ORIGINAL PAPER

First-line antiretroviral treatment failure and associated factors in HIV patients following highly active antiretroviral therapy at the Shashemene Referral Hospital, Oromia region, Ethiopia

Hunduma Dinsa Ayeno, Ahmedyasin Abdi Imer

Department of Pharmacy, College of Medicine and Health Sciences, Ambo University, Ambo, Ethiopia

Abstract

Introduction: Highly active antiretroviral therapy (HAART) restores immune function and reduces human immunodeficiency virus (HIV)-related adverse outcomes. However, treatment failure erodes this advantage and leads to an increased morbidity and compromised quality of life in HIV patients. The purpose of this study was to assess prevalence of first-line antiretroviral treatment failure and factor associated with treatment failure following antiretroviral therapy at the Shashemene Referral Hospital.

Material and methods: This was a retrospective cross-sectional study with first-line HAART failure card review and it was carried out at HAART clinic of the Shashemene Referral Hospital. The study included 69 HIV-positive patients who had started HAART between 2013 and January 6, 2016.

Results: The study showed that out of 69 study participants, 10 (14.5%) patients developed treatment failure, and among them, an immunologic failure occurred in 6 patients (60%), virologic failure was detected in 2 cases (20%), and clinical failure occurred in 1 patient (10%). Using multivariate logistic regression analysis, advanced World Health Organization (WHO) stage four (AOR = 47.6; 95% CI: 2.3-552.4) and good adherence (AOR = 0.094; 95% CI: 0.014-0.610) had significant negative association with treatment failure.

Conclusions: The overall first-line treatment failure rate was 14.5% (10 patients). Prevention and control of the development of advanced World Health Organization (WHO) stage, improving adherence, promotion of HAART initiation at active functional status and higher CD4 count, prevention of multiple or many opportunistic infections were the primary conclusions of our study.

Address for correspondence: Hunduma Dinsa Ayeno, Department of Pharmacy, College of Medicine and Health Sciences, Ambo University, Ambo, Ethiopia, e-mail: dhunduma@gmail.com

International Journal of HIV-Related Problems
HIV & AIDS Review

Introduction

The Joint United Nations Program (UNAIDS) on human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) projected that the number of people living with HIV has increased from 33.3 million in 2009 to over 34 million in 2010 [1]. HIV is a global public health problem significantly affecting the sub-Saharan region, including Ethiopia. It is the leading cause of death in sub-Saharan Africa. Approximately, between 22 and 28.5 million Africans are living with HIV and AIDS, with 2.4 to 3.4 million new infections occurring in 2006 [2].

HIV remains to have a significant damaging effect on many countries. Young people of working age are the most affected; therefore, HIV substantially hinders the economic development of some of the poorest countries in the world and has left millions of children without parents. Treatment for HIV is known as highly activated antiretroviral therapy (HAART) and it prevents HIV replicating, restoring patient's immunity, and therefore their health. With this treatment, patients can lead normal, productive lives [3]. After more than ten years of use, HAART treatment's effect has been documented in all of the World Health Organization (WHO) European region countries, reporting an increased survival, decreased HIV-associated mortality, and vastly improved quality of life among HIV-positive people. By the end of 2002, around 242,000 patients have been receiving HAART in the European region, including 7,000 in Central and Eastern Europe. By the end of 2007, about 435,000 patients have been on HAART in Europe, including 55,000 in Central and Eastern Europe. By mid-2007, HAART have been available in the public sector health services in every country of the region, except Turkmenistan, with a coverage estimated as very high (more than 75% of those in need of treatment) in at least 38 out of 53 Members of States [4].

Global HAART treatment for all individuals living with HIV had reached approximately 41% of people (15 million) by March 2015 [5]. Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of treatment failure (inability to suppress HIV viral replication to below current limit of detection, 50 copies/ml), toxic effects, or non-compliance within the first 8 months of therapy [6].

Treatment failure may be classified as virological, immunological, and clinical failure. Virological failure is defined as an increase of more than 1,000 copies of RNA/ml or the re-appearance of a signal after a period, during which it has been undetectable. WHO defines immunological failure as a decline trend in CD4 T cells count despite 6 months of treatment, or a failure to increase the CD4 T cells counts above 100 cells/mm³ after 12 months of treatment. Clinical failure is defined by the WHO as the appearance of any morbidity associated to category 4, despite 6 months of treatment [7].

Treatment failure is considered when HAART cannot control HIV infection due to poor adherence to HAART, drug resistance, poor absorption of drugs, inadequate dosing, and drug-drug interaction [8]. Immunologic failure is described as a return of CD4 cell count to or below pre-therapy baseline level and 50% decline from on-therapy CD4 cell peak level. Clinical failure is characterized by an occurrence or re-occurrence of opportunistic infection or malignancy signifying clinical disease progression. Virologic failure is considered when viral load is not suppressed to undetectable levels (< 400 copies/ml) after 6 months on HAART, and viral load not suppressed to undetectable levels (< 50 copies/ml) after 12 months on HAART [9].

Socio-demographic, clinical, immunologic/virologic factors, and poor adherence to treatment have been shown to be associated with ARV treatment failure in children. Also, ARV drug resistance is another factor. In children, first-line HAART failure rate was reported as 2.3% in Burkina Faso (with a mortality rate of 25% in these children), less than 1% in Rwanda, and 5.8% in South Africa [10]. Because of recent data suggesting that up to 16% of treatment-naïve patients have an evidence of antiretroviral resistance, guidelines recommend genotypic resistance testing prior to initiation of antiretroviral therapy [11]. HIV treatment failure is both clinical and public health concern, because if treatment failure issue is left unsolved, there may be development of a drug-resistant virus, which is a tremendous threat to the entire world. Therefore, the aim of this study was to assess the prevalence of first-line antiretroviral treatment failure and factors associated with first-line treatment failure at the Shashemene Referral Hospital.

Material and methods

Study area and period

This study was conducted at the Shashemene Referral Hospital, HAART clinic, in Kuyera town, Oromiya region, Ethiopia. The hospital offers different types of services, including outpatient department service with ophthalmology, dental clinic, epilepsy and psychiatry, obstetrics and gynecology, emergency outpatient department, gynecology outpatient department, and HAART clinic. Inpatient services consist of pediatrics ward, medical ward, surgical ward, leprosy ward, obstetrics and gynecology ward, and tuberculosis and leprosis ward. Pharmacy services are given to OPD and HAART patients. The HAART clinic was established in1995, and there were a total of 9,390 patients started HAART since its initiation, with a total of 2,282 of currently active patients. The study was conducted from 10 January to 6 June 2017.

Study design, source, and sample population

The was a retrospective cross-sectional study, which involved card review of HIV patients on follow-up from 2013 till June 6, 2017 at HAART clinic of the Shashemene Referral Hospital. The source population included all HIV-positive patients who attended HAART clinic of the Shashemene Refer-

ral Hospital from June 6, 2013 till 2016 and fulfilled inclusion criteria of the study. The sample population included HIV patients' files, which were available during data collection period.

Inclusion and exclusion criteria

All patient cards who were treated with first-line HAART for at least 12 months both adult and children were included in the study. All patient cards with first-line HAART regimen treatment for less than 12 month and unreadable patients' files were excluded.

Sample size and sampling technique

Sample size was determined using single population proportion by using the prevalence of treatment failure of 4.1%, $N = Z^2_{\alpha 2} \times pq/d^2 = 1.96 \times 1.96 \times 0.041 \times 0.959/0.05^2 = 60$, and by taking 15% allowance for missing data, the sample size was $n = 69$. Data was collected by systematic random sampling.

Study variables

Dependent variables consisted of presence of treatment failure. Independent variables included socio-demographic characteristics (age, gender, religion, marital status, and residential area) and baseline clinical and laboratory information (baseline body weight, baseline CD4 cell count, anti-HCV antibody, and anti-Hbs antibody). Data collection technique included first-line HAART drug received and type of treatment failure experienced by the patients collected by reviewing patients' medical files.

Data quality

There was regular supervision to data collectors by a supervisor to maintain the quality of data. The data collector was a researcher, and supervisor was an advisor for this study. Before data collection, the data collector was trained by the supervisor, and a pre-test was carried out on using few cards of patients, which were not included in the main study.

Data entry and analysis

Descriptive statistics such as frequencies and percentage were summarized and presented in the form of tables and graphs. Odds ratio and 95% confidence interval was used to verify significant association between dependent and independent variables, using bivariate and multivariate analysis by logistic regression model. In all cases, p-value < 0.05 was considered significant. All analyses were completed using statistical package for social sciences (SPSS), version 16.

Ethical consideration

Ethical clearance was obtained from research ethical review board of the University of Ambo. Formal letter of per-

mission was also obtained from the Shashemene Referral Hospital administration. Patient information from his medical file was kept confidential.

Results

In the current study, data of 69 HIV-positive patients of the Shashemene Referral Hospital from 2013 to 2017 was collected and analyzed with the following results. Out of 69 study participants, 43 patients (62.3%) were male and 39 (56.5%) were married. Age group of 31-44 years contained more patients than other age group, with 31 patients (44.9%); twenty-seven of study participants had only primary level of education (Table 1).

Baseline clinical characteristics

Nearly half of the patients (40.6%) have initiated their treatment at CD4 count of 100-200 cells/mm³. Thirty-eight of study participants (55.1%) initiated HAART at WHO stage one. Most of the patients (50; 72%) were at active functional status upon HAART initiation. Around 75% of patients had only minor opportunistic disease or were non-symptomatic at HAART initiation.

Table 1. Socio-demographics characteristics of HIV patients at the Shashemene Referral Hospital from 2013-2017 ($n = 69$)

Variables	Frequency (%)
Sex	
Male	43 (62.3)
Female	26 (37.7)
Age	
< 18	6 (8.7)
19-30	24 (34.8)
31-44	31 (44.9)
45-65	8 (11.6)
Marital status	
Married	39 (56.5)
Unmarried	14 (20.3)
Divorced	1 (1.4)
Widow(er)	2 (2.9)
Separated	10 (14.5)
Not applicable	3 (4.3)
Educational status	
Illiterate	17 (24.6)
Primary	27 (39.1)
Secondary	21 (30.4)
Higher education	3 (4.3)
Not applicable	1 (1.4)

Table 2. Baseline clinical characteristics of HIV patients at the Shashemene Referral Hospital from 2013-2017 (*n* = 69)

Variables	Frequency (%)
AIDS defining illness prior to ART initiation	
Non-symptomatic	52 (75.4)
Many opportunistic infections	17 (24.6)
WHO stage at ART initiation	
1	38 (55.1)
2	3 (4.3)
3	19 (27.5)
4	9 (13.0)
Functional status at ART initiation	
Bedridden	11 (15.9)
Ambulatory	8 (11.6)
Working	50 (72.5)
CD4 count at ART initiation	
< 99	13 (18.8)
100-200	28 (40.6)
> 200	28 (40.6)

Table 3. Treatment-related information of HIV patients at the Shashemene Referral Hospital from 2013-2017 (*n* = 69)

Variables	Frequency (%)
Adherence	
Poor	19 (27.5)
Moderate or mixed	9 (13.0)
Good	41 (59.4)
Initial first-line regimen	
D4T + 3TC + NVP/EFV	30 (43.5)
AZT + 3TC + ABC	4 (5.8)
AZT + 3TC + NVP/EFV	12 (17.4)
TDF + 3TC + NVP/EFV	23 (33.3)
WHO stage at ART initiation	
1	38 (55.1)
2	3 (4.3)
3	19 (27.5)
4	9 (13.0)

Treatment related information

As shown in Table 3, most of the patients (30; 43.5%) have initiated their treatment with stavudine + lamivudine + efavirenz/nevirapine regimen. Of 69 participants, 59.4% had good adherence to their treatment. The majority of patients started their treatment after an advanced WHO stage development, with 27.5% of patients, stage 3 and 13% of patients, stage 4. Around 40.5% of patients have already developed an advanced WHO stage by the time they initiated the treatment, and the frequency of treatment failure was more common in males (70%) than in females (30%) (Table 3).

Factors associated with treatment failure

Binary logistic regression estimated that poor adherence, eligibility by both clinical and CD4 count, baseline weak functional status, many opportunistic diseases and WHO stage 3/4 at baseline visit, CD4 count of less than 99 at the time of HAART initiation had significant association with treatment failure. However, in multivariate logistic regression analysis, only advanced WHO stage (stage 3 and 4) and poor adherence had significant association with treatment failure. It means that WHO stage 4 was 47.6 times more likely to have treatment failure, and WHO stage 3 and good adherent was less likely to have treatment failure than poor adherence (Table 4).

Discussion

This study showed that the prevalence of HIV first-line treatment failure was 14.5%. This result is similar to an outcome of study conducted at the Bugando Hospital Mwanza, Tanzania, in which immunologic failure rate was 17.1% [12] and much higher than study conducted at the University of Benin Teaching Hospital, Nigeria, where the failure rate was 1.19% [13] as well as study from the Gondar University Referral Hospital, Ethiopia [14]. This considerable difference is may be due to that the majority of patients in our study-initiated HAART after advancement of WHO stage, with 27.5% of patients presenting with stage 3 and 13% patients with stage 4. Around 40.5% patients presented already advanced WHO stage by the time they initiated the treatment.

Binary logistic regression showed that many factors have significant association with treatment failure, but multivariate regression revealed that only advanced WHO stage and poor adherence significantly associate with treatment failure. In the same way, study conducted at the Bugando Hospital Mwanza, Tanzania, showed that adherence below 95% was strongly associated with immunologic failure [12]. This study also discovered that an advanced WHO stage is an independent predicting factor for treatment failure, as a patient with stage 4 WHO classification at HAART initiation is 49 times at risk of developing treatment failure than a patient with stage 1 WHO at HAART initiation. Additionally, study conducted in western Kenya indicated that patients with stage 4 WHO at the time of HAART initiation are at higher risk of treatment failure compared to those in stage 1-3 WHO. Similarly, studies from Fiche and Kuyu hospitals, Ethiopia, showed that advanced WHO clinical stages 3 and 4 are identified as predictors of treatment failure [15].

Table 4. Factors associated with HIV treatment failure at the Shashemene Referral Hospital from 2013-2017 ($n = 69$)

Variables	Treatment failure		COR (95% CI)	AOR (95% CI)
	Yes	No		
Functional status at ART initiation				
Weak or bedridden	9	2	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Ambulatory	1	7	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Working	0	50	Undefined*	
Reason for ART eligibility				
CD4 count	1	24	30.9 (3.3-287.0)	23.3 (2.1-243.2)[a]
Clinical	0	9	Undefined*	
Transferred from another healthy center	0	19	Undefined*	
Both CD4 count and clinical	9	7	1	
Adherence				
Poor	7	12	0.088 (0.016-0.481)	0.094 (0.014-0.610)[a]
Mixed or moderate	1	8	0.410 (0.033-0.481)	0.296 (0.020-4.377)
Good	2	39	1	
CD4 count at ART initiation				
< 99	5	8	0.059 (0.006-0.584)	0.078 (0.007-0.906)[a]
100-200	4	24	0.222 (0.23-2.128)	0.420 (0.038-4.654)
> 200	1	27		
AIDS defining illness prior to ART initiation				
Non-symptomatic	3	49	11.43 (2.52-51.96)	1.999 (0.149-26.723)[a]
Many opportunistic diseases	7	10	1	
WHO stage at ART initiation				
Stage 1	0	38	Undefined*	
Stage 2	0	3	Undefined*	
Stage 3	2	17	60 (4.72-770.71)	47.6 (2.3-552.4)[a]
Stage 4	8	1	1	

[a]*Significant association.*Zero cell problem. COR – crude odds ratio, AOR – adjusted odds ratio*

Certain regimens may be more susceptible to development of resistance than others at differing levels of adherence [16]. In similar way, our study revealed that a treatment regimen with tenofovir + lamivudine + nevirapine/efavirenz had more occurrence of treatment failure (90%) compared to other regimens, which were related to study conducted at the Gondar Teaching Hospital indicating that most of the patients who failed first-line regimen were either on zidovudine + lamivudine + nevirapine (40%) or tenofovir + lamivudine + efavirenz (34.1%) [14]. This study showed that treatment failure rate was more frequent in males 70% (7 patients) than in females 30% (3 patients), and 31-44 years age group 80% (8 patients) were more affected than other age group. The study conducted at the Benin Teaching Hospital, Nigeria, also reported that most of first-line treatment failures occurred in 30-40 age group and was more frequent amongst males (1.3%) compared to females (1.1%) [13].

Limitations of study included viral load not determined regularly every six months for some patients or not docu-mented. Therefore, there was a lack of virological treatment failure assessment. The study was conducted using retrospective medical file reviews, in which some of recorded data may not be reliable, which affects quality of our analysis and predicting factors.

Conclusions

In this study, the overall first-line treatment failure rate was 14.5% (10 patients), where the most common type was immunologic failure occurring in 6 patients (60%), followed by virologic failure in 2 (20%), and clinical failure in 1 patient (10%). First-line treatment failure rate was more common in 31-44 years age group and more frequent in males than in females.

Even though significantly associated factors in multivariate regression was only advanced WHO stage and poor adherence, many other factors were significantly associated with treatment failure in binary logistic regression, including base-

line weak functional status, many opportunistic infections and CD4 count of less than 99 at baseline, eligibility by both clinical and CD4 count. TDF + 3TC + NVP/EFV treatment more frequently failed than other first-line treatment regimen.

The rate of treatment failure in the Shashemene Referral Hospital needs attention. Prevention and control of the development of advanced WHO stage, adherence improvement, promotion of HAART initiation at active functional status and higher CD4 count, prevention of multiple or many opportunistic infections, patients' education on the importance of adherence, regimen selection with no susceptibility for treatment failure are the most important interventions to reduce treatment failure.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest with respect to the research, authorship, and/or publication of this article.

References

1. Sokoya T. Occurrence and determinants of treatment failure in antiretroviral therapy at Tshwane district hospital. Johannesburg 2012. Available at: http://wiredspace.wits.ac.za/bitstream/handle/10539/13790/387798_OCCURRENCE%20AND%20DETER-MINANTS%20OF%20TREATMENT%20FAILURE%20IN%20ANTIRETROVIRAL%20THERAPY%20AT%20TSHWANE%20DISTRICT%20HOSPITAL.pdf?sequence=1&isAllowed=y
2. USAID regional HIV\AIDS program. Antiretroviral therapy literacy for community based care givers. Southern Africa HIV\AIDS information dissemination service. January 2009 – June 2013.
3. A Christian Aid report. Don't take on an empty stomach: why HIV treatment won't work without food. November 2007.
4. WHO. Report of the WHO expert consultation in European region. Copenhagen, 7 December 2007.
5. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2nd ed. Geneva: WHO; 2015.
6. Montessori V, Press N, Harris M, et al. Adverse effects of antiretroviral therapy for HIV infection. CMAJ 2004; 170: 229-238.
7. De la Hoz JM, Bolano L, Cardenas O, et al. Characterization of treatment failure in HIV positive patients in the Colombian Caribbean region. Colombia Medica 2014; 45: 162-167.
8. Makhubele TG. Immune activation and cigarette smoke exposure as potential determinants of failure of HAART in the setting of mother to child transmission. Dissertation, University of Pretoria, 2014.
9. Federal Ministry of Health of the Nigeria. National guidelines for HIV and AIDS treatment and care in adolescents and adults. 2nd ed. Abuja, Nigeria 2010; 22-23.
10. Ebonyi AO, Oguche S, Ejeliogu EU, et al. Risk factors for first line antiretroviral treatment failure in HIV-1 infected children attending Jos University Teaching Hospital, Jos, North Central Nigeria. J Adv Med Med Res 2014; 4; doi: https://doi.org/10.9734/BJMMR/2014/8869.
11. Del Rio C. Current concepts in antiretroviral therapy failure. Top HIV Med 2006; 14: 102-106.
12. Jaka H, Mshana S, Liwa A, Kalluvya S. Prevalence of immunological failure and durability of first line antiretroviral therapy at Bugando Hospital Mwanza, Tanzania. Tanzania Medical Journal April 2009; 24; doi: 10.4314/tmj.v24i2.53278.
13. Eze EU, Uyaguo OD. Prevalence of anti-retroviral treatment failure and salvage therapy in university of Benin Teaching Hospital Edo state, Nigeria. Ann Biomed Sci 2009; 8; doi: 10.4314/abs.v8i2.57342.
14. Ayalew MB, Kumilachew D, Belay A, et al. First-line antiretroviral treatment failure and associated factors in HIV patients at the University of Gondar Teaching Hospital, Gondar, Northwest Ethiopia. HIV/AIDS (Auckl) 2016; 8: 141-146.
15. Yassin S, Gebretekle GB. Magnitude and predictors of antiretroviral treatment failure among HIV-infected children in Fiche and Kuyu hopitals, Oromia region, Ethiopia: a retrospective cohort study. Pharmacol Res Perspect 2017; 5: e00296.
16. Reekie J, Mocroft A, Ledergerber B, Beniowski M, Lunzen J. History of viral suppression on combination antiretroviral therapy as a predictor of viorological failure after a treatment change. HIV Med 2010; 11: 469-478.

Annex I. Data collection format

A. Patient demographic information

Age: _____

Sex: _____

Marital status: _____

Religion: _____

Occupation: _____

Patient referral information: _____

Educational status: _____

Alcohol use: A – yes, B – no

B. Baseline data

1. List of comorbid illness if any: _____,_____,_____

2. Laboratory data: A – HBs Ag, B – Anti-HCV

3. Mode of exposure: _____

4. Functional status at HAART initiation: A – weak, B – moderate, C – active

5. AIDS defining illness prior to HAART

6. Patient pregnancy status

7. Specific abnormal physical examination and laboratory

8. If yes, for which abnormal laboratory finding and disease does patient need evaluation?

C. Treatment-related data

1. Reason for HAART eligibility: _____

2. WHO stage at HAART initiation: _____

3. CD4 count at the time of HAART initiation: _____

4. CD4 count every 6 months: 1st: _____, 2nd: _____, 3rd: _____

5. CD4 count every year: 1st: _____, 2nd: _____

6. History of treatment interruption: _____

7. Initial first-line regime: _____

8. Adherence to HAART regimen: A – poor, B – good, C – excellent

9. History of HAART regimen change: _____

D. HAART failure-related data

1. Type of treatment failure: A – virological failure, B – immunological failure, C – clinical failure

2. Reason for treatment failure: _____

3. Years from first-line HAART initiation to second-line HAART: _____

4. Failing HAART regimen: _____

5. CD4 count at switch to second-line regimen: _____

6. Viral load at switch to second-line: _____

7. WHO stage at switch of regimen: _____

8. Secondary HAART regimen: _____