TLE) whenever possible [5]. Patients are seen at the clinic monthly for drug refill and clinical evaluation in the initial six months after starting ART. Six months after starting ART, clinically stable patients may be given an appointment of two or

three months as agreed between the clinician and patients. CD4 cell counts and full blood counts (including hemoglobin) are scheduled every 6 months as part of a routine follow- up. Viral load monitoring was not available in these hospitals by the time this study was conducted. Therefore, patients were switched to second-line ART based on clinical and immunological criteria according to WHO or National Guidelines [6,7].

Mbeya Regional Hospital is located in Mbeya city and serves more than 800,000 patients per year [23]. The Hospital's CTC offers comprehensive care and support to all people living with HIV/AIDS since October, 2004 and in total, 8877 adults have ever been enrolled in this hospital's CTC. Currently, only 2,869 PLHA are on ART [23].

Mbalizi Council Designated Hospital, a designated hospital for Mbeya District is located along Tanzania-Zambia highway and serves more than one million patients per year [24]. A total of 2,753 adults have ever been enrolled in HIV chronic care from April 2009-December 2015 and the current number of persons on ART is 1,230 [24].

Study Design

This was facility-based cross-sectional retrospective follow-up study. The records of HIV-infected clients (≥15years) who were initiated on first-line ART between 1st January 2010 and 30th June 2016 were reviewed. A standardized questionnaire was used to collect data on the socio-demographic and selected clinical factors related to immunological failure. Data was collected from CTC 2 patient's cards and CTC 2 electronic database.

Sampling Procedure and Data Collection

The two hospitals were selected by convenient sampling. Systematic random sampling of all accessible records of patients fulfilling the eligibility criteria was used to determine the required study sample after proportional allocation of the sample for both hospitals. A total of 1219 patients' records were from Mbeya regional referral hospital and 522 were from Mbalizi designated council hospital. Baseline CD4 count and hemoglobin level was taken as a measurement occurring within a window of 3 months prior to the start of ART to 1 week after ART initiation. CD4 cell counts within two months of follow-up month of interest were used to determine CD4 cell count response at that month. The assessment of adherence was limited to information obtained from CTC 2 card where adherence levels are reported as GOOD or POOR indicating fewer than 2 missed days per month and 2 or more missed days per month respectively.

Data Analysis

Data were entered using EpiData version 3.1 (EpiData Association, Odense, Denmark) and then exported to STATA version 12.0 (StataCorp LLC, College Station, Texas, United States of America) for analysis. Patients were considered to be at risk from their date of first visit at CTC to the date of their last visit, death or end of the study period. In analyzing prevalence of immunological failure, all those without date of outcome available were not included. The analysis was done comparing the association between immunological failure and various characteristics. With univariate analysis Odds Ratio (OR) of immunological failure with the 95% confidence interval (CI) were estimated. Variables found to be associated with immunological failure ($p < 0.2$) in the univariate analysis were included in multivariate analysis. In turn multivariable models were used to evaluate multiple factors applying forward logistic regression. The $p<0.05$ was considered significant.

Ethical consideration

Ethical approval to carry out this study was sought from Joint CUHAS-BMC Research and Ethics committee with research clearance certificate number CREC/135/2016. Confidentiality of the data was fully guaranteed by using only patients' unique CTC registration number and obtained data were only accessible to investigators.

RESULTS

Patients' records review

The cumulative number of HIV-infected patients enrolled for ART within the study period was 5,508 (3,118-Regional hospital and 2,390-Mbalizi hospital). A total of 2,565 (46.6%) HIV-infected patients' records were eligible for inclusion.

Among all patients recruited, 1,653 (64.4%) were females. The median age was 41 years (IQR 35-48) with majority (75.4%) being in the age group of 25 to 49 years. About 41.6% were married. Majority (45.4%) attended primary education and 51% were living in urban areas.

Clinical Information of HIV-infected patients

At ART initiation, the median CD4 cell count was 194 (IQR, 92 - 344) cells/mm^3 and 75.9% (1945/2565) had a baseline CD4 cell count below 350 cells/mm^3. Most of these patients were in WHO stage 3, 44.5% (1127/2565). About 94.3% (2420/2565) of patients were working in their functional status at a time of enrollment and the median hemoglobin was 12 [IQR 11-14] g/dl. Majority of patients, 94.6% (2427/2565) were still on follow-up at the time of the last observation. The most common first-line ART regime was Tenofovir-based, 58.8% (1508/2565). For this study cohort, 98.7% (2533/2565) had good adherence to medication refill while 40.7% (1520/2565) were ever diagnosed as having tuberculosis after starting antiretroviral therapy (Table 1).

Table 1: Clinical data of patients on ART (≥ 15yrs) treated in two ART centers in Mbeya, Tanzania followed from Jan, 2010-June, 2016 (n=2565).

Variables and Category	Frequency (*n*)	IQR/Percentage
Median CD4 count	194	92-344
Baseline CD4		
<350cells/mm^3	1945	75.9
≥350cells/mm^3	618	24.1
Baseline WHO stage		
I	711	28.1
II	515	20.3
III	1127	44.5
IV	212	7.1
Baseline functional status		
Ambulatory	88	3.6
Bedridden	54	2.1
Working	2420	94.3
Baseline weight		
<45kg	367	15.2
45 to <55kg	775	32.1
>55kg	1267	52.6
Median baseline Weight	55	49-63
Baseline hemoglobin		
(≥13g/dL	969	37.8
11-12.9g/dL	747	29.1
8-10.9g/dL	404	17.8
<8g/dL	445	17.4
Median baseline hemoglobin count	*12*	*11-14*
Time lag since HIV diagnosis and start of ART		
Same month	1973	76.9
1-24months	447	17.4
>24months	145	5.7
Last follow-up status		
Active	2427	94.6
Lost to follow	47	1.8
Dead	15	0.6
Transferred out	76	3.0
Time on 1st line ART		
<1year	88	3.4
1 to 3 year	1216	47.4
>3years	1261	49.2
Prior ARV exposure		
Yes	289	11.3
No	2276	88.1
1st line ART regimen		
Tenofovir-based	1508	58.8
Zidovudine-based	1019	39.7
Other 1st line	38	1.5
Adherence		
Good	2533	98.7
Poor	32	1.3
Diagnosis of incident tuberculosis		
No	1045	59.3
Yes	1520	40.7

Prevalence of Immunological Treatment Failure

Out of 2,565 patients, 1,237 (48.2%) developed immunological treatment failure (ITF). Majority of HIV infected patients with ITF were in WHO stage III, 48.1%. Among 1,237 patients with ITF, diagnosis by the criterion of drop to/or below baseline CD4 cell count accounted for majority 76.8% (950) of patients. Sixteen percent (198/1,237) were diagnosed with failure based on the criteria drop by 50% of follow-up CD4 cell count from peak value' while the criterion used for the diagnosis of immunologic failure for the remaining 89 (7.19 %) of cases was a follow-up CD4 cell count persistently below 100 CD4 cells/mm3 of blood. Of the 1,237 patients with confirmed immunologic failure, 89.4% (1,106) were switched to second-line ART but only 6.1% (75) were switched within the same month after failure confirmation (Table 2).

Table 2: Time between immunological treatment failure and switching to second ART regimen.

Duration (months)	Frequency	Percentage
<month	75	6.1
1-6 months	463	37.4
7-12 months	188	15.2
>12 months	380	30.7

Predictors of Immunological Treatment Failure

Socio-demographic Characteristics predicting Immunological Failure

The significant independent Socio-demographic predictors of immunological treatment failure were; increased age (OR = 1.01, 95% CI = 1.002 – 1.020, p = 0.012) and clients from Mbalizi-Council Designated Hospital ((OR = 1.2, 95% CI = 1.1 - 1.5, p = 0.008). (Table 3).

Table 3: Univariate and Multivariate analysis of socio-demographic predictors of immunological treatment failure (n = 2565).

Patients socio-demographic characteristic	Immunological failure		Univariate		Multivariate	
	Yes (%)	No (%)	OR[95%CI]	*p*-value	OR[95%CI]	*p*-value
Health facility						
MRRH*		844(53.4)	1.0	-	-	-
Mbalizi		484(49.2)	1.2[1.0-1.4]	0.039	1.2[1.1 – 1.5]	0.008
Gender						
Male		485(53.2)	1.1[0.9-1.3]	0.290	-	-

Female		843(51.0)	1.0	-	-	-
Age	41[36-49]	40[35-48]	1.01[1.0-1.02]	0.016	1.01 [1.0-1.02]	0.012
Residence						
Rural		673(53.5)	1.0	-	-	-
Urban		655(50.1)	1.2[0.9-1.3]	0.079	1.2[0.9-1.3]	0.072
Marital status						
Single		447(50.1)	1.0	-	-	
Divorced		151(51.0)	1.0[0.7-1.3]	0.788	1.0[0.7-1.2]	0.806
Widowed		158(51.1)	0.9[0.7-1.2]	0.757	1.0[0.8-1.3]	0.980
Married		572(53.6)	0.9[0.7-1.0]	0.128	0.9[0.7-1.0]	0.136
Education						
Never*		450(52.2)	1.0	-	-	-
Primary		618(46.9)	0.8[0.7-0.9]	0.029	1.0[0.8-1.15	0.703
Secondary+*		260(48.2)	1.5[1.2-1.8]	0.0001	1.2[1.0-1.5]	0.056
Occupation						
Unemployed		669(52.2)	1.0	-	-	-
Business		329(50.0)	1.1[0.9-1.3]	0.353	-	-
Employed		330(52.7)	0.9[0.8-1.2]	0.840	-	-
Religion -						
Christian		1146(62.4)	1.0	-	-	-
Moslems		103(20.6)	0.1[0.8-1.2]	0.972	-	-
Others		79(34.8)	0.8[0.6-1.2]	0.307	-	-

MRRH*=Mbeya Regional Referral Hospital

Never* = never attended school

Secondary+*= secondary education or post-secondary.

Clinical Characteristics Predicting Immunological Failure

The significant independent clinical predictors of immunological treatment failure were; baseline CD4 cell count of ≥350cell/µl (OR = 7.2, 95% CI = 5.7-9.2, $p < 0.001$), baseline hemoglobin count of < 8g/dL (OR = 1.4, 95% CI = 1.1-1.8, $p = 0.017$), time lag of 1-24 months since confirmed HIV diagnosis (OR = 1.4, 95% CI = 1.1 - 1.8, $p = 0.009$, time lag of > 24 months since confirmed HIV diagnosis (OR = 1.9, 95% 1.2 - 3.0, $p = 0.009$) and start of ART of more than 24 months (OR = 1.9, 95% CI = 1.2-3.0, $p = 0.006$) and Zidovudine (AZT) based regimen (OR = 1.3, 95% CI = 1.1-16, $p = 0.010$). (Table 4).

Table 4. Univariate and Multivariate analysis of clinical predictors of immunological treatment failure (*n*=2565).

Clinical characteristics	Immunological failure		Univariate		Multivariate	
	Yes	No	OR[95%CI]	*p*-value	OR[95%CI]	*p*-value
	n (%)	*n* (%)				
Baseline CD4						
<350cell/µl,	747(38.4)	1198(61.6)	1.0	-	-	-
≥350 cell/µl	489(79.1)	129(20.9)	6.1[5.0-7.5]	<0.001	7.2[5.7-9.2	<0.001
WHO stage*						
I	378(53.2)	333(46.1)	1.0	-	-	-
II	260(50.5)	255(49.5)	0.9[0.7-1.1]	0.354	0.9[0.7-1.2]	0.522
III	511(45.3)	616(54.7)	0.7[0.4-0.8]	0.001	0.7[0.6-0.9]	0.007
IV	73(40.6)	107(59.4)	0.6[0.4-0.8]	0.003	0.6[0.4-0.9]	0.020

Functionality*						
Working	1163(48.1)	1257(51.9)	1.0	-	-	-
Ambulatory	40(45.5)	48(54.5	0.9[0.6-1.4]	0.631	1.0[0.6-1.7]	0.983
Bedridden	34(59.6)	23(40.4)	1.6[0.9-2.7]	0.086	1.1[0.6-2.1]	0.763
Baseline weight						
<45kg	189(51.5)	178(48.5)	1.0	-	-	-
45 to <55kg	356(45.9)	419(54.1)	0.8[0.6-1.0]	0.079	0.7[0.5-0.9]	0.004
>55kg	616(48.6)	651(51.4)	0.9[0.7-1.1	0.331	0.7[0.5-0.9]	0.008
Baseline Hb*						
≥13g/dL	449(46.3)	520(53.7)	1.0	-	-	-
11-12.9g/dL	357(47.8)	390(52.2)	1.1[0.9-1.3]	0.549	1.1[0.9-1.4	0.274
8-10.9g/dL	195(48.3)	209(51.7)	1.1[0.9-1.4]	0.514	1.2[0.9-1.6	0.170
<8g/dL	236(53.0)	209(47.0)	1.3[1.0-1.6]	0.019	1.4[1.1-1.8]	0.017
Time lag*						
Same month	927(47.0)	1046(53.0)	1.0	-	-	-
1-24months	220(49.2)	227(50.8)	1.1[0.9-1.3]	0.393	1.4[1.1-1.8]	0.009
>24months	90(62.1)	55(37.9)	1.8[1.3-2.6]	0.001	1.9[1.2-3.0]	0.006
LFS*						
Active	1185(48.8)	1242(51.2)	1.0	-	-	-
Lost to follow	18(38.3)	29(61.7)	0.7[0.4-3.3	0.156	0.6[0,3-1.1]	0.074
Dead	85(53.3)	7(46.7)	1.2[0.4-3.3]	0.728	1.1[0.6-2.0	0.839
Transferred out	26(34.2)	50(65.8)	0.5[0.3-0.9]	0.013	1.6[0.5-4.8]	0.411
Time on ART						
<1year	40(45.5)	48(54.5)	1.0	-	-	-
1 to 3 year	491(40.4)	725(59.6)	0.8[0.5-1.3]	0.350	0.6[0.3-0.9	0.023
>3years	706(56.0)	555(44.0)	1.5[1.0-2.4]	0.056	1.4[0.8-2,2]	0.213
ARV exposure						
No	154(53.3)	135(46.7)	1.0	-	-	-
Yes	1083(47.6)	1193(52.4)	0.8[0.6-1.0]	0.068	1.3[0.9-1.8]	0.138
ART regimen						
TDF*-based	738(48.9)	770(51.1)	1.0	-	-	-
AZT*-based	489(48.0)	530(52.0)	0.9[0.8-1.1]	0.639	1.3[1.1-1.6]	0.010
Other	10(26.3)	28(73.7)	0.4[0.2-0.8]	0.008	0.6[0.3-1.4]	0.227
Adherence						
Good	1221(48.2)	1312(51.8)	1.0		-	-
Poor	16(50.0)	16(50.0)	1.1[0.5-2.2]	0.840	-	-
Dx incident TB*						
No	741(48.8)	779(51.3)	1.0	-	-	-
Yes	496(47.5)	549(52.5)	0.9[0.8-1.1]	0.522	-	-

TDF** =*Tenofovir, *AZT*=*** Zidovudine***, Dx incident TB**=*diagnosis of incident Pulmonary Tuberculosis***, *LFS*=***last follow-up status***, Time lag*=*** duration since confirmed HIV+ and start of ART***, Hb*=***hemoglobin***, WHO stage** =*baseline WHO clinical stage***, *Functionality** =*baseline functional status

DISCUSSION

Prevalence of immunological treatment failure

In this study the prevalence of immunological treatment failure was high (48.2%). Majority 92.8% failed based on decrease in CD4 cell count to/or below the baseline before treatment. Studies at global level as well as in Sub-Saharan Africa demonstrated a variation on prevalence of ITF in the range of 10-32% regardless of the follow-up duration [11,14,16,25]. The high prevalence of immunological treatment failure as ours was also noted in Malawian study (48.0%). However, they used a criterion of a CD4 drop of 30% from the peak value to diagnose the failure [16]. In Tanzania, reported prevalence of ITF ranged from 7% to 57% [15-17]. At Bugando Medical Centre, Jaka *et al* reported the prevalence of 17.1% among 362 patients followed for a mean duration of 29 months [16]. The observed lower rate than ours is probably explained by the reason that in Bugando study, the confirmatory CD4 count was

incorporated to confirm immunological response recorded previously [16]. The same phenomenon also occurred in Nigerian study which used the same WHO criteria for immunological treatment failure but without a confirmatory CD4 count. The cumulative probability of immunological treatment failure was approximately 35% by 3 years [26], a figure closer to our estimation of 48.2%. When a confirmatory CD4 count was incorporated in the Nigerian study, the overall proportion of HIV-infected patients experiencing ITF reduced from 35% to 10% [26]. Mpondo *et al* reported a prevalence of 57% among 274 patients, followed for median duration of 26 months [17]. Comparably, lower rate in current findings is probably attributed by low median baseline CD4 count in Mpondo *et al* study (139.5 vs. 194cells/mm^3). This study also demonstrated that the majority of the failed patients were switched to second-line ART regimen. This is contrary to what has been revealed by Yirdaw *et al* in Ethiopia whereby only 7.5% were switched to second-line regimen [27]. The probable reasons for this observation could be providers' failure to identify treatment failure, lack of knowledge, or confidence to act or lack of adequate second line drugs [7, 27].

Most patients were switched within one and six months after the diagnosis of immunological failure and only 6.1% were switched almost immediately after the diagnosis of treatment failure. Delay in switching was also observed by Jaka *et al* whereby there was delay of initiation of second-line with mean delay of 5 weeks [16]. Delayed switching increases the risk of drug resistance, and subsequent higher viral load leading to a reduced drug of choice for second-line therapy hence impairing clinical outcomes [6, 15, 27].

Predictors of Immunological Treatment Failure

Predictors of immunological treatment failure vary and may relate to multiple factors as it was demonstrated in this study. The current study has demonstrated that increased age in years has a significant influence on likelihood of development of ITF. This is consistent with findings by Teshome *et al* in 2014 who also demonstrated that HIV-infected subjects with older age groups are more likely to have failure of therapy than younger age groups [28]. This effect of age on immune recovery is due to thymic involution related to old age and other regenerative mechanisms that could impair immune recovery [29,30]. However, findings from other studies in Sub-Saharan Africa [31, 32] found that younger age < 30 years was significantly associated with 50% increased odds of immunological failure. This was attributed to being single, engagement in high risk behaviors, lack of social capital and financial ability associated with younger age [31].

This study also demonstrated that patients attending District Council had a higher probability of developing ITF than those from the regional referral hospital. This finding can be explained by the fact that, these are two facilities with different level of experts. Moreover, at the regional level, CTC's health care personnel are many compared to a district hospital. Thus frequent and close monitoring and follow-up is expected to occur at the regional hospital than a district hospital.

One of the variables which also predicted immunological failure was AZT-based regimen, although over half of the patients were on TDF-containing first-line. The reasons behind the higher immunological treatment failure risk with AZT-based regimen, compared to TDF-based and other regimens were unclear as it was demonstrated in another Tanzanian study [15]. In Nigerian study, despite known superiority, convenient dosing, low toxicity and high potency of TDF, there were no statistically significant differences in virologic suppression by baseline drug regimen among the study cohort [31]. These encouraging results confirm that most of HIV-infected patients on ART experienced biological and clinical benefit. Thus, the current treatment regime is working properly, and contributes on improving the quality of life for people living with HIV [18, 28].

As previously found in the EuroSIDA survey [33], baseline CD4 counts (≥ 350v/s <350cells/mm^3) predicted immunological failure in the current study. This is also consistent with the findings from Mozambique [34]. One reason for this finding could lie in a lower clinician threshold for the modification of therapy in these patients, as they do believe that individuals with higher baseline CD4 are at lower risk of opportunistic infections. Additionally, it can also be hypothesized that patients with higher baseline CD4 count may be more likely to develop HIV treatment failure due to lower stigmatization as they consider themselves stable. Thus may not see the reason of paying attention to their falling CD4 cells count [33]. In the South African study [11], level of baseline CD4 cell count was not found to be associated with immunological treatment failure, probably attributed to low sample size in that study (n = 456). Our findings contrast sharply with those in Bugando Medical Centre where baseline CD4 count of less than 100cells/mm^3 was significantly associated with treatment failure [16]. This was also shown in other studies in Zimbabwe, Burkina Faso and Ethiopia [10, 30, 32]. The reason behind this is the fact that, if HIV-infected person is initiated on ART when CD4 is low, viral load may not be successfully suppressed leading to HIV treatment failure [10].

Study results demonstrated that low hemoglobin (<8g/dL) was a significant predictor of immunological treatment failure. Anude *et al* has shown a 71% increased odds of treatment failure with anemia (baseline median hemoglobin level was 10.9 [IQR: 9.3-12.4] g/dl, cut-off point was <10g/dl) at baseline

[31]. In Tanzanian study, Gunda *et al* reported that patients with moderate to severe anemia suffer a rapid HIV disease progression and high mortality than normal counterparts [35]. It is uncertain whether the association between anemia and immunological treatment failure is causal or whether anemia is rather a marker of progressive HIV disease. Nigerian study has narrated that malaria and chronic helminthiasis are two most common causes of anemia in adults that respond to potent chemo-therapeutic interventions [31]. Thus identifying and managing adults with anemia at baseline when ART is being initiated as well as providing anti-helminthes can improve anemia and possibly clinical outcome.

In this study, longer duration from HIV infection confirmation to ART initiation (>24 months' time lag since HIV diagnosis and start of ART) was the significant predictor of immunological failure. Evidence indicates that HIV drug resistance occurs more frequently in individuals who initiate therapy later in the course of HIV infection than those who initiate ART earlier. Fundamental to early initiation of ART is the assumption that patients will be diagnosed early in the course of HIV infection. A randomized controlled trial conducted in Haiti showed that patients who started ART with CD4 counts between 200 and 350 cells/mm^3 survived longer than those who deferred ART until their CD4 counts fell below 200 cells/mm^3 [36]. Another study carried out in Soweto, South Africa revealed that patients starting ART with advanced immunosuppression and very low CD4 cell counts (<100 cells/mm^3) maintained a significantly lower CD4 cell count level throughout the study period [11]. This put them at risk of increased morbidity for a number of years post-ART initiation and provides further justification to initiate ART earlier [11]. Thus early initiation of ART is important for desirable health outcome in terms of reducing risk of death, disease progression including tuberculosis and other opportunistic infections [5].

The findings of this study have limitations in the fact that immunological criteria alone may not assure the presence of treatment failure. El-Khatib *et al* has demonstrated that nearly two thirds of patients failing immunologically were virologically suppressed at clinical assessment [11]. Thus for this reason, CD4 cell count is a poor predictor of virologic outcomes [26] and the use of immunological criteria only for monitoring treatment responses may jeopardize clinical management. Also the fact that confirmatory CD4 cell counting was not done that could lead to overestimation of immunological treatment failure.

CONCLUSIONS

Prevalence of immunological treatment failure was high (48.2%) among HIV-infected patients attending CTCs in two hospitals in Mbeya region. Increased age, being patient from District hospital, baseline CD4 cell values of ≥350cells/µl, severe anemia (hemoglobin count <8g/dL), longer duration from HIV infection diagnosis to ART initiation and AZT-based regimen were the significant predictors of immunological failure. Health care providers should be guided to focus on predictors of immunological failure so that they can identify and early switch to second line ART can be done among those who are failing on first line ART.

REFERENCES

1. (2015). WHO. HIV/AIDS Fact sheet N°360.
2. (2014). The United Republic ofTanzania. Global Aids Response Country Progress Report.
3. Mills EJ, Bakanda C, Birungi J, Chan K, et al. (2011). Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: A cohort analysis from Uganda. Ann Intern Med. 155(4): 209-16.
4. (2013). UNAIDS report on the global AIDS epidemic.
5. (2015). The United Republic of Tanzania National Guidelines for Management of HIV and AIDS (fifth edition).
6. (2013). World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.
7. (2010). World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach.
8. (2009). Tanzania National Aids Control Program. National Guidelines for the Management of HIV and AIDS (third edition).
9. (2015). Bayou B, Sisay A and Kumie A. Assessment of the magnitude and associated factors of immunological failure among adult and adolescent HIV-infected patients in St. Luke and Tulubolo Hospital, Oromia Region, Ethiopia. 21: 291-10.
10. Bangure D, Mungati M and Chemhuru M. (2015). Factors Associated with Human Immunodeficiency Virus First Line Treatment Failure in Zvishavane District ,. Austin J HIV/AIDS Res Open. 2(1):1-6.
11. El-Khatib Z, Katzenstein D, Marrone G, Laher F, et al. (2011). Adherence to drug-refill is a useful early warning indicator of virologic and immunologic failure among HIV patients on first-line art in South Africa. PLoS One. 6(3).
12. Gupta RK, Jordan MR, Sultan BJ, Hill A, et al. (2012). Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: A global collaborative study and meta-regression analysis. 380(9849):1250-58.
13. Kumarasamy N, Vallabhaneni S, Cecelia AJ, Yepthomi T, et

al. (2006). Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. J Acquir Immune Defic Syndr. 41(1): 53-58.

14. Reynolds SJ, Nakigozi G, Newell K, Ndyanabo A, et al. (2009). Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda. AIDS [Internet]. 23(6): 697-700.
15. Vanobberghen FM, Kilama B, Wringe A, Ramadhani A, et al. (2015). Immunological failure of first-line and switch to second-line antiretroviral therapy among HIV-infected persons in Tanzania: Analysis of routinely collected national data. Trop Med Int Heal. 20(7): 880-92.
16. Jaka, HM, Mshana SE, Liwa AC, Peck R, et al. (2009). Prevalence of immunological failure and durability of first line antiretroviral therapy at Bugando Hospital Mwanza, Tanzania. Tanzania Medical Journal 24(2): 5-8.
17. Mpondo BCT, Kilonzo SB, Meda JR and Gunda DW. (2015). Prevalence and predictors of Immunological failure among HIV-infected adults on HAART in Northwestern Tanzania: A cross sectional study. Tanzania Med J. 27(1): 55-69.
18. (2013). Mtesigwa B. Response To Antiretroviral Therapy in Hiv- Infected Patients Attending Care and Treatment Centre in Dar-Es-Salaam , Tanzania. A Dissertation Submited in Partial Fulfilment of the Requirements Forthe Degree of Master of Science in One. Health Molecular Biology Of Sokoine University Of Agriculture. Morogoro, Tanzania (unpublished).
19. Kwobah CM, Mwangi AW, Koech JK, Simiyu GN, et al. (2012) Factors Associated with First-Line Antiretroviral Therapy Failure amongst HIV-Infected African Patients: A Case-Control Study. World J AIDS. 2(4): 271-8.
20. Kapesa A, Magesa D, William A, Kaswija J, et al. (2014). Determinants of immunological failure among clients on the first line treatment with highly active antiretroviral drugs in Dar es Salaam, Tanzania. Asian Pac J Trop Biomed. 4Supplem(Suppl 2): S620-4.
21. Fox MP, Cutsem GV, Giddy J, Maskew M, et al. (2012). Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. J Acquir Immune Defic Syndr. 60(4): 428-37.
22. (2011-12). Tanzania HIV/AIDS and Malaria Indicator Survey.
23. (2015). Mbeya Regional Referal Hospital. HIMS report.
24. (2015). Council Designated District Hospital. HIMS report.
25. Geretti AM. (2007). Epidemiology of antiretroviral drug resistance in drug-naive persons. Curr Opin Infect Dis. 20(1): 22-32.
26. Rawizza HE, Chaplin B, Meloni ST, Eisen G, et al. (2011). Immunologic criteria are poor predictors of virologic outcome: Implications for HIV treatment monitoring in resource-limited settings. Clin Infect Dis. 53(12): 1283-90.
27. Yirdaw KD, Hattingh S. (2015). Prevalence and predictors of Immunological Failure among Patients on HAART in Southern Ethiopia. Plos One. 10(5).
28. Teshome W and Assefa A. (2014). Predictors of immunological failure of antiretroviral therapy among HIV infected patients in ethiopia: A matched case-control study. PLoS One. 10(5).
29. Zoungrana J, Poda A, Sondo K, Diallo I, et al. (2016). Prevalence and Factors Associated with Treatment Failure during Antiretroviral Therapy Atbobo-Dioulasso University Teaching Hospital (Burkina Faso). Austin Journal of HIV/AIDS Research. 3(2): 2-6.
30. Teixeira L, Valdez H, McCune JM, Koup RA, et al. (2001). Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. AIDS. 15(14): 1749-56.
31. Anude CJ, Eze E, Onyegbutulem HC, Charurat M, et al. (2013). Immuno-virologic outcomes and immuno- virologic discordance among adults alive and on anti-retroviral therapy at 12 months in Nigeria. BMC Infectious Diseases. 13: 113.
32. Marimoutou C, Chêne G, Mercié P, Neau D, et al. (2001). Prognostic factors of combined viral load and CD4+ cell count responses under triple antiretroviral therapy, Aquitaine cohort, 1996-1998. J Acquir Immune Defic Syndr. 27(2): 161-7.
33. Dragsted UB, Mocroft A, Vella S, Viard J, et al. (2004). Predictors of Immunological Failure after Initial Response to Highly Active Antiretroviral Therapy in HIV-1 – Infected Adults : A EuroSIDA Study. J Infect Dis. 190(1): 148-55.
34. Palladino C, Briz V, Bellon JM, Bertolo I, et al. (2013). Predictors of attrition and Immunological failure in HIV-1 patients on highly active antiretroviral therapy from different healthcare settings in Mozambique. PLos One. 8(12).
35. Gunda DW, Kilonzo SB and Mpondo BC. (2016). Magnitude and correlates of moderate to severe anemia among adult HIV patients receiving first line HAART in Northwestern Tanzania: a cross sectional clinic based study. Pan Afr Med J. 23(26): 1-8.
36. Severe P, Antoine M, Juste J, Ambroise A, et al. (2010).Early versus Standard Antiretroviral Therapy for HIV-infected Adults in Haiti. New Engl J of Med. 363(3): 257-65.
37. Keiser O, Tweya H, Braitstein P, Dabis F, et al. (2010). Mortality after failure of antiretroviral therapy in sub-Saharan Africa. Tropical Medicine and International Health. 15(2): 251-258.