Research Article

Advances in Hematology and Oncology Research

Magnitude of Virological Treatment Failure and Its Determinate Factors Among Adults on First Line Antiretroviral Treatment at Defence Main Health Department - Level II & Level III Hospitals In Ethiopia

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Abstract

Introduction: *Highly active antiretroviral therapy (HAART) played a critical role in the medical management of HIV infected individuals by restoring the immune function and minimizes HIV related outcomes. But treatment failure minimized these advantages and leads to an increment of morbidity and mortality with poor quality of life in all HIV patients.*

Objective: *The aim of this study was to assess the virological treatment failure and its determinant factors of patients on first line HAART at five commandant Hospitals, Ethiopia.*

Methods: *A Retrospective hospital based study design was used to determine magnitude of treatment/virology failure and its determinant factors, among HIV positive adults enrolled to HAART program at five commandant Hospitals from February 1 to May 30, 2018. Data abstracted from patient charts or electronic data base was cleaned, coded, entered and analyzed using EPI data version 3.1 and SPSS version 23 statistical software package. Descriptive statistics, proportion of treatment failure cases among those diagnosed to have treatment failure was calculated. Bi-variate and multiple logistic regressions were used to analysis association between the outcome and the independent variables were taken as significant at $P < 0.05$ (2 tail test) and 95% confidence intervals (CIs).*

Result: *Among the 326 participants enrolled, 229(70.2%) were males. The mean ages were 36.84 years (SD+7.716) years and the median months on HAART from initiation were 81.50 months. A total of 75(23%) participants were found to have treatment failure among those 50(15.3%) immunological failure, 7(2.1%) virological failure and 16(4.9%) all Treatment failure (VF, IF&CF in one). The mean CD4 T-cells at base line and at study time were 213.3 cells/ µl. Long duration on treatment (AOR= 4.231, 95% CI: 1.453-12.320) , IPT cycle (AOR = 3.060, 95% CI: 1.388-6.746), Type of drug AZT based therapy (AOR =2.572, 95% CI: 1.357-4.875), experience of PEP (AOR=7.950, 95% CI: 1.945-66.915) and lost to follow up (AOR= 9.104, 95% CI: 2.973-27.873) were found to be significant predictors of treatment/virologic failure and showed positive odds ratio.*

Conclusion: *This study demonstrates high treatment /virologic failure and the determinant factors of treatment/virologic failures among HAART first line adult are still changing. Therefore, evidence-based intervention and early detection of treatment failure must be made to further identify the potential causes and set standardized protective mechanisms of treatment/virologic failures.*

Keywords: Treatment Failure, First Line HAART, HIV, Determinant Factors, Adults, Ethiopia

Abbreviations

AIDS: Acquired Immune Deficiency Syndrome
ART: Anti-Retroviral Therapy
EDHS: Ethiopia Demography and Health Survey
EHNRI: Ethiopia Health and Nutrition Research Institute
EPHI: Ethiopia Public Health Institute
FHRH: Commandment Hospitals
HIV: Human Immune-deficiency Virus
HIVDR: HIV Drug Resistance
HMIS: Health Management Information System
LTFU: Lost to Follow Up
MDT: Multi-Disciplinary Team
MOH: Ministry of Health
MRN: Medical Registration Number
PLHIV: People living with HIV

SMART: Screening and Management of Anti-Retroviral Treatment
RHB: Regional health Bureau
RLS: Resource Limited Setting
UAN: Unique Antiretroviral Number
WHO: World Health Organization

Introduction

Over the last decade, concerted efforts by governments and stakeholders brought about better access to HIV care and treatment services with a resultant decline in new HIV infections and HIV associated morbidity and mortality [1]. The HIV prevalence among adults aged 15-49 in Ethiopia was an estimated at 1.5% in 2011 EDHS [2]. The overall adult antiretroviral therapy (ART) coverage has reached 73% following the launching of a free-and-accelerated national ART program in Ethiopia in 2005 [3].

Emerging Challenge of HIV Program: Treatment failure is under diagnosed and under-reported as well. For instance, the proportion of treatment failure cases diagnosed by clinical or immunologic criteria and subsequently switched to second line ART is less than 2%, nationwide [3-4]. According to facility HIV program reports, as of September 2015, the number of HIV positive clients enrolled to ART program and currently retained on ART at different Commandment Hospitals. Following introduction of active treatment failure screening program in 2012, the number of treatment failure cases at different Commandment Hospitals have reached to 207 (3.3%). Still, in the face of increasing rate of emergence of drug resistance in resource limited setting, this low detection rate raised huge concern among clinician and researchers. Unavailability of an active screening method to detect treatment failure in a timely fashion is a critical gap in the Ethiopian ART program. Such missed opportunity allows clients to continue on a failing ART regimen that may not suppress viral replication [5-10].

Moreover, the clinical and immunologic TF criteria have its own limitation for it misclassifies clients. On one hand, the criteria results in under- diagnosis of treatment failure and hence delay switch to second line therapy. On the other hand, the criteria results in over-diagnosis of treatment failure among clients who have achieved desirable HIV viral suppression but without immunologic or clinical recovery. This leads to unnecessary switching to second-line ART [11-13].

Lack of clear guideline on management of treatment failure poses challenge to national ART programs in resource limited setting [14-15]. Utilization of HIV viral load test is low even though the test is performed free-of-charge at a public HIV viral load testing laboratory located in different towns some meters close to Commandment Hospitals. The laboratories are nationally accredited HIV viral load testing center in Addis Ababa. The center adheres to a Standard Operating Procedure (SOP) developed for HIV viral sample transportation and viral load test procedures customized from Ethiopian Public health Institute [16].

Thus, it is high time to strengthen active TF screening, confirm diagnosis and switch to second line ART in timely fashion. Establishing correct diagnosis of treatment failure is critical to prevent unnecessary switches to more expensive and toxic second-line regimens.

Statement of the Problem

Following implementation of an active screening program at Commandment Hospitals, over 3% treatment failure cases were identified by immunologic or clinical criteria and most have accessed HIV viral load test services to confirm treatment failure in Ethiopia. Surprisingly, the HIV clinic realized that a number of treatment failure cases had actually discordant TF diagnosis result; one that fulfilled national criteria of immunology or clinical treatment failure, and yet achieved desirable HIV viral suppression. Then, these are the question posed by the HIV experts: what is the magnitude of virology failure? How prevalent is discordance between treatment failure criteria? What is the implication on clinical management of HIV? What is the implication to ART monitoring? And what are the major determinant factors that contribute to treatment failure?

In summary, reaching at correct diagnosis of treatment failure is critical because, on one hand, incorrect diagnosis of treatment failure leads to unnecessary treatment switches to more expensive and toxic second-line regimens jeopardizing future treatment option. On the other hand, delayed detection of treatment failure and continuation of a failing regimen may result in accumulation of viruses resistant to first-line ART and possible transmission of resistant virus to sex partners.

Hence, investigators propose this Retrospective hospital based study to determine the magnitude of virology failure and prevalence of discordance between clinico-immonologic and virology TF criteria among adults whose first line ART has failed at Commandment Hospitals.

Investigators strongly believe that findings of the study will inform HIV clinicians on diagnosis and management of treatment failure. Further, the study may generate locally relevant research questions for scientific debate on caveats of diagnosis of treatment failure in Ethiopia.

Significance of the Study

This is a retrospective hospital based study set out to determine of magnitude of virology failure and its determinate factors and rate of disagreement between different treatment failure diagnostic criteria among HIV positive adults enrolled to antiretroviral therapy program at commandment Hospitals.

The evidence was used to improve quality of ART services at five commandment Hospitals by providing information on magnitude of virology failure and rate of disagreement between different treatment failure diagnostic criteria. Such local evidence assists clinicians to timely identify treatment-failure-at-risk patients and closely follow them to ensure optimal adherence and improved access to HIV viral load test services to reach to correct diagnosis of treatment failure. Correct diagnosis of treatment failure avoids unnecessary switch to costly and toxic second line ART. Therefore, the scope of this study is limited to level 3 hospitals and findings may not be representative of national HIV program or other facilities in Ministry of Defence.

Literature Review

Global burden of HIV: Over 90% of living with HIV (PLHIV) and 97% of new HIV infections worldwide are found in resource-limited settings. The HIV pandemic has created an enormous challenge for infected individuals, affected families and overall health systems in resource limited settings. Over the last decade,

concerted efforts by governments and stake holders brought about better access to HIV care and treatment services with a resultant decline in new HIV infections and HIV associated morbidity and mortality. Consequently, as of the end of 2011, over 8 million PLHIV in low- and middle-income countries had access to ART [1].

In Ethiopia, at the end of September 2013, an estimated 439, 310 ART needy PLHIV were enrolled into national ART program, and 308,860 are retained on treatment [1-3].

Challenges of Antiretroviral Treatment Program: Accelerated scale up of ART program in resource limited setting faces many challenges such as suboptimal adherence and high attrition from ART programs [3,4]. In addition, an increasing rate of emergence and transmission of HIV Drug Resistance has raised concern among clinician, program managers and researchers. An observational cohort study from HIV clinic in South Africa which enrolled 19,645 patients (29,935 person-years) showed that 9.9% of first line ART (4.5/100 person-years) failed at median 16 (IQR: 12-23) months following ART initiation.

Five years following ART treatment, the failure rate was 16.9% and 7.8% when using a confirmatory threshold of 400 and 10,000 copies/ml, respectively. The same study reported a 10.1% overall rate of switch to second-line ART by five years [5]. Since 2005, over 379, 190 PLHIV were ever enrolled to Ethiopian national ART program, and 275,026 PLHIV are currently taking ART; however, the proportion of treatment failure cases detected and subsequently switched to second line ART is less than 2%, nationally [3]. This is much lower than an overall rate of switch to second-line reported in other Sub Saharan countries [5]. Here, one can argue that treatment failure is under-diagnosed in Ethiopia, and transition to second line ART has a slower rate.

Studies conducted in sub-Saharan Africa and globally revealed that the magnitude of treatment failure in resource limited setting is on the rise [6-12]. Barth and colleagues (2010) conducted a systematic review of studies from 18 countries to analyzevirological data of 63,684 patients on first-line ART and describe the virological efficacy and drug resistance outcomes of ART programmes in these sub-Saharan African countries. Overall, on-treatment analysis, 10 351(78%) of 13 288 patients showed virological suppression after 6 months of antiretroviral therapy, 7413(76%) of 9794 after 12 months, and 3840(67%) of 5690 after 24 months. Stricter definitions (viral loads greater than 40–500 copies per mL) resulted in higher proportion of failing regimen of 19% of 5942 patients [6]. A systematic review of studies on prevalence of HIV-1 drug resistance in treatment-naïve individuals in resource-limited settings since roll out of ART programs, showed the highest estimated rate of increase at 29% per year (95% CI 15 to 45; p=0•0001) in East Africa; an estimated prevalence of HIV-1 drug resistance at eight years after ART program is 7•4% [7].

Moreover, there is an increase incidence of resistance to non-nucleoside reverse transcriptase inhibitors in East Africa (36% per year; p<0•0001) and Southern Africa (23% per year; p=0•0049). Among the subset of studies reporting treatment failure with HIV-specific resistance mutation data (27 studies with 734 patients), the most common mutations were the M184V mutation, found in 65% of patients, and the K103N mutation, found in 52% of patients [7]. Among patients initiating first-line no nucleoside reverse-transcriptase inhibitor-based therapy, the data suggest that 76%-90% of living patients achieve HIV RNA suppression by 12 months after ART initiation. HIV drug resistance, primarily due to M184V and NNRTI mutations, has been identified in 60%-72% of patients with detectable HIV RNA at 12 months [6,7].In absence of viral load monitoring, unnecessary regimen switches are common, resulting in increased treatment costs and loss of future options for treatment succession. Also, late detection of treatment failure results in high frequencies of accumulated mutations conferring broad cross-resistance to NRTIs, which may impair the effectiveness of second line regimens [11-13].

Diagnosis of treatment failure: World Health Organization (WHO) recommends viral load determination, if feasible, to improve the identification of treatment failure. Due to financial and logistical constraints in resource limited settings, however, access to this expensive and technically demanding test is limited. Therefore, as a substitute, WHO-recommended clinical criteria and CD4 cell counts are commonly used by clinicians to diagnose ART failure and guide treatment switch [14-15].

Several studies in African countries, however, have shown poor association of clinic-immunological criteria with virological failure in patients on first-line ART. A multicentre prospective observational cohort of HIV-1–infected adults who receive ART at 13 clinical sites in Africa compared two modes of diagnosis of treatment failure, clinical-and-immunological failure (CIF) without viral load testing (CIF-only) and CIF with targeted viral load (VL) testing. Of 250 patients with CIF switching to second-line ART, targeted VL was performed in 186. Unnecessary switch at reference HIV RNA of 1000 copies per millilitre occurred in 46.9% of CIF-only patients versus 12.4% of patients with targeted VL ($P < 0.001$). Applying a more stringent HIV RNA cut-off of 400 copies per millilitre, unnecessary switches occurred in 45(18.1%) patients in the CIF-only group versus 16(8.6%) patients in the targeted VL group ($P < 0.001$) [16-18].

Following implementation of an active screening program at CHS, over 3% treatment failure cases were identified by immunologic or clinical criteria and most have accessed HIV viral load test services to confirm treatment failure in Ethiopia. Surprisingly, the HIV clinic realized that a number of treatment failure cases had actually discordant TF diagnosis result; one that fulfilled national criteria of immunology or clinical treatment failure, and yet achieved desirable HIV viral suppression. Then, these are the question posed by the HIV experts: what is the magnitude of virology failure? How prevalent is discordance between treatment failure criteria? What is the implication on clinical management of HIV? What is the implication to ART monitoring?

In summary, reaching at correct diagnosis of treatment failure is critical because, on one hand, incorrect diagnosis of treatment failure leads to unnecessary treatment switches to more expensive and toxic second-line regimens jeopardizing future treatment option. On the other hand, delayed detection of treatment failure and continuation of a failing regimen may result in accumulation of viruses resistant to first-line ART and possible transmission of resistant virus to sex partners.

Hence, investigators propose this Retrospective hospital based study to determine the magnitude of virology failure and prevalence of

discordance between clinico-immonologic and virology TF criteria among adults whose first line ART has failed at Commandment Hospitals.

Investigators strongly believe that findings of the study will inform HIV clinicians on diagnosis and management of treatment failure. Further, the study may generate locally relevant research questions for scientific debate on caveats of diagnosis of treatment failure in Ethiopia.

Objective of the Study

General Objective

To produce evidence on magnitude of virological treatment failure and describe rate of disagreement among different treatment failure diagnosis criteria (clinical, immunologic and biological) and thus contribute to efforts to improve management of treatment failure at five commandment Hospitals from 2015 to 2017 in Ethiopia.

Specific Objectives

1. To determine magnitude of virological treatment failure among adults on first line antiretroviral (HAART)treatment at Commandment Hospitals
2. To identify determinant factors for Treatment failure among adults on first line antiretroviral (HAART) treatment at Commandment Hospitals

Methods and Materials

Study Area and Period

The study was carried out at five commandments hospitals located at different regions of the country: Addis Ababa, Torhayloch Hospital ART Clinic, North command, Mekelle Referral hospital ART Clinic, Central Command, Shire, Level 3 hospital ART Clinic, North West Command, Bahirdar, Referral hospital ART Clinic and East command, Harrar, Referral hospital ART Clinic. The study area is Commandment Hospital. The study period is Jan 2016 up to December 30 December 2017 and the data collection was February to May 2018.

Study Design

A Retrospective hospital based study design was used to determine magnitude of virology failure and describe agreement between diagnostic criteria of treatment failure, clinical-immunology and virology, among HIV positive adults enrolled to ART program at Commandment Hospitals quantitative data archived at facility ART data base and Treatment Failure Screening Sheet (TFSS) of the treatment failure data base (Appendix -1) was abstracted using data abstraction tools (Appendix -2).

Population

Source of Population

The source population constitutes all HIV positive adults enrolled to ART program at five Commandment Hospitals.

Study Population

All HIV positive adults who are on first line ART for at least six months and diagnosed to have treatment failure at commandment hospitals.

Inclusion and Exclusion Criteria

Inclusion Criteria

All HIV positive adults >15 years who were enrolled in first line HAART and who attended the clinic for routine visits, followed the treatment for at least six months and treatment failure is diagnosed on grounds of clinical or immunologic and virology criteria during the study period was included.

Exclusion Criteria

All HIV positive adults on second line treatment and on first line treatment followed the HAART for less than six months and those patients having Acute Febrile Illness (AFIs) which can increase viral load falsely and when criteria to diagnose treatment failure is not available on medical records. This includes clinical or WHO criteria, immunology or CD4 and HIV viral load test was excluded from this study.

Sample Size and Sampling Technique

Secondary data of all adults who are on first line ART for at least six months and diagnosed to have treatment failure at commandment hospitals was included when they meet inclusion criteria listed below.

Data Collection Tools and Technique

Secondary information was collected from ART data base and medical records of TF cohort patients' using a pre-tested data abstraction form (Appendix -2). Electronic ART records was accessed to collect the following information: Socio-demographic information such as age, gender, residence and marital status, Clinical and treatment information such as previous ART experience, body weight, duration of use of ART, clinical (WHO stage), ART regimen, adherence level, functional status, Laboratory information such as CD4 count and HIV viral load test and ART program monitoring information such as number of HIV positive adults ever enrolled, currently on ART.

Study variables

Dependent Variable

Treatment failure (TF)

Independent Variables

Socio-demographic factors such as age, gender, residence and marital status.

Clinical and treatment factors such as previous ART experience, body weight, duration of use of ART, clinical (WHO stage), ART regimen, adherence level, pill burden, functional status, Laboratory information such as CD4 count and HIV viral load test and ART program monitoring information such as number of HIV positive adults ever enrolled, currently on ART.

Operational Definitions

Clinical Failure

New or recurrent WHO stage 4 condition excluding Immune Reconstitution Inflammatory Syndrome and clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, esophageal candidiasis and recurrent bacterial pneumonia [13].

Immunologic Failure

In the absence of concomitant infection that may cause transient decline in CD4 count, presence of one of the following defines immunologic failure [13].

1. Fall of CD4 count to pre-therapy baseline (or below)
2. 50% fall from the on-treatment peak value (if known)
3. Persistent CD4 levels below 100 cells/MM3 for >12 months

Virology Failure: Plasma viral load level of over 1,000 copies/ ml in duplicate tests and after six months on ART [13].

Treatment Failure

A person who fulfils a Clinical or Immunologic or virology criteria or combination of any of the above:

First line ART: The ART regimen initially started based on national guideline [13].

Second line ART: ART regimen switched from first line on grounds of treatment failure.

Substitution: Changing an antiretroviral drug at a time due to reasons such as side effect or potential drug-drug interaction.

Switching Therapy: Changing two or more ARVs due to treatment failure

Data quality assurance

The data abstraction form was pre-tested at F.D.R.E Air force hospital. Two nurses from each hospital experienced in HIV care was create a unique study code for each eligible patient medical record. This unique study identification code was linked to the patient identification (UAN and MRN/HMIS number) and saved in a separate paper-based or electronic file that was remain in the facility.

For this study, the study-specific patient information was linked to the unique study code.
Two nurses from each hospital experienced in HIV care was recruited to collect data and trained on how to abstract data from, objectives of study and ethical principles of a study. An experienced physician was supervise data abstraction and check for data completeness, clarity and accuracy.

The data was entered into an EPI data database prepared for this study with in-built validity checks. Frequencies of selected study variables were used to assess the completeness of the data. Additionally, 10% of the data was double entered for quality check. The raw dataset was cleaned and prepared for analyses.

The completed data abstraction forms was stored in a locked file cabinet at Research and development center and Electronic files was saved on password-protected computers installed at data rooms in same facility. Only members of the study team were access and manage the electronic files to assure quality of stored data and prevent breach of confidentiality with analysts accessing files on an as-needed basis.

At a minimum, the data was stored until the final analysis and dissemination on the study were complete. Principal investigators was follow the recommendations of appropriate IRB for the duration of storage of all hard copy and electronic records (tentatively for 3 years after the completion of the analysis), as well as for the method of eventual destruction of data including the shredding of any original paper-based information and systematic deletion of original data files. Investigators will take responsibility for managing and storing the aggregated data to be used within this study protocol.

Data Processing and Analysis Procedure

Data abstracted from patient charts or electronic data base was cleaned, coded, entered and analysed using EPI INFO version 3.5.3 and SPSS version 21 statistical software package.

Frequency, percentage and tables were used to present results. Descriptive statistics including counts, percentages, medians, ranges, means, and standard deviations was calculated. Proportion of virology treatment failure cases among those diagnosed to have treatment failure was calculated. Continuous variables were compared using the Wilcoxon rank-sum test; while categorical and dichotomous variables were compared using the chi-square test and Fishers exact tests, as appropriate. Association between the outcome and the independent variables was taken as significant at $P<0.05$ (2 tail test) and 95% confidence intervals (CIs).

Ethical Consideration

The study was conducted after getting ethical approval from IRB of Defence University College of Health Science; Military hospital was communicated through written paper obtained from DUCHS and permission was obtained from the administrator of the hospitals. As indicated above, data collected for the purpose of this study do not include patient identifying information. Study was only use HIV program information that is documented or collected systematically for the purpose of monitoring HIV program at commandment hospitals.

Data collectors were trained on research ethical principles, confidentiality and accuracy of data before data is abstracted from ART registers or data base. Investigators and supervisors will assure confidentiality and privacy of data processed in this study.

Consent and Recruitment

Written consent was obtained from the health facility to access patient medical records. The consent form to abstract secondary patient information is annexed (Appendix 3).

The consent form was prepared in simple English and explains purpose of the study; intended use of the study findings, potential risks and benefits, and provides assurance of confidentiality. Further the consent forms will explain the meaning of participation; that participation is completely voluntary, and that health facility reserves the right to withdraw at any time and with no consequences. The study team will adhere to ethical principles and the protocol. Should there be any question or concerns as to any ethical procedures; the participant institution has a right to terminate its participation or contact study contact person. No patient's was interviewed nor asked to present to health facility for the purpose of this study.

This study will not gather data from vulnerable populations.

Confidentiality

The study will proceed with appropriate ethical clearances. Principal investigators are certified in human subjects' protection training and train staffs involved during data collection and analyses on human subjects' protection and in the conduct of study procedures.

This training will include methods for obtaining informed consent, stressing the importance of voluntary participation. This training will use modelling, problem solving and practice on interviews. All persons involved in the study will respect participants, cultures, values and beliefs from initial contact to dissemination of study findings. All secondary data from patient charts and electronic

records was de-identified during abstraction and the de-identified data was used for data analysis.

Any participant identifying information such as UAN and MRN/HMIS number was kept separately from the study data set. The presentation of results will ensure that findings cannot be linked to specific individuals. Facility-specific findings will only be shared with that specific facility.

All electronic files were saved on a password-protected computer. Following analysis, reports, manuscripts and presentations will contain aggregated information so as to avoid breach in confidentiality of individual patient data. Principal investigators will retain the password protected data and information for no more than three years after analysis or publications and will not use these beyond the scope of the study.

Handling of unexpected or adverse events: All cases that may warrant immediate attention by clinicians during review of medical records or data analysis was linked to HIV clinic. Examples of unexpected events may include detectable HIV viral load or incorrect medication. For this purpose, the one file linking patient medical record number (UAN or MRN/HMIS number) to the study code was accessed by HIV clinic staff to retrieve patient charts.

Dissemination of the Result

The result of the current study will be submitted to Defence University, College of Health Sciences, Defence Health Main Directorate, and Ethiopia Military hospitals. The result of this research will be also published on reputable journals which will disseminate the existing condition concerning treatment failure of HIV adult patients in ART service at military hospitals.

Result

Socio-Demographic Characteristics

A total of 326 study participants were enrolled in this study. The mean age of the study participant was 36.84 years (sd+7.716) and 83(34.9%), 79(33.2%) and 76(31.9%) fall in 1age categories of 36 to 45 years, 26 to 35 years and 18 to 25 years respectively.

More than half of the study participants, 229(70.2%) were males. Among the study participants, 303(92.9%) were from urban setting and 234(71.8%) of the participants were married. Regarding the educational level of study participants, 132(40.5%) attended elementary school and 118(36.2%) were attended their secondary school and occupation of the soldiers were private soldiers (Table 1).

Table 1: Socio-demographic characteristics (N=326)

Variables	Category	Number	Percent (%)
Age	15-25	24	7.4
	26-35	124	38
	36-45	136	41.7
	>46	42	12.9
	Total	326	100
Sex	Male	229	70.2
	Female	97	29.8
	Total	326	100
Residence	Urban	303	92.9
	Rural	23	7.1
Marital status	Single	51	15.6
	Married	234	71.8
	Separated	7	2.1
	Divorced	27	8.3
	Widow/Widowed	7	2.1
Educational status	Not literate	21	6.4
	Primary	132	40.5
	Secondary	118	36.2
	Tertiary	55	16.9
	Health professional	8	2.5
	House wife	61	18.7
	Driver	19	5.8
	Retired/Board	104	31.9
	Private soldiers	134	41.1

Baseline Clinical and Immunologic Characteristics

The mean CD4 count at ART initiation was 213.3 cells/ µl (range 1–851 cells/ µl) and half of the CD4 184(56.4%) falls on between 101-350 cells/ul. Almost half of study participants, 162(49.7%) had suffered an AIDS defining illness (clinical status) i.e. WHO stages III and IV conditions at the time of ART initiation. The proportion of participants who commenced HAART after developing signs or symptoms suggestive of mild immunosuppression (WHO stage II) and with no sign and symptom (WHO stage I) was more than half 164(50.3%).

Opportunistic infections are the most dominant diseases in HIV/AIDS. Out of 326 study participants, documented opportunistic infections were 15(4.5%) starting from HAART initiation. Regarding immunological criteria almost all of the participants increase their CD4 count from baseline 306(93.9) and most of study participants have got IPT 265(81.3) with first cycle 105(32.2) (table 2).

Types of ARV First Line Regimen during Initiation

During treatment initiation, different types of first line (initial regimen) HAART drugs were used as choice of treatment for adults living with HIV/AIDS. Having this point, d4T based regimen contained NNRTIs of both NVP (d4T/3TC/NVP) and EFV (d4T/3TC/EFV) were 36(11) and 20(6.1) respectively.

Similarly, the AZT based regimen was highest into AZT/3TC/NVP and AZT/3TC/EFV 58(17.8). On the other hand TDF based regimens consisted of TDF/3TC/EFV and TDF/3TC/NVP were 184(56.4) and 10(3.1) respectively (Table 2).

Regarding treatment regimen change, only 81(24.8%) study participants received a substitution while they were on first line regimen. Out of the total substitutions, AZT based substitution was 69(69.7%) followed by TDF 15(15.2%) and D4T 15(15.1%) respectively.

During study time the current first line HAART regimen, out of 326 participants, 194(59.5) were following TDF based regimen while 76(24.3%) were following AZT based regimen.

The rest 22(8.2%) were following D4T based regimen were considered as current regimen. About 15(4.5%) of the participants in first line regimen had had documented opportunistic infection throughout the HAART treatment course (Table 2).

Table 2: Baseline clinical and immunologic characteristic (N= 326)

	Category	Frequency (%)
Immunological criteria	Current CD4 count decreased from baseline	4 (1.2)
	Decreased by 50% from peak CD4 value	7 (2.1)
	Persistently below 100 for 12 month	5 (1.5)
	Constant CD4 count	4 (1.2)
	Increase CD4 from baseline	306 (93.9)
	Total	**326(100)**
Have patient got Treatment Failure	Yes	22(6.7)
	No	304 (93.3)
	Total	**326(100)**
Have patient got IPT	Yes	265 (81.3)
	No	61(18.7)
	Total	**326(100)**
IPT cycles	Fist cycle	105(32.2)
	Second cycle	12(3.7)
	Third cycle	209(64.1)
	Total	**326(100)**
T-stage	T1	310(95.1)
	T2	10(3.1)
	T3	5(1.5)
	T4	1(0.3)
	Total	**326(100)**
Duration of ART	Less than 5 years	67(20.6)
	Greater than or equal to 5 years	259(79.4)
	Total	**326(1000)**
Base line body weight	<50	105 (32.2)
	50-75	202 (62.0)
	76-100	**19(5.8)**
Current Body weight	<50	53(16.3)
	50-75	226(69.3)
	76-100	**47(14.4)**
Baseline first line HAART regimen	D4T/3TC/NVP	36 (11)
	D4T/3TC/EFV	20 (6.1)
	AZT/3TC/NVP	58(17.8)
	AZT/3TC/EFV	18 (5.5)
	TDF/3TC/NVP	184 (56.4)
	TDF/3TC/EFV	10 (3.1)
	Total	**326(100)**
Currently first line HAART	D4T/3TC/NVP	2 (11)
	D4T/3TC/EFV	20 (6.1)
	AZT/3TC/NVP	58(17.8)
	AZT/3TC/EFV	18 (5.5)
	TDF/3TC/EFV	184 (56.4)
	TDF/3TC/NVP	10 (3.1)
	Total	**326 (100)**
Baseline CD4 results	≤ 100	100(30.7%)
	101-350	184(56.4%)
	351-500	26(8.0%)
	≥501	16(4.9%)
	Total	**326(100)**
Baseline WHO stages	I -II	164(50.3%)
	III- IV	162(49.7%)
	Total	326 (100%)
Baseline patient functional status	Ambulatory	3(0.9%)
	Working	323(99.1%)
	Total	**326(100%)**
Documented Opportunistic infections	Yes	15(4.5%)
	No	311(95.5%)
	Total	**326(100%)**
Drug substitution/ change/switch	Yes	81(24.8%)
	No	245(75.2%)
	Total	**326(100%)**

Prevalence Clinical, Immunologic and Virologic Failures

Clinical Failure

WHO stages I (no AIDS case) and II (mild AIDS case) were almost more than half of the clinical presentations 164(50.3%) participants. One hundred sixty two (49.7%) of participants were at stage III and V (Table 3).

Immunologic Failure

Quantitative restoration of CD4+ T cells is one of the principal evidences for immune recovery during HAART. Out of 326 study participants, 75(23%) encountered total treatment failure in which 50(66.7%) and 16(21.3%) were Immunological and all three common (VF, IM and CF) respectively. Over time analysis of immunologic failure has shown that 47 (94%) study participants encountered immunological failure greater than or equal to five years while 15(22.4%) less than five years (Tables 3 and 4).

Virologic Failure

During the study period, out of 326 study participants in first line HAART regimen, prevalence of virologic failure (≥1000 RNA copies per ml) was found to be 2.1% (7/326); out of seven6 (1.8%) males. Since the start of HAART, out of the total study participants, 7(9.3%) of them encountered virological failure greater than or equal to five years (Table 3).

Treatment Failure

In detecting treatment failure in HAART, clinical, immunologic and virologic failures are important. Generally, the prevalence of treatment failures were 75(23%), out of these treatment failure

7(9.3%), 50(66.7%), 2(2.7%) and 16(21.3) of them encountered virologic failure, immunologic failure, clinical failure and common failures respectively. The mean of months on which they were on HAART was 83.16 months and the median time was 81.5 months with a standard deviation of 31. 75 with a maximum of 176 months (14 years).The median time from HAART initiation to identification of treatment failure was 47 months for virologic failure and 63 months for immunologic failure. Moreover, the backbone of treatments which showed treatment failure of AZT/3CT/NVP and AZT/3CT/EFV was 76(23.3%) and TDF/3CT/NVP and TDF/3CT/EFV was 194 (59.5%) (Table 3).

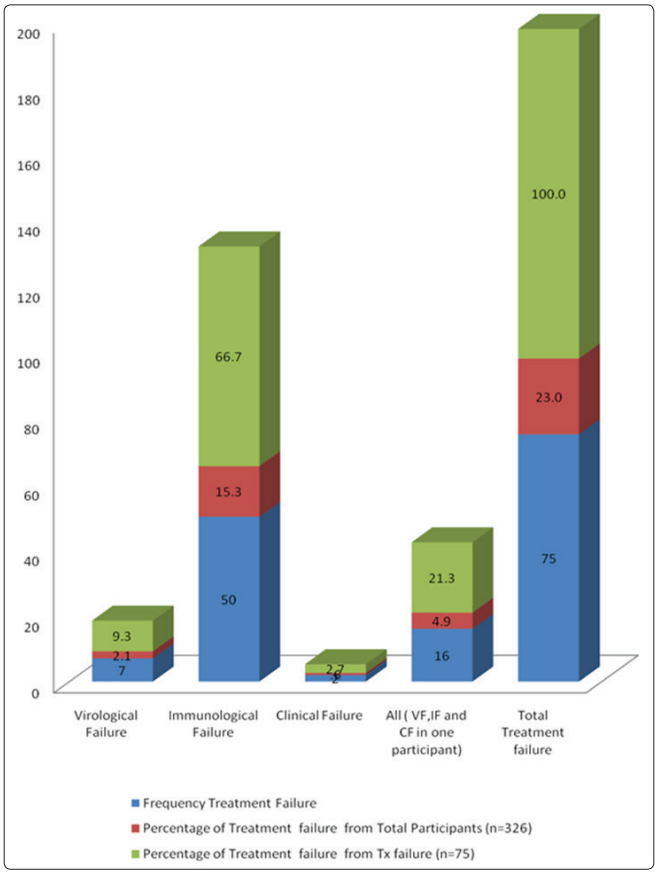

Figure 1: Types of Treatment Failure

Table 3: Treatment Failure after Initiation of HAART in HIV/AIDS Patients (N=326)

	Categories	Frequency (%)
Presence of treatment failure	Yes	75(23%)
	No	251(77%)
Clinical failure	Yes	2(0.6%)
	No	324 (99.4%)
Immunologic failure	Yes	50(15.3%)
	No	276(84.7%)
Virologic failure	Yes	7(2.1%)
	No	319(97.9%)
All Treatment failure (VF,IF&CF in one)	Yes	16(4.9%)
	No	310(95.1%)
Years from ART initiation	<=5 years	67(20.6%)
	>5 years	259(79.4%)
First line HAART regimen	D4T/3TC/NVP	36 (11%)
	D4T/3TC/EFV	20 (6.1%)
	AZT/3TC/NVP	58(17.8%)
	AZT/3TC/EFV	18 (5.5%)
	TDF/3TC/NVP	184 (56.4%)
	TDF/3TC/EFV	10 (3.1%)
Has the patient been on Second line ART	Yes	17(5.2%)
	No	309(94.4%)

Performance Characteristics of Clinical and Immunologic Failures in Prediction of Virologic Failure

In this study, by ROC curve analysis the area under the curve (AUC) was 0.759 (95% CI: 0.672-0.847) (Figure 2). Immunologic failure had fair predictive values to virologic failure. Sensitivity of immunologic failure compared to the golden standard, virologic failure, was 62.2% whereas the specificity of immunologic failure was 89.6%. Positive predictive value (PPV) was 41.8% and Negative predictive value (NPV) was 95.2% (Table 4).

ROC curve analysis of clinical failure showed that the area under the curve was 0.484 (95% CI: 0.393-0.576). This area indicated that clinical failure was less predictive of the occurrence of virologic failure. The performance of clinical failure to identify treatment failure, sensitivity was 17.8%, specificity was 89.3%, positive predictive value was (17.0%) and negative predictive value was (90.1%) (Table 4).

Table 4: Performance Characteristics of Clinical and Immunologic Failures in Predicting Virologic Failure

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Clinical failure	17.8	89.3	17.0	90.1
Immunologic failure	62.2	89.6	41.8	95.2

Determinant Factors of HIV/AIDS Treatment Failure among Patients on First Line HAART

Bi-Variate Logistic Regression Analysis

Using bi-variate logistic regression, association was assessed between age, gender, Residence educational status, previous ART exposure, drug adherence, WHO clinical stage, documented opportunistic infections, IPT, CPT, CD4 baseline, immunologic failure, duration of treatment, baseline patient functional status, regimen substitutes, baseline regimen, 1st line current regimen with virological failure at various intervals. In this analysis, different criteria were checked like crude odds ratio and p-value for multiple logistic regression analysis consideration.

Therefore, ART duration, IPT cycles, Suspected Treatment failure, WHO clinical stage, ART drug adherence, Original first line ART, current body weight, PEP, duration of treatment and Lost to follow up were entered to analysis (Table 6 and 7).

The bi-variate associations were observed without controlling the effect of other confounding factors it is very difficult to conclude whether the observed statistically significant association was because of the existing causal relationship between the given independent variables and the treatment failure. Since both the dependent and independent variable coded to dichotomous and multiple logistic regression analysis was used to confirm the independent associations.

Table 6: Bi-Variate Logistic Regression Analysis of Socio Demographic Associated Factors with Virological Failure

Variables	Categories	All (n=326)	TF (n=75)	Odds Ratio (OR, 95% CI)	P-value
Gender	Female	97	19	1	1
	Male	229	56	0.898 (0.436-1.775)	0.893
Age group	15-45	284	67	0.679 (0.307-1.49)	0.350
	>45	24	8	1	1
Residence	Urban	303	72	1	1
	Rural	23	3	1.730 (0.399-7.517)	0.465
Educational status	Iterate	21	5	0.491 (0.18-1.336)	0.164
	Elementary	132	40	0.751 (0.471-1.934)	0.473
	secondary	118	20	1.282 (0.355-5.22)	0.336
	Tertiary	55	10	1	1

Table 7: Bi-Variate Logistic Regression Analysis of Clinical Associated Factors with Virologic Failure

Variables	Categories	All (n=326)	TF(n=75)	Odds Ratio (OR,95% CI)	P-value
Suspected treatment (ITFS)	Yes	34	20	0.163 (0.078-0.343)	0.000
	No	291	55	1	1
Duration of ART treatment	<5 years	67	5	1	1
	<= 5 years	259	70	4.593 (1.773-11.894)	0.002
ART Drug adherence	Good Adherence	316	69	1	1
	Poor adherence	10	6	0.186 (0.051-0.679)	0.011
IPT cycles	First Cycle	105	13	2.784 (1.447-5.354	0.002
	Second Cycle	12	3	1.180 (0.309-4.511)	0.809
	Third cycles	209	59	1	1
Types of drugs	AZT based	132	46	0.329 (0.193-0.560)	0.000
	TDF based	194	29	1	1
WHO clinical stage	I-II	164	26	1	1
	III-IV	162	49	2.302 (1.364-3.936)	0.002
Experience on PEP	Yes	30	1	10.045 (1.346-74.0947)	0.024
	No	295	74	1	1
Lost to follow up	Yes	25	16	7.292 (3.071-17.315)	0.000
	No	301	59	1	1

Multiple Logistic Regression Analyses

Multiple logistic regression analyses there were statistical significant associations between the following factors and treatment failure: Suspected Treatment failure, duration of ART, IPT Cycles, and types of first line ART drugs, experience to PEP, and lost to follow up were significantly associated with treatment failure with P-value (P<=0.05). However, there were no statistical significance associations (p> 0.05) between, ages, gender, residence, educational status, WHO Clinical Stage, adherence to ART during the study period with treatment failure.

In this study, long duration (years) on treatment was independent predictor to treatment failure. Long duration on HAART treatment greater than five years was strong risk factor for treatment failure/ Virologic failure as the patients with long time on first line HAART treatment (adjusted odds ratio= 4.231, 95% CI: (1.453-12.320) were 4.231 times more likely to have treatment failure when compared to patients with short duration on treatment less than five years with p-value 0.008* (Table 9).

Isoniazid preventive therapy (IPT) was defined as effective and safe prevention of tuberculosis (TB) in people living with HIV and treatment of latent TB infection. IPT has three cycles to complete the therapy. These are first cycle, second cycle and third cycles. IPT first cycle was independently associated risk factor of treatment failure as patients with incomplete two left cycles (adjusted odds ratio=3.060, 95% CI: (1.388-6.746)) were 3 times more likely risk of treatment failure when compared patients whose completed IPT third cycle with P-value 0.006. Similarly when compared patients who were taking AZT based therapy (adjusted odds ratio=2.572, 95% CI: 1.357-4.875) and these patients who were taking TDF based therapy were 2.572 times more risky to develop and associated with higher risk of treatment failure (Table 9).

Based on WHO criteria, experience of Post exposure prophylaxis (PEP) was assessed and checked whether had associated with treatment/virologic failure and found to be significant predictor of the presence of treatment failure/virologic failure. Experience of Post exposure prophylaxis (PEP) was high risk factor for treatment/ virologic failure as the patients with without experience of PEP (adjusted odds ratio= 7.950, 95% CI: 1.945-66.915) were 7.950 times more likely to have treatment/virologic failure when compared to the patients who had not experienced PEP. Similarly lost to follow up was high risk to develop treatment failure when compared to patients without lost to follow-up?

High lost to follow up was associated risk factor for developing treatment failure as the patients were lost their medication for at least a month (Adjusted odds ratio=9.104, 95% CI: 2.973-27.873) were 9.104 times more risky when compared to the patients who these without lost to follow (Table 9).

Table 8: Multiple Logistic Regression Analysis of Socio Demographic Associated Factors with Virologic Failure

Variables	Categories	All (n=326)	TF (n=75)	Crude Odds Ratio (COR, 95% CI)	P-value	Adjusted Odds Ratio AOR(95% CI)	P-value
Gender	Female	97	19	1	1	1	1
	Male	229	56	0.898 (0.436-1.775)	0.893	1.232 (0.504-3.520)	0.340
Age group	15-45	284	67	0.679 (0.307-1.49)	0.350	3.161 (0.523-12.031)	0.454
	>45	24	8	1	1	1	1
Residence	Urban	303	72	1	1	1	1
	Rural	23	3	1.730 (0.399-7.517)	0.465	0.493 (0.241-2.588)	0.239
Educational status	Iterate	21	5	0.491 (0.18-1.336)	0.164	1.746 (0.225-9.473)	0.119
	Elementary	132	40	0.751 (0.471-1.934)	0.473	1.865 (1.699-11.792)	0.352
	secondary	118	20	1.282 (0.355-5.22)	0.336	3.972 (2.185-8.455)	0.534
	Tertiary	55	10	1	1	1	1

Table 9: Multiple Logistic Regression Analysis of Clinical Associated Factors of Virologic Failure

Variables	Categories	All (n=326)	TF(n=75)	Crude Odds Ratio (OR,95% CI)	P-value	Adjusted Odds Ratio AOR(95% CI)	P-value
Suspected treatment (ITFS)	Yes	34	20	0.163 (0.078-0.343)		6.017(2.482-14.590)	0.000*
	No	291	55	1	1	1	1
Duration of ART treatment	<5 years	67	5	1	1	1	1
	<= 5 years	259	70	4.593 (1.773-11.894)	0.002	4.231(1.453-12.320	0.008*
ART Drug adherence	Good Adherence	316	69	1	1	1	1
	Poor adherence	10	6	0.186 (0.051-0.679)	0.011	0.851(0.152-1.543)	0.201
IPT cycles	First Cycle	105	13	2.784 (1.447-5.354	0.002	3.060(1.388-6.746)	0.006*
	Second Cycle	12	3	1.180 (0.309-4.511)	0.809	2.821 (0.507-15.68)	0.236
	Third cycles	209	59	1	1	1	1
Types of drugs	AZT based	132	46	0.329 (0.193-0.560)	0.000	2.572(1.357-4.875)	0.004*
	TDF based	194	29	1	1	1	1
WHO clinical stage	I-II	164	26	1	1	1	1
	III-IV	162	49	2.302 (1.364-3.936)	0.002	3.212(1.452-4.782)	0.163
Experience on PEP	Yes	30	1	10.045 (1.346-74.0947)	0.024	7.950 (0.945-66.915)	0.056
	No	295	74	1	1	1	1
Lost to follow up	Yes	25	16	7.292 (3.071-17.315)	0.000	9.104(2.973-27.873)	0.000*
	No	301	59	1	1	1	1

Discussion

As HAART continues to be scaled up in Ethiopia especially in military set up, with more Primary Health Care (PHC) facilities providing ART services, increasingly more efforts and resources need to be directed at ensuring that patients who continue to enrol at these facilities receive quality care to optimize their health. This particular study was designed to identify treatment outcomes, mainly virologic failure, as a way to assess programme performance at ART facility in ministry of defence.

Virologic failure is a golden standard for detecting treatment failure in HAART. Prevalence of treatment failure was 23% (75/326) among the study participants. The mean and median time on treatment was 83.16 and 81.50 months which signifies high suppression rate 97.7% (viral load below detection limit). There is a possibility of improving the suppression rate near to 100% by providing an efficient early HAART service such as letting patients to commence ARV early and ensuring adherence of patients to treatment. Similar study conducted from Cameron reported as (23.2%) and also from costal Kenya (24%) which is comparable to the result of the present study [19,20]. Compared to other study in Uganda reported prevalence of treatment failure 9.9% this study revealed a lower prevalence of treatment failure than the present study [21]. The probable reason for the same prevalence of treatment failure in the present study might be that the great majority 303(92.9%) of participants being urban dwellers which gives them an advantage over the rural dwellers in getting information from a number of media and easily accessible to health facilities.

It is also possible that the existence of nearby ART clinic which is at a distance of 10 km, on average, might give the chance the urban dwellers to frequently visit the clinic for further information. The present study, however, showed higher treatment failure rate compared with 4.1% which was reported from Gondar [22]. The higher prevalence in the present study might be because of poor adherence and high duration on treatment that could possibly increase treatment failure.

In treatment failure, viral load criteria identified failure significantly earlier (median, 47.0 months; $p<0.001$) than did CD4 count criteria (median, 60.0 months). In this survival analysis, time to failure is compared between immunologic and virologic monitoring methods among the entire 326 participants. The present study indicated a higher time to failure (97 months) compared to a median time of 15 months which was reported from South Africa, 24 months from Cameron, 24 months from Gondar, Ethiopia, 19.7 months from Addis Ababa, Ethiopia [19,23-25]. Interestingly, as duration on HAART increased, drug failure increased especially in long duration of 73-158 months treatment. This is, however, independently associated with treatment failure.

A similar study conducted in Cameron showed long time duration of treatment to be one of determinant factors for treatment failure and this particular factor, long duration on treatment, for example, for above 60 months among patients in Gondar, Ethiopia, was found to be an independent predictor for an increased risk of HIV treatment failure [24,26].

Using multivariate logistic regression, there was an association between treatment failure and the following factors: long duration of treatment (73-176 months, $p<0.05$), Suspected on HAART treatment, duration on HAART, IPT cycle, Type of HAART regimen, experience of PEP and lost to follow up. However, there was no statistical significant association ($p> 0.05$) between treatment failure and the following factors: educational status, CPT, Documented Opportunistic infection, CD4 baseline, base line regimen, and regimen substitutes.

Before patients commence HAART, it is essential that they should be adequately prepared for this life-long drug therapy. HAART treatment necessitates a change in life style and social habits. Poor patient treatment follow up may lead to poor drug adherence by patients, increasing the likelihood of treatment failure. A similar study in South Africa has shown that incomplete adherence as one of the risk factors for treatment failure [23]. Similarly, a study in Kenya has shown that unsatisfactory adherence to have strong correlation with virologic failure [20]. In Gondar, Ethiopia, poor adherence during follow up has been shown to be associated with treatment failure [24].

Experience of PEP and Lost to follow up were associated factor to treatment failure and in line with study done in Addis Ababa, Ethiopia [27,28]. In the present study, AZT drug regimen currently taken by patients, and suspected treatment failure were the factors that were associated with treatment failure/virologic failure [29].

Limitation: Viral load was done only once at cut off value >1000 RNA copies/ml due to machine shortage and lack of trained manpower. Consequently, there may be missed classification of HIV treatment failure as of not repeated after three months according to WHO point of care standard. Retrospective study did not show the current situations.

Conclusion

The present study reported moderate prevalence of treatment failure and needs attention. Viral load testing is best in early detection of treatment failure than CD4 T cells count and should be used in a routine ART laboratory. Both clinical and immunologic failures did not complement each other to predict virologic failure. Nevertheless, immunologic failure in the present study was found to be fair in predicting treatment failure compared to other studies. Furthermore, the present study showed that long duration of treatment, suspected treatment failure, IPT cycles, Type of HAART regimen, and experience on PEP and lost to follow up to be determinant factors of treatment failure/virologic failure.

Recommendations

Based on the findings of the present study, the following are recommended.

- ✓ Follow up of IPT cycles is very curial in order to minimize the treatment.
- ✓ Select the right Type of HAART drug /regimen / according to HIV Guideline in take
- ✓ After confirming the HIV positive status, the onset of treatment should quick and the patients should be followed to detect any suspected treatment failure to improve HAART service.
- ✓ Duration of time on first line HAART should be checked frequently to protect unnecessary drugs (failed treatment) and early switch to second line HAART is important.
- ✓ Early suspected treatment failure and other risk factors should be monitored regularly as per the HIV treatment guidelines.
- ✓ Restrict follow the patients and get contacts so as to avoid lost to follow
- ✓ Avoiding delays in ART initiation, reinforcing adherence interventions, developing and widely implementing affordable viral load test monitoring is important.

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