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Determinants of first line antiretroviral immunologic treatment failure among adult HIV Patients at Dessie Referral Hospital, may, 2015

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Determinants of first line antiretroviral immunologic treatment failure among adult HIV Patients at Dessie Referral Hospital, South Wollo zone, Ethiopia, June, 2015

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral
cART	combined Antiretroviral Therapy
CD4	Cluster of Differentiation
CPT	Cotrimoxazol Prophylaxis Therapy
EDHS	Ethiopia Demographic and Health Survey
ETB	Ethiopian Birr
HAART	Highly Active Anti-Retroviral therapy
HAPCO	HIV/AIDS Prevention and Control Office
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Virus
IF	Immunologic Failure
IDU	Intravenous Drug Users
MTCT	Mother To Child Transmission
OIs	Opportunistic Infections
OR	Odds Ratio
PIHCT	Provider Initiated HIV Testing and Counseling
PLHIV	People Living With HIV
PMTCT	Prevention of Mother To Child Transmission
SPSS	Statistical Package for Social Sciences
TB	Tuberculoses
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

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Abstract

Introduction: Immunologic treatment failure in adult HIV patients on ART based on WHO treatments failure criteria which is recommended as anti-retroviral treatment failure diagnostic criteria especially for resource limited settings like Ethiopia where the gold standard viral load determination is not accessible. Patient, who start treatment with advanced stage in which factors lead to treatment failure is not well understood and well studied.

Objective: The aim of this study was to identify determinants of first line antiretroviral treatment immunologic failure among adult HIV Patients at Dessie Referral Hospital may, 2015

Methods: A hospital based Unmatched case control study was conducted at Dessie Referral Hospital. Detailed reviews of patient record were made by using structured check list in which all required information have been collected. From adult HIV patient on antiretroviral treatment two hundred nine cases with immunological treatment failure were taken as a whole where as 209 controls have been selected in the ratio of 1:1 with computer generated simple random sampling. Data have been entered and cleaned using Epi Info version 7 then exported to SPSS version 20 for analysis. Bivariable analysis has been executed then all explanatory variables with p-value of <0.2 were entered into multivariable logistic regression. Determinant factors have been identified based on p-value and AOR with 95% CI.

Results: In this study base line CD4 count <50 and between 50-200 cells/micro-litter, opportunistic infections and inconsistent adherence were found to have more chance of developing immunologic failure where as being female and base line regimen ZDV+3TC+EFV were protective factors.

Conclusion and recommendations: lower base line CD4 count, opportunistic infection, inconsistent adherence were found to be determinant factors to develop immunologic failure. Therefore clinicians and related health programs shall focus on the identified risk factors.

1. Introduction

1.1 Statement of the problem

Introduction of ART in sub- Saharan Africa was a hot debate due to many concerns about adherence, logistics and resistance even if we have a significant scale up implementation. The immunological approaches of WHO has considerable importance for this region even though it is risk for unrecognized virologic failure and the subsequent development of ART-drug resistance (1).

Expanding access to ART is changing the global HIV epidemic in momentous ways as a result AIDs-related mortality rates are declining rapidly. The scale up of ART avert an estimated 4.2 million deaths in low and middle income countries in 2002-2012.The scale up of ART is also contributing significantly to the ongoing drop in annual new HIV infection around the world in all segment of population(2).

According to WHO 2013 Report about 21.2 million peoples are eligible for ART in Africa (3). In Ethiopia scale up of free ART services has been one of the greatest achievement of the HIV program response over the last decade. By the end of June 2013 the number of people ever enrolled in chronic care reached 728,874 while the number ever started ART was 439,301 and 317,443 were currently received ART. Only 70.3% of individuals who ever started ART were currently on treatment indicating challenges in patient retention(4).

HIV is fully suppressed in only one in four people living in sub-Saharan Africa. Death rate is greater in those patients with treatment failure than those with none(5). So attention is needed for communities to achieve the health benefit of ART. One of the critical decision made in ART is when to switch from an initial regimen to another treatment due to treatment failure which requires consideration of multiple factors like what types of monitoring (clinical, immunological, virologic) in available to guide switching, establishing criteria for treatment failure, integrating data from different types of monitoring, making decision and follow up and monitoring to determine patient outcomes. Establishing criteria for treatment failure by considering different determinant factors is one of the critical clinical decisions made in antiretroviral therapy which helps early identification of failing regimen and prevent drug resistance(6).

Ethiopia has now reached a symbolic mile stones for curbing the spread of the epidemic, where the number of newly started client on ART has suppressed the number of new infections in adults>15 years .Of the estimated 593,400 adults living with HIV at the end of 2013; 298,512 were on treatment(50%) (7).

1.2 literature review

1.2.1 Immunological antiretroviral treatment failure:

Failure of first line ART results in high morbidity and mortality. A four years cohort follow up study in India show that amongst 1431 PLHIV, 19.2% died,18.4 % LFU, of the remaining patients 62.3% follow up,21.6% experienced immunological failure. Those patients are more likely to be males, illiterate with a history of pulmonary TB while on ART. Sub-optimal CD4 testing among PLHIV was associated with history of TB prior to initiation of ART and stage 3& 4 of HIV diseases at enrollment (8).

Cochrane review in low resource settings, it appears that monitoring strategies which uses immunologic monitoring in addition to clinical monitoring for guiding when to switch therapy results in fewer patient deaths, fewer AIDS-defining illness, and fewer unnecessary switches(6).

In twenty four studies of systematic review, studies found that reduced risk of mortality, progression to AIDs or death and diagnosing non-AIDs defining illness and an increased risk of grade three or four laboratory abnormality in patients initiating ART at least 350 cells/mul which supports WHO 2013 guideline recommendation (9).

1.2.2 Socio-demographic characteristics

Study in South Africa show that individuals experiencing treatment failure from individuals experiencing success with regard to male sex, age above 40 years(10, 11).

A study in northern parts of Ethiopia immunological failure was 1.78 times more likely among older age groups than younger one as well patient who have attained tertiary level education were 3.51 times more likely to experience immunological failure when compared with those who have never attend formal education (12).

Study conducted at Addis Ababa public health hospitals on 103 cases and 206 controls show that majorities, 53.4% of cases and 59.7% of controls were females. Regarding to marital status 42.7% of cases and 80% of controls were married(5).

1.2.3 Baseline information

A retrospective cohort study in India show that suboptimal CD4 testing among PLHIV at stage III and IV of HIV diseases at enrollment were significantly associated with immunological treatment failure(13).

A case control study in African people show that a large HIV treatment program in western Kenya with low baseline CD4 count <50/ml was independent predictors of first line treatment failure but baseline hemoglobin level, and HIV disclosure status were not significantly associated with risk of treatment failure(14).

Predictor of mortality after failure of firs line ART were weight in the lowest quartile for sex, CD4 T cell count ≤100, adherence <90% at the time of failure and not switching to second line ART. Patient who failed first line ART based on immunological criteria and did not switched to second line therapy faced a high mortality than those who switched after failure(15).

Study on immunological failure at Adama and Yergalem hospital, in ETHIOPIA was found that patient with lower baseline CD4 count were more likely to have immunological treatment failure and it is noticed that patient with immunological treatment failure have optimal rate of immune recovery in the first six months of treatment with HAART(12).

A retrospective study effects of incident tuberculosis on immunological response of HIV patient with HAART shows 22.2% were found to have immunological failure with a rate of 8.5 per 100 person years with high immunological failure rate 20.1% per 100 person year of TB patients at the first years of life(16).

1.2.4. Treatment related factors

Study in Thailand demonstrated that even in resource settings, the high rate of success could be expected in the cohort with good and suitable drug adherence. Poor adherence was the predictors for unfavorable outcome of cART. After two years of cART initiation the increment of median CD4 count from base line was 152 cells/mm3 and 294 cells/mm3 among those with and without immunological failure respectively(11, 17).

A case control study in Dar es Salaam, Tanzania show that history of poor antiretroviral therapy adherence due to exposure to drug holydays with loss to follow up, history of changing care and treatment clinics and the lack of treatment supporter were found to be strongly associated with the occurrence of first line HAART immunologic failure(18, 19).

Study made in Italy on trends of ART drug resistance over time show that resistant to NRTIs and NNRTIs decline from 79.1 – 40.8% and 77.8 to 53.8 % respectively with $p<.0001$ in a time period comparison 2003-2004 to 2010-2012 with the lesson of mutation associated with NRTIs and NNRTs treatment failure declines over time regardless of specific class combination and epidemiological characteristics of treated population(20).

Treatment interruption, history of pulmonary TB treatment during HAART follow up time and history of chronic gastric problem were independently associated with first line antiretroviral treatment failure(5).

Majority of patients about 65% taking antiretroviral therapy experienced at least one mild to severe adverse effect in the course of treatment which can affect the patients treatment outcome. Due to this reason ART switch was done in about 62.8% patient while 37.2% of patient switched two times within three years(21).

1.2.5 Behavioral factors

A meta-analysis study which compared antiretroviral resistant rates in IDU, the risk of development of antiretroviral resistance did not differ significantly between IDU and non-IDU (22).

Immunologic failure is found to be associated with HIV status disclosure(AOR=3.11,95% CI=1.19-9.53) and lack of disclosure of HIV status to family members (AOR=3.49,95% CI=1.59-8.34) (18).

A case control study conducted in Addis Ababa, show that most of the cases 70.9% and 76.7% controls disclose their HIV sero-status during HAART initiation. Majority of cases 63.1% and 74.8% of controls were not using any of the substance. However 7.8% of cases and 3.4% of controls use soft and hard drinks while 21.4% of cases and 14.1% of controls use two or more substances during the time of HAART initiation(5).

1.3 justification of the study

Achieving the vision of zero new infection, zero discrimination and zero AIDS related deaths requires that every one needing HIV treatment so giving emphasis on the issue of treatment failure have a great input for those countries with a limited access of ARV drug supply. Even though there are different class of ARV drugs like fusion inhibitor, nucleoside and nucleotide reverse transcriptase inhibitor, and protease inhibitors we have limited access to newer, more potent antiretroviral regimens and monitoring technique are often limited. So maintaining maximum efficacy of the available ARV drugs can be considered as the best alternative to fight against HIV/AIDS in resource limited country like Ethiopia.

Antiretroviral treatment failure leads development of drug resistant virus and let the patient to remain in the failing regimen unless it is detected early.

Therefore this research lead to identify basic determinant factors which result antiretroviral treatment failure based on WHO immunological treatment failure criteria and findings can help for ART related programs and as a baseline for other researchers.

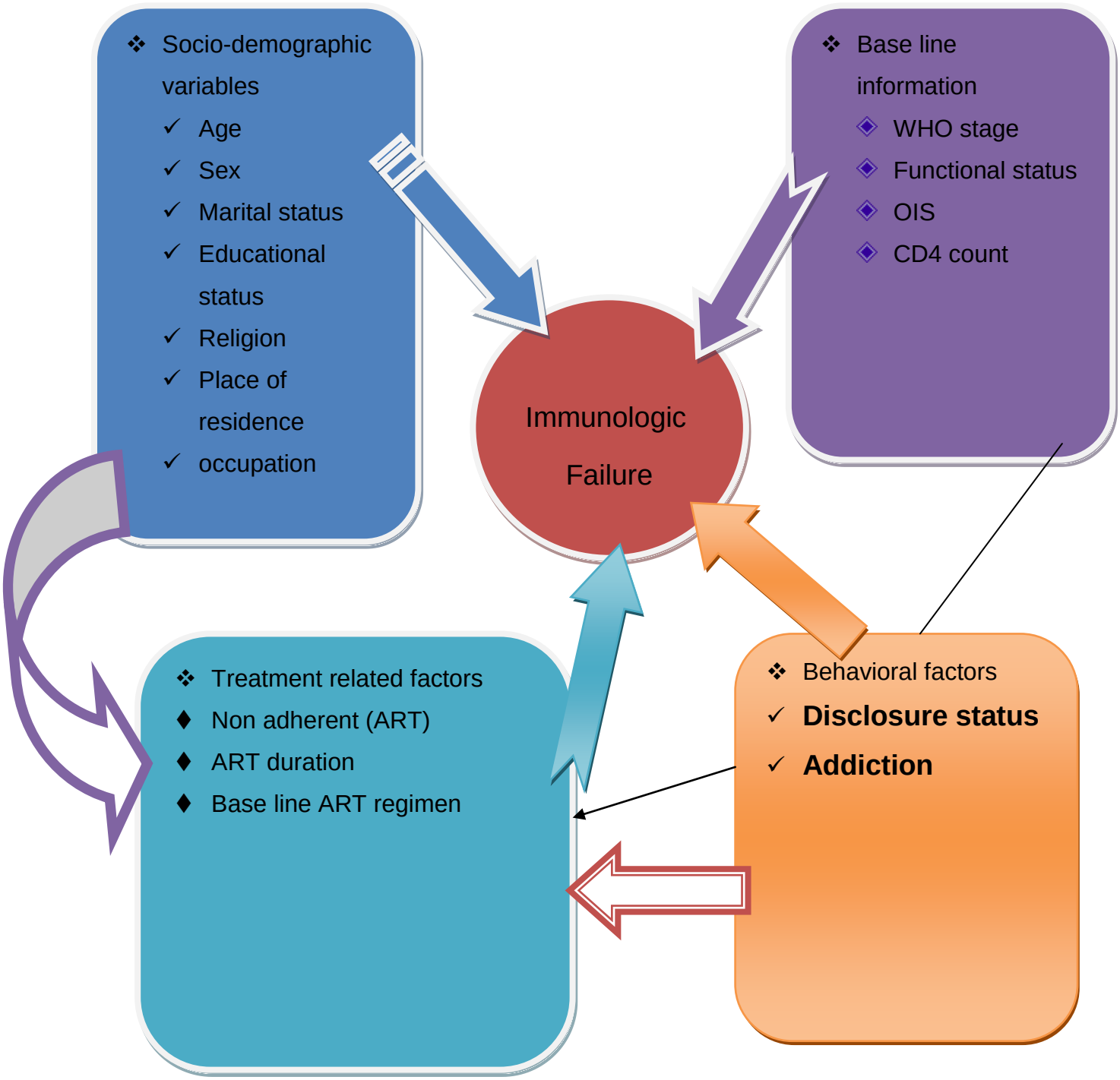

Fig.1 Conceptual framework adopted from literature review

2. General objective:-

- To identify determinants of first line antiretroviral immunologic treatment failure among adult HIV Patients at Dessie Referral Hospital June, 2015

3. Methods

3.1. Study design

A hospital based Unmatched case control study was employed.

3.2. Study area and period:-

The study was conducted at Dessie Referral Hospital ART clinic from May 22-June 6/2015.

The ART Clinic of Dessie Hospital starts its service on March 2005 with having 12461 ever enrolled adult HIV patient and 9113 ever started adult HIV patients at present. Out of this there are 4907 adult HIV patient on first line ART, 209 on second line ART. In the ART clinic there are one physician, three BSc and two diploma nurses, eight adherence counselor and seven case managers.

3.3 source population:-

All adult HIV patients' age≥15years on ART at Dessie Referral Hospital.

3.4: study population:-

Adult HIV patient with first line antiretroviral immunologic treatment failure and without first line antiretroviral immunological treatment failure. Cases are those adult HIV patients on ART greater than six months of therapy with having immunological treatment failure according to WHO criteria or declared as treatment failure by the physician/informal switching team in Dessie Referral Hospital where as controls are those adult HIV patients on ART greater than six months of therapy without having immunological treatment failure.

Case ascertainment:-cases have been selected by reviewing ART register, treatment failure data base, treatment failure screening sheet and from the detail of the patient history so as to classify as immunologic treatment failure.

3.5 inclusion criteria

Patients with HIV infection on ART with the following criteria were included:-

- ≥ 15 years of age in adult ART clinic
- Had at least six months of follow up and two consecutive CD4 cell count after ART initiation.
- WHO immunological failure criteria as cases

3.6 exclusion criteria

- Patients referred from other ART treatment center with incomplete base line information.
- Patient with incomplete chart/ART intake form.

3.7 Sample size and sampling technique

Sample size was calculated using Epi Info version 7 for unmatched case control study design based on the assumption that treatment interruption is significant predictor of first line ART treatment failure from previous case control study with 4.4% of controls and 35.9% of cases were exposed to treatment interruption and the level of significance α=0.05, the power of the test(1-β)=80%, the control to case ratio(r)=1,the proportion of exposure among controls(p1)=4.4% with the proportion of exposure among cases(p2)= 35.9% and AOR=5.4.The final sample size calculated by using the above assumption gives 57 cases and 113 controls with a total of 170 study subjects. However, since there are 209 actual cases and I have about 20 independent variables, it was found preferable to take all the total cases in 1:1 ratio to have a total of 418 study subjects.

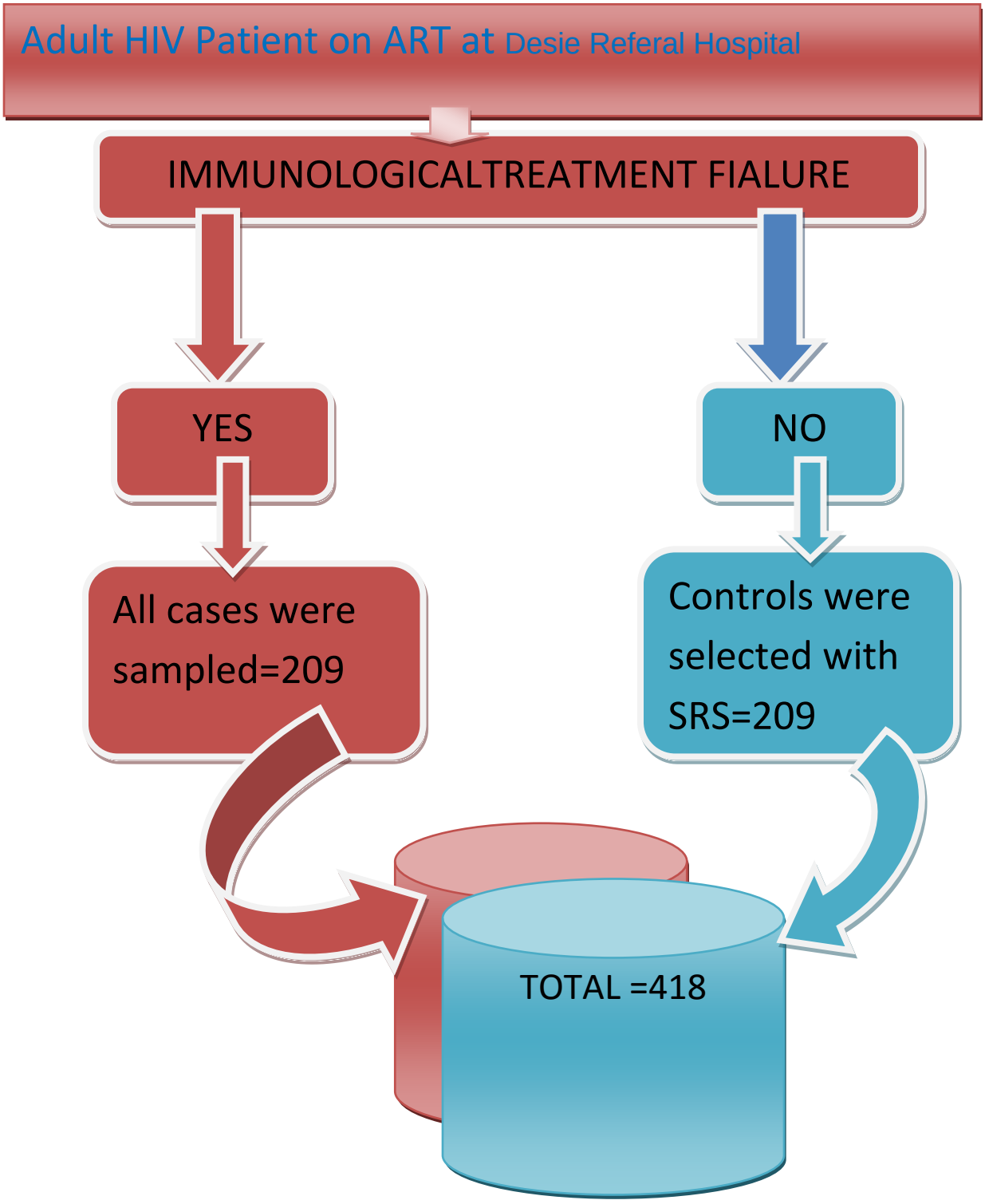

Fig-2: Schematic presentation of sampling technique.

3.8 Variables of the study

3.8.1 Dependent variable:-Immunologic treatment failure

3.8.2 Independent variables

- **Socio-demographic variables**
  - ✓ Age
  - ✓ Sex
  - ✓ Marital status
  - ✓ Educational status
  - ✓ Place of residence
- Base line information
  - Who stage
  - Functional status
  - OIS
  - CD4 count
- Treatment related
    - ♦ Non adherent (ART)
    - ♦ ART duration
    - ♦ Base line ART regimen
- Behavioral factors
- ✓ addiction
- ✓ Disclosure status

3.8. Operational definition:-

Immunologic failure: patient having immunological first line antiretroviral treatment failure according to WHO treatment failure criteria.

Cases: Adult HIV patient on antiretroviral therapy at Dessie Referral Hospital with first line antiretroviral treatment failure confirmed by physician/informal switching team.

Controls: Adult HIV patient on antiretroviral therapy at Dessie Hospital without first line antiretroviral treatment failure.

Inconsistent adherence: Adult HIV patient who have at least one record of fair or poor in the course of his/her treatment.

Consistent adherent: Adult HIV patient who have no record of fair or poor in the course of his/her treatment or have good adherent.

Informal switching team: - Members of health professionals which include Medical Doctor/physician, ART trained nurses/Health officer; they meet only so as to determine treatment regimen change or switching for especial cases, which needs specialty and team discussion.

Switching team: Members of health professionals which include Medical Doctor/physician, ART trained nurses/Health officer; they meet regularly so as to determine treatment regimen change or switching for each and every case, which needs specialty and team discussion.

Adult HIV patient: A patient with HIV on Anti-Retro viral Treatment of age $\geq$ 15 years.

3.9. Data collection procedure:-

Detailed reviews of patient record was made so as to identify cases and controls then by using structured check list all required information was collected. Study units were selected independently from cases and controls. All cases with immunological treatment failure having complete records were taken as a whole where as controls were selected with simple random sampling method after creating a sampling frame for control group then so as to know the interval of sample selection the total population of the group were taken from the frame then divided by the total sample size then to start with the first study subject simple random sampling technique was applied.

3.10 Data quality control

To keep the quality of the study, data extraction format was prepared based on federal ministry of health of Ethiopia standard ART guideline, ART follow up form and ART intake form, the format have been tested before actual data collection have been conducted, Data collectors and supervisors were ART trained. Moreover, data quality was also assured during collection, entry and analysis. Training was given for data collectors and supervisors before data collection and there were close follow up of data collectors by supervisors and PI including observation of how they collect the recorded data.

3.11 Data processing and analysis:

Data have been first checked manually for completeness and consistency by supervisors and principal investigators during data collection and rechecked again before data entry. Normality assumption was performed before any statistical soft ware has been used. Data was entered and cleaned using Epi Info version 7 then exported to SPSS version 20 for analysis and interpretation. Descriptive analysis was conducted to summarize the data. Bivariable analysis has been executed to see the association between independent and outcome variables. All explanatory variables associated with outcome variables with $p<0.2$ was entered into

Multivariable logistic regression analysis. Multicolliniarity test was done to check whether there are correlated independent variables.

4. Ethical consideration:-

Ethical clearance was obtained from Institutional Review Board of University of Gondar, School of medicine and health science. Formal letter of cooperation was written for Dessie Referral Hospital. Informed written Consent from Dessie Referral Hospital was obtained and permission letter has been written to the unit of ART clinic. The data collectors collect the data after obtaining permission from the unit department. Information and confidentiality has been maintained by enrolling data collectors who work at ART clinic.

5. Results:

5.1 characteristics of study subjects

5.1.1 **Socio demographic characteristics**

A total of 209 cases 209 controls have been included in the study. From these study subjects majority of them, 235(56.2 %) were females out of whom 102(48.8%) were cases and 133(63.6%) were controls while majority cases, 107(51.2%) were males.

The mean age of the study participant was 35 (± 9.2 std) years from whom majority of cases 93(44.5%) were in the age category of 25-34years (table 1).

Table I: socio demographic characteristics of adult HIV patient on ART at Dessie Referral Hospital, South Wollo Zone 2015.

Socio characteristics	demographic	Immunological failure case Number (%)	control Number (%)
Age	15-24	11(5.3%)	23(11.0%)
	25-34	93(44.5%)	81(38.8%)
	35-44	77(36.8%)	71(34.0%)
	>=45	28(13.4%)	34(16.3%)
sex	male	107(51.2%)	76(36.4%)
	female	102(48.8%)	133(63.6%)
Marital status	married	102(48.8%)	106(50.7%)
	never married	32(15.3%)	37(17.7%)
	separated	16(7.7%)	10(4.8%)
	divorced	32(15.3%)	30(14.4%)
	widowed	27(12.9%)	26(12.4%)
Level of education	no education	44(21.1%)	45(21.5%)
	primary	57(27.3%)	63(30.1%)
	secondary	77(36.8%)	79(37.8%0
	tertiary	31(14.8%)	22(10.5%)
Residence	urban	155(74.2%)	159(76.1%)
	rural	54(25.8%)	50(23.9%)
Religion	orthodox	106(50.7%)	100(47.8%)
	Muslim	97(46.4%)	104(49.8%)
	other	6(2.9%)	5(2.4%)

Occupation	employed	43(20.6%)	44(21.1%)
	not employed	117(56.0%)	80(38.3%)
	farmer	11(5.3%)	10(4.8%)
	Marchant	17(8.1%)	19(9.1%)
	daily laborer	21(10.0%)	28(13.4%)
	others		28(13.4%)

Others-protestant, catholic

5.1.2 Base line clinical characteristics of study subjects

Out of 418 study population 203(48.4%) were on WHO stage III from whom 121(57.9%) and 82(39.2%) were cases and controls respectively.

Relatively oral candidiasis, pulmonary tuberculosis and bacterial pneumonia were common opportunistic infection observed in both cases and controls with relative higher occurrence among cases than controls (table 2).

Table 2: Base line clinical characteristics of adult HIV patient on ART at Dessie Referral Hospital, South Wollo Zone 2015.

Base line clinical characteristics		Immunological failure	
		case Number (%)	control Number (%)
Base line opportunistic infection	no	42(20.1%)	104(49.8%)
	yes	167(79.9%)	105(50.2%)
Base line functional status	working	62(29.7%)	121(57.9%)
	ambulatory	137(65.6%)	83(39.7%)
	bed redden	10(4.8%)	5(2.4%)
base line WHO stage	stage I	14(6.7%)	62(29.7%)
	stage II	39(18.7%)	48(23.0%)
	Stage III	121(57.9%)	82(39.2%)
	stage IV	35(16.7%)	17(8.1%)

5.1.3 Base line laboratory characteristics of study subjects

The median base line CD4 count of study subject were 111.5 while the median CD4 count of cases and controls were 104 and 120 respectively (figure 1).

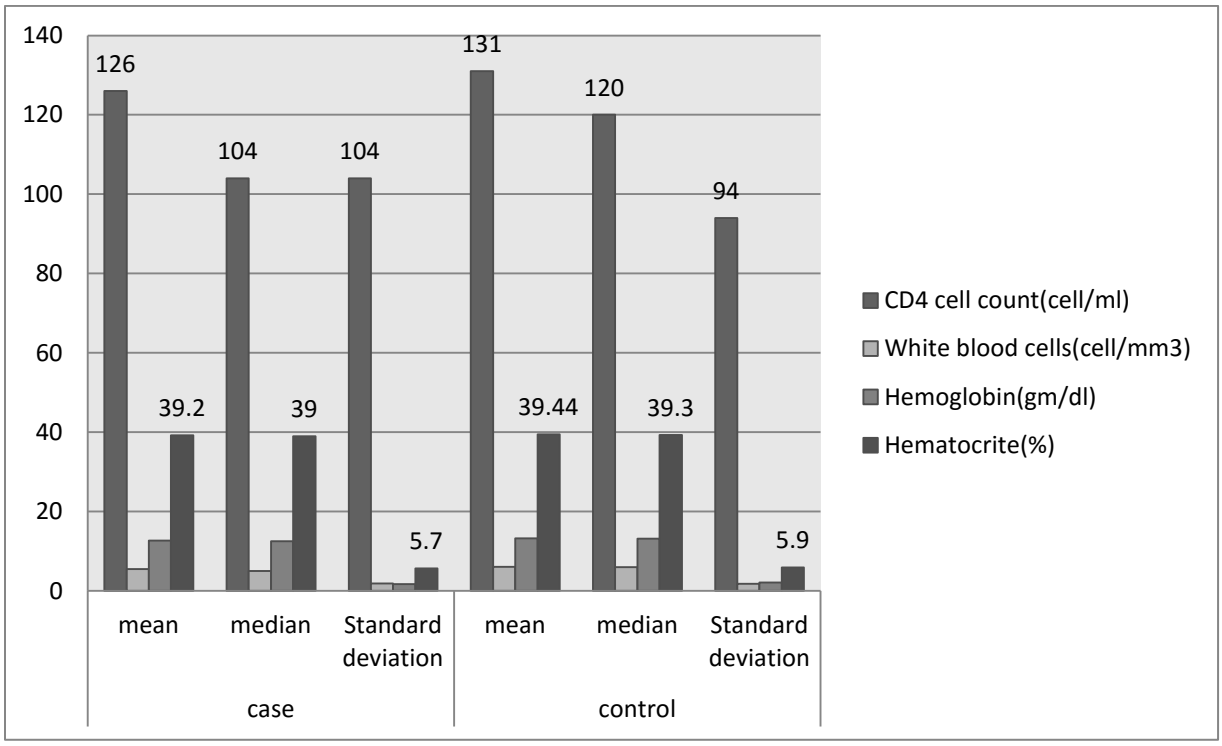

Figure I: Base line laboratory characteristics of adult HIV patient on ART at Dessie Referral Hospital, North Wollo Zone 2015

5.1.4 Treatment related characteristics

Relatively majority of study participants 109(26.1%) and 106(25.4%) were on d4T + 3TC+ NVP and ZDV + 3TC + NVP treatment regimen respectively, in which most of the cases 66(31.6%) were on d4T + 3TC+ NVP.

The mean ART duration of study subjects were 79.6(± 25.8) where as the mean ART duration of cases and controls were 82(± 24 STD) and 77(± 25 STD) respectively.

Three hundred sixty four (87%) of the study participant were found to be consistently adherent to their ART drug from whom the majority of them 203(97.1%) were controls

(table 3).

Table 3: Treatment related characteristics of adult HIV patient on ART at Dessie Referral Hospital, south Wollo Zone 2015.

treatment related characteristics		Immunological failure	
		Cases Number (%)	controls Number (%)
Base line ART regimen	1a=d4T+3TC+NVP	66(31.6%)	43(20.6%)
	1b=d4T+3TC+EFV	36(17.2%)	31(14.8%)
	1c=ZDV+3TC+NVP	52(24.9%)	54(25.8%)
	1d=ZDV+3TC+EFV	31(14.8%)	53(25.4%)
	1e=TDF+3TC+EFV	13(6.2%)	23(11.0%)
	TDF+3TC+NVP	11(5.3%)	5(2.4%)
Consistence of adherence	consistent adherence	161(77.0%)	203 (97.1%)
	inconsistent adherence	48(23.0%)	6(2.9%)
duration of ART	<=24	7(3.3%)	4(1.9%)
	25-48	21(10.0%)	29(13.9%)
	>=49	181(86.6%)	176(84.2%)

5.1.5: Behavioral characteristics

From 209 cases and 209 controls only 59(14.1%) do not disclose their HIV status from whom majorities 42(20.1%) were cases with 17(8.1%) were controls (table 4).

Table 4: Behavioral characteristics of adult HIV patient on ART at Dessie Referral Hospital, south Wollo Zone 2015.

behavioral characteristics		immunological failure case Number(%)	control Number (%)
disclosure status	Yes	167(79.9%)	192(91.9%)
	No	42(20.1%)	17(8.1%)
addiction	no addiction	147(70.3%)	180(86.1%)
	Alcohol	29(13.9%)	13(6.2%)
	soft drug	27(12.9%)	14(6.7%)
	hard drugs	6(2.9%)	2(1.0%)

5.2. Bivariable analysis

5.2.1 Factors which fulfill the screening criteria in bivariable analysis at p-value < 0.2

being female, Study population with age category 25-34 ,opportunistic infections WHO stage II, III and IV ,Study participants with ambulatory and bed redden condition, base line CD4 count <50 and CD4 count from 50-200,

Study participants with treatment regimen d4T+3TC+EFV, ZDV+3TC+NVP,

And ZDV+3TC+EFV, Study participants with inconsistent adherence and without disclosure status, Study participants with alcohol and soft drugs (table 5).

5.3. Multivariable analysis.

In multivariable analysis patients with base line CD4 count <50 and between 50-200 cells/micro-litter, presence of opportunistic infection and inconsistent adherence were more likely to have immunologic failure whereas being female and base line regimen ZDV+3TC+EFV were protective (table 5).

5.3.1 Multivariable analysis of socio demographic characteristics

From socio demographic characteristics being female were 55% less likely to develop immunologic failure than being male [AOR=0.45, 95%CI: 0.25-0.80] (table 5).

5.3.2 Multivariable analysis of clinical and laboratory base line characteristics

Study participants with baseline CD4 count of <50 cells/micro-litter [AOR=8.04, 95%CI: 3.53-18.3] and 50-200 cells/micro-litter [AOR=2.52, 95%CI: 1.24-5.12] were 8.04 and 2.52 time more likely to develop immunologic failure respectively than those study participants with a CD4 count of >200 cells/micro-litter.

Study subject with opportunistic infection [AOR=3.3, 95%CI: 1.76, 6.17] were found to have more chance of developing immunological failure than none (table 5).

5.3.3 Multivariable analysis of treatment related characteristics

Study participants with treatment regimen ZDV+3TC+EFV were 65.8% less likely to develop immunologic failure than study participants with treatment regimen d4T+3TC+NVP [AOR=0.34, 95%CI: 0.16, 0.75].

Study participants with inconsistent adherence were 9.26 times more likely to develop immunological failure than who were consistently adherence [AOR=9.26, 95%CI: 3.14, 27.31] (table 5).

Table 5. Bivariable and Multivariable analysis of determinant factors associated with immunologic failure among adult HIV patients in Dessie Referral Hospital North Wollo zone, Ethiopia, June 23, 2015.

Variables		Immunologic failure		Crude OR (95%CI)	Adjusted OR (95%CI)
		Cases	controls		
AGE	15-24	11(5.3%)	23(11.0%)	1	
	25-34	93(44.5%)	81(38.8%)	2.401(1.103, 5.226)*	
	35-44	77(36.8%)	71(34.0%)	2.268(1.032, 4.984)*	
	>=45	28(13.4%)	34(16.3%)		
Sex	male	107(51.2%)	76(36.4%)	1	
	female	102(48.8%)	133(63.6%)	.545(.368, .805)*	.451(.252, .806)*
occupation	employed	43(20.6%)	44(21.1%)	1	
	not employed	117(56.0%)	80(38.3%)	1.497(.901, 2.486)	
	farmer	11(5.3%)	10(4.8%)		
	Marchant	17(8.1%)	19(9.1%)		
	daily laborer	21(10.0%)	28(13.4%)		
	others	0(0.0%)	28(13.4%)		
Base line WHO stage	stage I	14(6.7%)	62(29.7%)	1	
	stage II	39(18.7%)	48(23.0%)	3.598(1.756, 7.374) **	
	Stage III	121(57.9%)	82(39.2%)	6.535(3.431, 12.445)**	
	stage IV	35(16.7%)	17(8.1%)	9.118(4.017,20.697)**	
Base line functional status	working	62(29.7%)	121(57.9%)	1	
	ambulatory	137(65.6%)	83(39.7%)	3.221(2.138, 4.854)**	
	bed redden	10(4.8%)	5(2.4%)	3.903(1.278, 11.919)*	
Base line Opportunistic infection	no	**42(20.1%)**	**104(49.8%)**	**1**	
	yes	**167(79.9%)**	**105(50.2%)**	**3.94(2.55,6.08)**	**3.3(1.76,6.17)**

Base line CD4 count	**<50**	**74(35.4%)**	**33(15.8%)**	**6.95(3.63, 13.314) ****	**8.04(3.53, 18.3)****
	50-200	115(55.0%)	114(54.5%)	3.127(1.774, 5.511) **	2.52(1.24, 5.117)*
	>200	20(9.6%)	62(29.7%)	1	
adherence to ART	consistent adherence	161(77.0%)	203(97.1%)	1	
	Inconsistent adherence	48(23.0%)	6(2.9%)	10.09(4.21, 24.162)**	9.26(3.14, 27.31)
Base line ART regimen	1a=d4T+3TC+NVP	66(31.6%)	43(20.6%)	1	
	1b=d4T+3TC+EFV	36(17.2%)	31(14.8%)		
	1c=ZDV+3TC+NVP	52(24.9%)	54(25.8%)	.627(.365, 1.078)*	
	1d=ZDV+3TC+EFV	31(14.8%)	53(25.4%)	.381(.212, .685)*	.342(.156, .749)*
	1e=TDF+3TC+EFV	13(6.2%)	23(11.0%)	.368(.169, 804)*	.
	TDF+3TC+NVP	11(5.3%)	5(2.4%)		
disclosure status	yes	167(79.9%)	192(91.9%)	1	
	no	42(20.1%)	17(8.1%)	2.840(1.56, 5.18)**	
addiction	no addiction	147(70.3%)	180(86.1%)	1	
	alcohol	29(13.9%)	13(6.2%)	2.73(1.37, 5.443)*	
	soft drug	27(12.9%)	14(6.7%)	2.36(1.195, 4.667)*	
	Hard drugs	6(2.9%)	2(1.0%)		

*p-value ≤ 0.05 and **p-value≤ 0.001

6. Discussion

The study focuses on the determinant factors of first line antiretroviral treatment immunologic failure, one of WHO treatment failure criteria especially in resource limited settings. In this study base line CD4 count <50 and between 50-200 cells/micro-litter, opportunistic infection and inconsistent adherence were more likely to have immunologic failure whereas being female and base line regimen ZDV+3TC+EFV were protective.

In socio demographic characteristics the odds of developing immunologic failure in females were 55% less likely than males which are inconsistent with the study conducted in South Africa which shows treatment success in males than females the possible explanation might be due to especial focus of maternal care in relation to HIV and ART which in turn increases adherence.

In this study, Study participants with baseline CD4 count of <50 cells/micro-litter shows the odds of developing immunologic failure 8.04 times higher than those study participants with base line CD4 count >200 cells/micro-litter where as the odds of developing immunologic failure in study participants with base line CD4 ranging from 51-200 cells/micro-litter were 2. 52 times higher than those study participants with base line CD4 count >200 cells/micro-litter. This result is in line with studies conducted in Addis Ababa public health hospitals which shows Patients with base line CD4 count below 50cell/µl failed 2.7 times than that of with >150 cell/µl with 95% CI 1.24 to 5.64(5), studies conducted at Debremarkos Hospital which shows Patients with baseline CD4 count of less or equal to 100 cells/mm3 were 2.16 times more likely to have immunological failure compared to those patients with CD4 count greater than 100 cells/mm3(23, 24). This might be due to the direct and indirect effect of HIV in the immune system which results challenge of the immunity to boost CD4 cell counts.

Study population with opportunistic were found to have 3.3 times more chance of developing immunological failure than without opportunistic infection . This finding is in line with study conducted in Addis Abeba, Hawassa and Debremarkos hospital ,Ethiopia in which Patients having history of pulmonary TB treatment during HAART

follow up failed almost 3 times than that of without history with 95% CI 1.55 to 5.34, The probability of developing new opportunistic infections like tuberculosis is high if the baseline CD4 count is low and Patients having recurrent pneumonia infection at the initiation of HAART were 1.62 times at higher risk of immunological failure compared to those patients without recurrent pneumonia(5, 12, 23). This may be due to the immunochompromizing effect of opportunistic infection and HIV in the immune system.

Study participants with inconsistent adherence were 9.26 times more likely to develop immunological failure than who was consistently adherence this finding were in line with study conducted in African patients which shows poor ART adherence were independent predictors of first-line treatment failure this is due to low level of plasma drug level creates a good opportunity to create viral resistant strain which in turn results treatment failure (19).

Study participants with treatment regimen ZDV+3TC+EFV were 66% less likely to develop immunologic failure than study participants with treatment regimen d4T+3TC+NVP. This finding were inconsistent with studies conducted in African people, western Kenya which shows Zidovudine use as part of the NRTI backbone is associated with treatment failure this difference may be due to difference in first line regimen and parameters to change ART regimen due to side effects.

The limitation of the study was as it is conducted by reviewing patient records there are variables which can not addressed and the study was focused only in immunological failure of first line ART drugs.

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7. Limitation of the study

- As it is conducted by reviewing patient records there are variables which could not be addressed.
- The study was focused only in immunological treatment failure of first line ART drugs.

8. Conclusion

Low base line CD4 count <50 and between 50-200 cells/micro-litter, opportunistic infections and inconsistent adherence were mere likely associated determinant factors for immunologic failure whereas being female and base line regimen ZDV+3TC+EFV were protective factors. Therefore clinicians and Anti-Retroviral treatment related programs shall give emphasis so as to manage such risk factors.

9. Recommendation

9.1 For health professionals

Physicians/clinicians, Anti-Retroviral Treatment trained nurses and health officers, adherence counselors need to work collaborately so as to manage such risk factors.

9.2 For Dessie referral Hospital

Better to establish Anti-Retroviral treatment switching team from the concerned medical staff.

9.3 For Ministry Of Health and Regional Health Bureau

Better to design and strength those programs which allows establishment of Anti-Retroviral Treatment switching team and adherence strengthening.

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11. Annexes

11.1 Data extraction format/check list

This data extraction format is prepared for the collection of socio-demographic, clinical, treatment and immunologic information that are important for the assessment of immunological failure and associated factors. All this information will be retrieved from the patients ART intake form, follow up sheet and patient card without mentioning the names of the patient. This information will be collected by the nurse/health officer who is working in the ART clinic of Desie Hospital.

Mr./Sr……..(Nurse/Health officer) is/are requested to extract the **existing data** as you are participating in this research project.

Part I:- socio-demographic variables

Circle the corresponding number of response and say incomplete (IC) when the data was not documented.

no	variables	Response with corresponding no/code	Remark/skip to
101	Age , at enrollment in years	……	
102	sex	1. Male 2. female	
103	Marital status	1. never married 2. Married 3. Separated 4. Divorced 5. Widowed 6. IC	
104	Levels of education	1. No education 2. Primary 3. Secondary 4. Tertiary 5. IC	
105	Residence	1. Urban 2. rural	

106	religion	1. orthodox 2. Muslim 3. catholic 4. protestant 5. others (spacify)……	
107	occupation	1. Not employed 2. Employed 3. Farmer 4. Marchant /retialor 5. Daily laborer/migrant worker 6. Others (specify)……..	

Part II:-Base line information/at the time of enrollment, date of enrollment……EFY

201	Base line CD4 count	List ……..	
202	Opportunistic infection	List……	
203	Functional status at the time of enrollment	1. Working 2. Ambulatory 3. Bedridden	
204	WHO stage	1. Stage I 2. Stage II 3. Stage III 4. Stage IV	
205	Body weight	……Kg	
206	laboratory information	Hg……Mg/dl Hct……% WBC……../mm3	

Part Iv:-Antiretroviral treatment related variables

401	Duration of HIV test in month	……..	ART INTAKE/FOLLOW UP FORM
402	Time of eligibility for ART in month	Total month…….. Date of start……..	
403	Eligibility criteria for ART at enrolment	1. Immunological /CD4……. 2. Who stage…….. 3. Both	

		4. Virological failure 5. all	
404	Initial regimen of ART at enrollment	1. 1a=d4T+3TC+NVP 2. 1b=d4T+3TC+EFV 3. 1c=ZDV+3TC+NVP 4. 1d= ZDV+3TC+EFV 5. 1e=TDF+3TC+EFV 6. TDF+3TC+NVP 7. 2a=ABC+ ddI + LPV/r 8. 2b=TDF +3TC + LPV/r 9. 2c=ZDV+3TC+ LPV/r 10. 2d= ZDV+ABC+LPV/r 11. Others (specify)…… ……	
405	Duration on ART	Total MONTH…….. Date of start……	
406	Exposure history of ARV drugs before starting first line ART	1. YES 2. NO	if "no" skip to 208 Otherwise go to 207
407	Which ARV/ART drug/regimen	List the regimen/drug……. …….	
408	Enrolled to CPT in the last six month	1. Yes 2. No	
409	Adherence to ART in the last 6 month	1. G-good 2. F-fair 3. P- poor	
410	Any change or switch of ARV Regimen OR individual drug	1. Yes 2. no	If no skip to …..other wise go to 211
411	Switching time after original treatment	Total month…….. Date of switching……	

412	Write the current ART regimen or in the previous six months	1. 1a=d4T+3TC+NVP 2. 1b=d4T+3TC+EFV 3. 1c=ZDV+3TC+NVP 4. 1d= ZDV+3TC+EFV 5. 1e=TDF+3TC+EFV 6. TDF+3TC+NVP second line ART 1. 2a=ABC+ ddI + LPV/r 2. 2b=TDF +3TC + LPV/r 3. 2c=ZDV+3TC+ LPV/r 4. 2d= ZDV+ABC+LPV/r 5. Others (specify)…… ……	
413	Reason for change or switch of ARV regimen or individual drug	1. Toxicity of drug 2. Pregnancy 3. TB-co treatment 4. Drug stock out 5. Treatment failure 6. Others (specify)…… ……	

Part V:-behavioral factors

501	Disclosure status	1. Yes 2. no	
502	addiction	1. tobacco 2. alcohol 3. soft drugs 4. hard drugs 5. IC	
503			

11.2 Information sheet and consent form

Title of the research project

Determinants of first line antiretroviral immunologic treatment failure among adult HIV Patients at Dessie referral hospital, May, 2015: A case control study.

Name of principal investigator_____Abinet Dagnaw

Name of the Organization_____ University of Gondar, school of medicine.

Name of sponsor _____Amhara regional health bureau

Information sheet and consent form were prepared for database and patient card unit workers at Dessie referral hospital for this research project which assess determinant factors of immunologic failure of first line antiretroviral treatment failure.

Introduction

This information and consent form were prepared with the aim of explaining the research project that joins a research investigator. The main aim of the research project was to assess determinant factors of immunologic failure of first line antiretroviral treatment failure at Dessie referral hospital.

Purpose of the research project

The aim of this study was to examine determinant factors related to immunologic failure of first line antiretroviral treatment failure at Dessie referral hospital.

11.3 Declaration

I, the undersigned, senior master of clinical tropical infectious diseases and HIV medicine student declare that this thesis is my original work in partial fulfillment of the requirement for the degree of Master of Science.

Name: _____

Signature: _____

Place of submission: School of medicine and Health Sciences, University of Gondar.

Date of Submission: _____

This thesis has been submitted for examination with my/ our approval as university advisor(s).

Advisors

	Name	Signature
1.	_____	_____
2.	_____	_____

11.4 Assurance principal investigators

The under signed senior clinical tropical infectious diseases and HIV medicine student agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for the provision of required progress reports as per terms and conditions of the research and publications office of the university of Gondar .

Name of the student: Abinet Dagnaw (BSc)

Signature_____

Date: may, 2015

Approval of the advisor(s)

Name of advisors: signature date

1. Mr. Alemayehu Shimeka (BSc,MPH) _____ _____
2. Dr. Dessalew Mekonnen (MD, Associate professor) _____ _____