Prevalence of immunological failure and durability of first line antiretroviral therapy at Bugando Hospital Mwanza, Tanzania

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Abstract

Background: Highly active antiretroviral therapy (HAART) for the treatment of HIV infection has led to profound reductions in the incidence of mortality due to AIDS-related causes in recent years. Immunological status is common parameter used to monitor HIV treatment success in developing countries. This a crossectional retrospective follow up study was conducted to determine the prevalence of immunological treatment failure and risk factors associated to it among patients on ARV therapy at Bugando Medical Centre.

Method: A crossectional Retrospective study was conducted among all patients on ART from 2005 attending BMC CTC clinic. Using standard data collection form all demographic data, adherence levels, and CD4 + counts were recorded and analyzed using SPSS 11.5 computer software to determine the prevalence and predictors of immunological failure.

Results: A total of 2975 patients were on ART during the study period, in the analysis 362 patients were included and followed backwards for mean duration of 29 months. The base line CD4 of more than 100cells/µl was found in 43.6% of patients studied. A steady CD4 increase in the first 7 months, followed by slow increase in subsequent months was noted. The prevalence of immunological treatment failure was 17.1% (95% CI 17.1%±3.9). Adherence below 95% was strongly associated with immunological treatment failure (p=0.00001). There was significant association between baseline CD4 of more than 100cell/ µl and immunological treatment failure (p=0.001). No significant difference was found between Home based care (HBCP) and immunological treatment failure (p=0.06). The average time to treatment failure for the first line regimen was 20 months, with 59% of failed patients having a lag time of 5 weeks before appropriate changes in their ART regimen were done.

Conclusions and recommendation: Immunological failure was significantly associated with adherence below 95% and low baseline CD4 count of less than 100cells/µl. The multi-disciplinary HIV treatment and care should reinforce adherence during each patient encounter. Strategies to maximise adherence will help to ensure treatment success. We also recommend early HIV testing and referral to care before severe immnosuppression develops. A switch to second line ARV regimen should be considered after a period of adherence intensification.

Key words: Immunological failure, CD4, Prevalence, HAART, HIV

Background

HIV/AIDS is a global problem with more cases in developing countries, in 2004 it was estimated that about 40-million people were living with HIV /AIDS worldwide[(1)]. By the end 2007 worldwide about 33.2 million people were estimated to be living with HIV and 2.5 million people became newly infected and 2.1 people died of AIDS[(1)] In Tanzania the number of people living with HIV is estimated to be 1,400,000 and the general prevalence in adults' population aged 15-49 years is about 6.5% with estimated 140,000 deaths annually.[(1)] At Bugando Medical Centre the CTC started in October 2004, currently there are 7328 patients registered in the centre and about 2975 patients on HAART. Despite the significant progress that has been made in HIV care since the advent of HAART, therapies continue to fail in a large number of cases generally because of resistance which is primarily driven by sub-optimal adherence. The HIV treatment can be monitored using clinical, immunological and virological criteria.[(1)] In developing countries including Tanzania, treatment response is mainly monitored on clinical and immunological grounds. The clinical failure is defined as a new or recurrent WHO stage IV conditions; the occurrence of new opportunistic infections while on ART is the surrogate markers of treatment failure.[(2,3,4)] Immunological failure is when the fall of CD4 count to pre therapy or baseline/fall by 50 % from peak value during treatment or persistent CD4 levels below 100cells/µl[(1)]. The CD4 count increases very fast in the first 3 months, then at slower rate in the following 3 months and later it becomes flat by 10-12th month, this increase doesn't relate to age, sex or the regimen used.[(5)] An average increase of CD4 of 27 cells/µl per month has been reported; the expected immunological response to treatment is rising of CD4 by more than 50cells/µl after 6 months of treatment there after the increase is 5.5 CD4 cell/µl per month and more than 100/ul per year.[(6, 7, 8)]. Globally, the prevalence of treatment failure occurs in 30% of the patients on HAART [9]. However, this prevalence varies between continents, with a study in North America reporting a prevalence of 12%[(10)], while a study in Uganda reported the prevalence of immunological failure of 38%.[(11)] HIV/AIDS patients in Tanzania and other countries in Sub-Saharan Africa are at higher risk to develop treatment failure due to poor adherence, which constitutes a serious challenge to those receiving ART.[(12, 13)] The adherence of more than 95% is associated with viral load suppression of 81%, however 90-95% adherence will be associated with viral suppression of 64%, the 80-90% adherence will be associated with suppression of 25% and adherence of less than 70 will suppress only 6%.[(14)] To be successful, ARV medications must be taken at least 95 % of the time.[(15)]

Other factors which have been found to be associated with treatment failure include; viral resistance**,** low baseline CD4 less than 100cell/µl, a higher baseline viral load**,** and patients age more than 40yr.[(16-19)] The non linkage to home based care and lack of disclosure of HIV status to family members have also been associated with poor adherence hence treatment failure.[(20,21)]

Information on the magnitude of treatment failure is lacking in many centres in Tanzania and Africa in general. Therefore this study was done to determine the prevalence and risk factors for immunological treatment failure and recommend interventions to minimize these risks. It also tried to estimate the average regimen durability.

Methods

Study design

A crossectional retrospective follow up study of patients who are receiving HAART from January 2005 to June 2008 was conducted. The study was conducted at Bugando Medical Centre Care and Treatment Clinic (CTC). The Centre has registered a total of 7328 HIV

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patients, of which 2975 patients are on ARVs since 2005 and about 256 new patients are seen monthly, (http://www.bugandomedicalcentre.go.tz). In the analysis using Kish and Lisle formula only 362 patients were included with mean duration follow up of 29 months

Table 1: Baseline demographic and Clinical Characteristics of study population

Vaiagbles	N (%)
Gender	
Male	239 (66%)
Sex	123 (44%)
Age	
Mean	39
Median	40
Interquartire range	(33- 47)
Marital Status	
Married	141(39%)
Single	89(24.6%)
Divorced	42(11.6%)
Widow	90 (24.9%)
Education	
No formal education	36 (9.9%)
Primary	246(67.1%)
Secondary	60 (16.6%)
College	23 (6.4%)
Occupation	
Peasant	130 (36%)
Civil Servant	41 (11%)
Self employment	130 (36%)
Private sector	40 (10.9%)
Student	21 (6.1%)
Home based care	
Yes	294 (81.2%)
No	68 (18.8%)
Disclosure of HIV Status	
Yes	305 (84.3%)
No	57 (15.7%)
Baseline CD4	
Mean	121cells/µl
<100cells/ul	158(43.6%)
>100cells/ul	204(56.4)
Adherence	
>95%	332 (91.7%)
90%-95%	22 (6.1%)
90%-80%	6 (1.7%)
<80%	2 (0.6%)
Previous Drug Regimen	
T30	285 (78.7%)
Combivir/Efavirenz	48 (13.2%)
Combivir/Nevirapine	24 (6.6%)
D4T/3TC/Efavirenz	4 (1.1%)

Inclusion Criteria

All HIV patients who were receiving HAART for at least 12 months, aged more than 11 years, willing to participate in the study and be able to give an informed consent were recruited serially until the sample size was reached. All patients with less than four CD4 count records and incomplete information were excluded.

Data Collection

All information from eligible patients was collected using standard data collection form which included: age, sex, residence, marital status, educational levels and occupation. Other variables like home based care affiliation, social support, disclosure of HIV status, the baseline CD4 count and trend after HAART initiation, previous drug regimens, opportunistic infections and level of adherence, were collected from patients' files/records using routine laboratory results, hospital data base, hospital clinic forms etc. Using adherence forms, adherence was recorded for all previous visits and a visit during recruitment of patients. Individuals were classified based on defined adherence levels of more than 95 %(good) and less than 95% (poor), those who had <95% were further grouped 90-95%, 80-90, less than 70% [14], this was done depending on the missed doses of ARV. Blood sample was collected using EDTA Vacuum bottle (BD) for all 362 participants for CD4 count to confirm immunological response recorded previously. CD4 counts were determined using FACS (Becton and Dickson). The last reading was compared with previous three readings which were taken 4-6 months apart. Data were cleaned and analyzed using the SPSS 11.5 data analysis software. The categorical factors associated with immunological failure were analysed using Chi square, a p-value of 0.05 or less was considered statistically significant. Multivariate analysis was done on factors which were found on univariate analysis to be associated with immunological failure using the logistic regression method. This study was approved by WBUCHS/BMC ethics and research board and all ethical issues were observed.

Results

The study population was made up of 362 adult patients on HAART of whom 239 (66%) were female and 123 (34%) were male. About 39.2% of study population aged 31-40 years with mean of 39 years and (IQR 33- 47) table1. Most 218(87.8%) of patients started ARVs when CD4 count was below 200 cells/µl, the mean baseline CD4 cell count was 121 cells/µl. Baseline CD4 count less than 100cells/µl was significantly associated with immunological failure(p=0.004). Sharp increase in mean CD4+ count in the first 6 months followed by a plateau in subsequent months was observed

The prevalence of treatment failure was 62/362 (17.1%) with mean duration follow up of 29 months. Among failed patients the mean durability of first line regimen before failure was 20 months with (IQR 15-27). Twenty five (41%) of failed patients were initiated second line treatment immediately after the diagnosis of failure. There was delay of initiation of second line with mean delay of 5 weeks and (IQR0-8). In this study 48% of patients with immunological failure had WHO stage one.

A total of 294(81.2%) patients were linked to HBC (Home based care). Among patients linked to HBC 52 (17.7%) were classified as immunological failure compared to 10/68 (14.7%) of patients who were not linked to HBC (p=0.953). A total of 305(84.3%) of the study population had their HIV status known to the family members. Among patients with known HIV status to family members, 15.7% had immunological failure compared to 24.6% of those with unknown HIV status, (p=0.091). In this study a total of 332(91%) had good adherence of more than 95% among these (47)14.1% had immunological failure compared to 45.5% of the study population with adherence below 95% (p=0.00001). Among patients with CD4 ≤100 cells/ml 35/158 (22%) had treatment failure compared to only 26/204(12.7%) of CD4 cells≥ 100cells/ml (p=0.04).

Table 2: logistic regression analysis for risk factors for immunological treatment failure

Factor	Level	Prevalence of Treatment failure n/N (%)	Crude OR (95% CI) univariate	Adjusted OR (95% CI) multivariate
Gender	Female	24/123 (19.5)	1(P=0.39)	1 (P=0.58)
	Male	38/239 (15.9)	0.78 (0.44-1.37)	0.84 (0.45-1.56)
Age	≤ 24	1/28 (3.6)	1 (P=0.19)	1 (P=0.07)
	25-34	18/85 (21.2)	7.3 (0.92-57.05)	11.0 (1.27-94.80)
	35-44	22/132 (16.7)	5.4 (0.70-41.85)	7.65 (0.91-63.94)
	45-54	15/87 (17.2)	5.6 (0.71-44.66)	10.06 (1.16-87.37)
	≥55	6/30 (20.0)	6.8 (0.76-60.14)	9.54 (0.98-92.55)
Marital Status	Never married	8/89 (9.0)	1 (P=0.099)	
	Married	27/141 (19.2)	2.4 (1.04-5.55)	
	Divorced	9/42 (21.4)	2.8 (0.98-7.77)	-
	Widow	18/90 (20.0)	2.5 (1.04-6.17)	
Education	No formal education	3/36 (8.3)	1 (P=0.189)	
	Primary	40/243 (16.5)	2.17 (0.63-7.41)	
	Secondary	15/60 (25.0)	3.67 (0.98-13.70)	-
	College	4/23 (17.4)	2.32 (0.47-11.47)	
Occupation	Peasant	25/130 (19.2)	1 (P=0.37)	
	Civil Servant	9/41 (22.0)	1.2 (0.50-2.79)	
	Self employment	21/130 (16.2)	0.8 (0.43-1.53)	
	Private sector	6/40 (15.0)	0.7 (0.28-1.96)	
	Student	1/21 (4.8)	0.2 (0.03-1.64)	-
Home based care	No	10/68 (14.7)	1 (P=0.55)	
	Yes	52/294 (17.7)	1.25 (0.60-2.60)	-
Disclosure of HIV Status	No	14/57 (24.6)	1 (P=0.11)	
	Yes	48/305 (15.7)	0.56 (0.28-1.10)	-
Baseline CD4	< 100 cells/µl	36/158 (22)	1 (P=0.04)	
	≥ 100 cells/ µl	26/204 (12,7)	0.51 (0.19-0.34)	(P< 0.04)
Adherence	≤95%	15/30 (50.0)	1 (P<0.001)	(P<0.001)
	>95%	47/332 (14.2)	0.16 (0.08-0.36)	
Previous Drug Regimen	Other combination T30	18/76 (23.7)	1 (P=0.098)	
		44/286 (15.4)	0.59 (0.32-1.09)	

Discussion

In this article, we present the first data on immunological failure and its associated risk factors at the CTC clinic at Bugando Medical Centre Mwanza, Tanzania. A total of 362 patients on HAART for more than 12 months with regular CD4 records were analyzed. A female preponderance, age distribution and drug regimen in this study are similar to other studies from Sub-Saharan Africa.[11, 22] The mean baseline CD4 is this studies was 121cells/µl, this signifies late presentation of patients; this confirms observations from other African studies with baseline CD4 counts between 100-200cells/µl [5, 23].

As defined earlier an immunological response was taken to be increased CD4 count of more than 50 cells/µl raised after 6months of HAART. The prevalence of immunological failure in the present study was 17.1% at a median duration of 20 months, despite an initial good immunological response. CD4 trends in this study showed a sharp increase in the first six months followed by a plateau in subsequent months, similar findings were observed in other studies.[5,6] Our observed immunological failure rate is higher than that of 11.1% reported after 12months of HAART among people living with HIV in 70 centers in 27 countries across Europe, Israel and Argentina by Ulrich et al.[23] In Ulrich's survey, only one immunological failure criteria of CD4 reversion to pre-HAART level was used, this and a short duration of follow up could explain the discrepancy between his study and our findings. Using one criterion alone the immunological treatment failure in our study would have been 8.3% almost similar to Ulrich's study. A study from India in a similar tertiary care setting but a large sample of 1370 people living with HIV noted an immunological failure prevalence rate of 26.1%.[24] In Malawi they observed a very high immunological failure rate of 48%[25]; however in their study the used immunological failure criterion of a CD4 drop of 30% from the peak value was used. This could partly explain their higher immunological failure rate.[25] When compared to a study in Uganda which reported a rate of 38%, our rate is low, and this could be explained by the fact that patients in their study had a very low mean baseline CD4 count of 104cells/µl in their study compared to 121cells/ µl in our study [1, 8,17, 18,].

The prevalence of immunological failure in our study could be underestimated because this study was a retrospective and hence was prone to miss patients with immunological failure who were lost to follow up or died. On the other hand it could be overestimated because no virological tests were done to confirm immunological failure. It is possible as it has been observed in Uganda, that some of the patients who were diagnosed to have immunological failure were misclassified [11].

Our study established that poor adherence less than 95%, low baseline CD4 counts of less than 100 were significant risk factors for developing immunological failure. This has also been reported by other studies.[17, 18, 14]. Our findings contrast sharply with that in San Francisco in 1999-2000 where adherence was not protective against treatment failure.[1] Noteworthy, is the fact that in the Francisco study, the predominant regimen was that which consisted of protease inhibitors and nucleoside reverse transcriptase inhibitors. There is evidence that for boosted protease inhibitor based regimens, it is not necessary to have adherence of more than 95% for optional results[1].No significant association between linkage to HBC, disclosure of HIV status, and drug regimen with immunological treatment failure. This contrasts to previous studies, which reported an increased immunological failure rate among patients with no HBC linkage and lack of disclosure of HIV status.[17, 18]

The average regimen durability in this study was 20 months; that is the average time from initiation of ART first line to time of diagnosis of treatment failure. This is very close to the study by Ray et al, whereby the average regimen durability was 18 months.[25] Five weeks delay to initiate second line regimen was observed; a five weeks delay may not be long enough to allow significant accumulation of mutations associated with drugs with a high genetic barrier, however there are concerns for nevirapine with a very low genetic barrier.[1]

Several clinical implications can be derived from this study: First the late presentations of most of our patients portend a poor response to HAART in terms of morbidity and mortality. Thus deliberate efforts should be made to promote early access to HIV care and treatment before severe immunosuppression occurs. In the health care setting, this can be done through routine provider initiated HIV testing and counselling (PITC) for all health care seekers. At the HIV Care and Treatment Clinic, multi-disciplinary strategies which maximise adherence should

be promoted to ensure durable suppression of viral replication. Secondly, a first ART regimen durability of less than two years is worrisome in resource-constrained setting with a limited formulary. Early entry into HIV care and adherence support should be part of a comprehensive strategy to keep patients on a first line regimen as long as possible. Thirdly, efforts should be made to regularly monitor ART response using CD4 count testing according to national guidelines. This will help to avoid putting patients on a failed regimen for a prolonged period, as this would severely limit future treatment options as a result of accumulated resistant mutations.

Conclusions

Prevalence of immunological failure is relatively high in our CTC clinic and low level of adherence below 95% and low baseline CD4 are strongly associated with immunological treatment failure. Most of the patients had late diagnosis of immunological failure of about 5weeks and the average durability of first line HAART regimen was about 20 months.

Recommendations

In order to reduce the prevalence of immunological treatment failure there is a need to promote early HIV testing by strengthen PITC(provider initiated testing and counselling) for health care seekers, before the development of severe immuno-suppression and to employ multi-disciplinary strategies which maximise adherence, to ensure treatment success. A large multi-centred study to determine the incidence and associated factors of immunological failure, virological failure and a possible resistance pattern is recommended. There is also a need for studies to evaluate the WHO recommended immunological failure criteria using viral load criteria as a gold standard. This should be done by determining the sensitivity and specificity of immunological criteria in detecting the regimen failure.

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