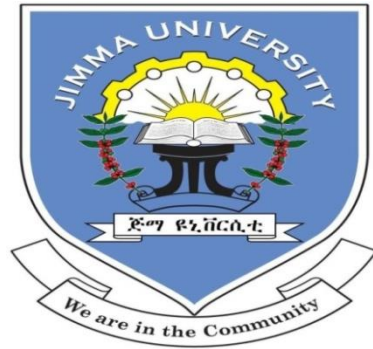


**Retrospective Study Of Regimen Change Among HIV/AIDS Patient Initiated
On First Line Highly Active Anti Retroviral therapy In Asella Hospital Art
Clinic, Asella, South East Ethiopia.**



BY: Aman Haji

**A RESEARCH PAPER TO BE SUBMITTED TO DEPARTMENT OF
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**COLLEGE OF PUBLIC HEALTH AND MEDICAL SCIENCES
DEPARTMENT OF PHARMACY**

**RETROSPECTIVE STUDY OF REGIMEN CHANGE AMONG HIV/AIDS
PATIENT INITIATED ON FIRST LINE HIGHLY ACTIVE ANTI
RETROVIRAL THERAPY IN ASELLA HOSPITAL ART CLINIC**

BY: AMAN HAJI

ADVISOR: MR. Wote Amelo (B. PHARM, MSC)

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ABSTRACT

Background: AIDS, which is acquired immune-deficiency syndrome, is treated by highly active anti-retro viral therapy with cocktail of drugs including Nucleoside reverse transcriptase inhibitors, Non-Nucleoside reverse transcriptase inhibitors and protease inhibitors. Anti-retro viral therapy (ART) has markedly decreased the morbidity and mortality due to HIV disease. However, toxicities, co morbidities, and treatment failure, among others would result in frequent initial ART regimen change.

Objective: To determine the reasons for initial anti-retroviral regimen change among adult patients on anti-retroviral therapy in Asella hospital ART clinic.

Methods: A retrospective cross-sectional study was conducted by using patient information sheet record cards from Jan 01, 2013-Dec 31, 2013.

Result: One hundred forty five patients switch their first regimen in Asella referral hospital within the study period. The most frequent prescribed first regimens before switch were AZT/3TC/NVP (36.55%), AZT/3TC/EFV (19.31%), D4T/3TC/NVP (13.79%), TDF/3TC/NVP (13.1%), D4T/3TC/EFV (10.34%) and TDF/3TC/EFV (6.89%). Toxicity (70.34%) followed by co-morbidity (16.55%), pregnancy (5.52%), Treatment failure (4.83%) and Drug stock out (2.76%) were the most common reasons for modification of antiretroviral therapy. The main toxicity was rash (51.96%) and peripheral neuropathy (28.48%).

Conclusion: The proportions of patients who modify HAART in our resource-constrained setting present a challenge to the limited treatment options that currently present. Within these, the main reasons for modifications in the study setting were toxicity, co morbidity and planning pregnancy or pregnant were the top three.

Recommendation: The hospital should develop ADR data base so as to easily record and report adverse effect of drugs.

Key words: Ethiopia, Adults, Anti retro viral therapy, Regimen switch, Toxicity and Rash.

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ABBREVIATIONS AND ACRONYMS

AIDS: Acquired immune deficiency syndrome
ART: Anti retro viral therapy
ARV: Anti retro viral
AZT: Zidovudine
CD4: Cluster of Differentiation 4
CBE: Community based education
D4T: Stavudine
EFV: Efavirenz
FMOH: Federal Ministry of Health
HAART: Highly active anti-retro viral therapy
HIV: Human immune virus
NNRTI: Non-nucleoside reverse transcriptase inhibitor
NRTI: Nucleoside reverses transcriptase inhibitor
NVP: Nevirapine
PIs: Protease inhibitors
PMTCT: Prevention of maternal to child transmission
3TC: Lamivudine
TB: Tuberculosis
TDF: Tenofovir
UNAIDS: Joint united nation programs on AIDS
VCT: Voluntary counseling and testing
WHO: World health organization

DEFINITION OF TERMS

Adverse drug reaction: Refers to any undesired responses to drug administration, as opposed to therapeutic effects, which are desired responses.

HAART: Highly active anti retro viral therapy with a combination of two NRTIs with PI or NNRTI.

Lactic acidosis: A compound that forms in the cells as the product of glucose metabolism in the absence of oxygen

Lipo atrophy:-Loss of subcutaneous fat

Lipo dystrophy: Any disturbance of fat metabolism or any distribution of fat in the body

Peripheral neuropathy: Problems with the functioning of nerves outside the spinal cord

Regimen: A drug or drug combination used for one course of treatment.

Switch: Change of HAART regimen from one to another

Toxicity: Degree to which something is poisonous.

1. INTRODUCTION

1.1 Background

Human Immune Virus (HIV) is responsible for a worldwide pandemic and it is the cause of Acquired Immune Deficiency Syndrome (1).

According to latest statistics 33.4 million individuals worldwide are living with HIV, of which 15.7 million (47%) are women and 2.1 million (6.3%) are children under 15 years. In addition there are 2.7 million new infections and 2.0 million deaths from AIDS worldwide (2).

Sub-Saharan Africa remains the region most heavily affected by HIV. 1.9 million People living in sub-Saharan Africa become newly infected with HIV, bringing the total number of people living with HIV to 22.4 million. Moreover an estimated 1.4 million AIDS related deaths occur in sub-Saharan Africa. But the rate of new HIV infections and death has slightly declined as a result of improved access to ART (2).

The HIV/AIDS epidemic in Ethiopia continues to pose a threat to the lives of its people. According to the single point estimate in 2007, 977,394 people are living with the virus in Ethiopia. Resulting, a prevalence rate of 2.1% (1.7% among males and 2.6% among females; 7.7% urban and 0.9% rural areas) for a total estimated population of 73 million. The number of new infections is 125,528 including 14,147 HIV positive births of which females' account 57.4% (3).

Since beginning of Highly Active Antiretroviral Therapy (HAART) in 1996, there have been dramatic declines in morbidity and mortality due to HIV. But these advancements were not without a cost in terms of drug resistance and side effects. A concern about these negative effects has led to a more conservative approach to the timing of initiation of therapy and to clinical trials of intermittent therapy in an attempt to decrease the total exposure to drugs over time. Antiretroviral management brings a complex series of choices; when to initiate therapy, what

regimen to use, which drugs within each class, when to change therapy, and which alternative drugs to use (4).

According to Ethiopian guideline, criteria for initiating antiretroviral therapy in adults and adolescents with documented HIV infection are as follows

1. If CD4 Testing is Available:

WHO Stage 4 disease irrespective of CD4 cell count.

WHO Stage 3 disease with CD4 cell count $<350/\text{mm}^3$

2. If CD4 testing is Unavailable:

WHO Stage 3 and 4 disease irrespective of total lymphocyte count.

WHO stage 2 with a total Lymphocyte Count $<1200/\text{mm}^3$

Accordingly, the first line ARV regimen in Ethiopia include a triple therapy, two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one Protease Inhibitor (PI), if this is not possible, a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or else a triple therapy of three NRTIs. Based on the guideline, common ART regimens in Ethiopia are; TDF/FTC/EFV, AZT/3TC/EFV, AZT/3TC/NVP, D4T/3TC/NVP or D4T/3TC/EFV (6).

1.2 statement of the problem

After introduction of ART all over Ethiopia, many factors lead to the ineffectiveness of Anti retro virals (ARVs) and change in the combinations. Rationale for treatment switch may be either pre-emptive (risk of long term toxicity, poor adherence a sub-optimal regimen, co-morbidity, treatment failure.), when virological suppression is usually retained or reactive to virological rebound or (because of resistance or poor adherence) or an established acute and /or chronic toxicity (6).

Toxicity or adverse drug reaction (ADR) is creating adherence problem and affect patients' willingness to take drugs. Some studies showed that ADR starting from simple rash up to life threatening Steven Johnson's syndrome and other life threatening adverse effects like hepatotoxicity, mitochondrial damage and bone marrow toxicity create adherence and compliance difficulties (7).

Co morbidity and drug-drug interactions are the other reasons for ART regimen modification. This interaction makes TB co-morbidity treatment difficult and challenging. The drug-drug interactions between rifampicin and antiretroviral groups, NNRTIs and PIs results in ineffectiveness of ARV drugs, ineffective TB treatment or an increased risk of drug toxicity. For example, rifampicin stimulates liver enzymes, which metabolize PIs and NNRTIs that can lead to decreased blood level of these drugs. PIs and NNRTIs can also enhance or inhibit this same enzyme system and lead to altered blood level of rifampicin (8).

The other reason for ART regimen change is treatment failure which is defined as either clinical failure (New or recurrent WHO stage 4 condition like pneumocystis carinii pneumonia, Toxoplasmosis of the brain, and Kaposi's sarcoma, Extrapulmonary tuberculosis etc) ,immunological failure (50% fall from the on-treatment peak value (if known) or virologic failure (a virological rebound after complete suppression (5).

1.3 Significance of the study

Since there are few studies done on the reason of modification of ART regimen in this country, it is believed that valuable information will be gained from the study.

The result will be used as a base line data for future investigators in this area

- For reasons of antiretroviral regimen change.
- For potentially providing strategic plan and decision making on ART drugs management.
- As general information for planning by policy makers.

2. LITERATURE REVIEW

A study conducted in United Kingdom (UK) showed that the commonest ARV combination were NNRTIs and AZT/3TC (9).

The main cause of switching were toxicity (51%), virologic failure(30%), adherence difficulties (14%), treatment simplification (10%). 44% of those for whom adherence difficulties were cited as a reason changed to once daily therapy compared to 27% of those who switched for other reason. Of the 38 who switched from treatment simplification, seven switched to ZDV/3TC/EFV and Six to ABC/AZT/3TC, whilst 17 switched to a once daily regimen. Of 19 patients (4%) who were pregnant or planning pregnant and who changed therapy, 15 were on EFV, 3 on ABC/ZDV/3TC and one on D4T before switching (9).

Anti-tuberculosis medication was cited as a reason to switch in 6 patients and antiepileptic in two. Two patients switched to 3TC/EFV regimens because of hepatitis B virus co morbidity. From switching of therapy due to toxicity: 10% were due to lipoatrophy, 6% with hypercholesterolemia, and 4% with hyper triglyceridemia (9).

With respect to individual drug associations, 54% of patients with metabolic and/or lipid toxicity were on a D4T – containing regimen compared with over all frequencies of 17% and 18% respectively, 72% of patients with Lipid and/or metabolic toxicities had been on their initial therapy for 2 years or more(9).

Other reported toxicities precipitating therapy alteration included (CNS related toxicity (40 patients), GIT related toxicity (25 patients), peripheral neuropathy (18 patients), and an anemia (16 patients) (9).

According to the study conducted in Southern India 82% of patients were male, with mean age of 53.8 years. The 4 most common first line regimens were D4T/3TC/NVP (63%),

AZT/3TC/NVP (19%), D4T/3TC/EFV (9%) and AZT/3TC/EFV (4%) 13% patients' substituted therapy because of the occurrence of adverse effect (10).

The most common adverse effects in this group of patients were itching and/or skin rash (66% not include mild allergic reaction and hepatotoxicity) (27%). The median CD4 counts at initiation of therapy for those who developed a rash or hepatic toxicity were 113 cells/ml and 65 cell/ml respectively (10).

Other adverse effects include nausea and vomiting (25%) and anemia (23%). 15% of the patients who substituted therapy because of adverse effect did so because of D4T related toxicities (persistence symptomatic peripheral neuropathy) and lipo atrophy (2.2%) (10).

83% of patients were on NVP containing regimens of those, 13% substituted therapy because of an adverse effect; rash and hepatic toxicity (26%) and (21%) respectively and those on NVP were more likely to substitute therapy because of adverse effect and other regimens group was more likely to change because of cost (10).

Of the 33 patient with hepatic toxicities, 82% were on rifampicin – containing anti-TB medications at the time of development of the adverse effect. Of the 183 patients who initially substituted therapy because of an adverse effect, 33% modified their second line regimen, moving to a third line regimen in a median time of 97days. Of the 60 patients previously cited, 37% because of adverse effect, 13% treatment failure and cost (17%) changed their first line regimen (10).

Study conducted in Swaziland indicated that majority (66.5%) of patients were female with a median age of 36 years. The most common regimens initiated were D4T/3TC/NVP (36.1%) and AZT/3TC/NVP (37.9%). Nearly one fifth of the patients were initiated on AZT/3TC/EFV, whilst 5% were initiated on D4T/3TC/EFV. Less than 1.6% of the patients were initiated on a protease-inhibitor based (PI) regimen (11).

Peripheral neuropathy and lipodystrophy (including lipoatrophy) were the most common toxicity-based reasons, 23.4% and 22.6% of all changes respectively. These were mainly drug substitutions of d4T (peripheral neuropathy, n=32 d4T substitutions, and lipodystrophy, n= 30 d4T substitutions and n=1 AZT substitution) (11).

Most patients who had d4T substituted because of mitochondrial-related toxicities had the drug replaced by AZT and in some few cases, abacavir (ABC). In cases of peripheral neuropathy, substitution of ART drugs was only after the symptoms did not remit to use of analgesics, amitriptyline and also carbamazepine in some cases. Incidence rate for reasons related to drug contra-indications was 9.5 per 100py (95% CI: 6.5-13.9) and this was because of TB treatment (13.1%, n=18) and pregnancy (6.6 %, n=9) is contraindicated to use NVP concurrently with rifampicin based TB treatment hence patients on NVP based regimens and also starting TB treatment had NVP replaced with EFV. In pregnant patients, EFV was substituted for NVP (11).

In Study conducted in Dessie Regional Referral hospital, 122 patient cards were assessed. From these 59% of the study populations were females. The median age was 32. Most patients were receiving a starting regimen of AZT/3TC/EFV 44(36%), AZT/3TC/NVP, D4T/3TC/NVP and D4T/3TC/EFV are 27%, 19% and 18% respectively, the most known cause of ARV switching includes toxicity (66%), co morbidity 14(%), planning pregnancy (11%), treatment failure (8%) and adherence difficulty (3%), from toxicity reported, anemia is the most common reason from drug point of view, 50% toxicity is due to AZT/3TC/EFV, from this anemia is the only adverse effect resulted, AZT/3TC/NVP (28%) is the second more cause of toxicity for switching. 11% of toxicity is due to D4T/3TC/EFV, which resulted in peripheral neuropathy (8 patients), Rash (one patient) and lipoatrophy (one patient) due to D4T (12).

Due to Tuberculosis 56% of patients switch from D4T/3TC/NVP to D4T/3TC/EFV, and one patient switches from AZT/3TC/NVP to AZT/3TC/EFV since he developed disseminated TB and start anti TB treatment. Due to pregnancy, 11 patients switched from D4T/3TC/EFV to D4T/3TC/NVP, 3 patients from AZT/3TC/EFV to AZT/3TC/NVP which mainly due to EFV teratogenic effect. Only eight patients face treatment failure from their first regimen, which occurred mainly from D4T containing regimen (90%), and one from AZT/3TC/NVP. These are

due to immunological failure (5 patients) and development of opportunistic infection (3 patients) reported as treatment failure (12).

Study done in Nekemte referral hospital showed that majority of the patients (61.3%) were in the age of 20-34 years and 57.7% of the patients were females. 42.2% of patients were on D4T/3TC/NVP at the beginning of antiretroviral treatment and the rests were on D4T/3TC/EFV(27.5%),AZT/3TC/EFV(12,7%)TDF/3TC/EFV(9.9%),AZT/3TC/NVP(4.2%),TD F/3TC/NVP(2.8%)and AZT/3TC/Lpr/r(o.7%) (13).

The main reason for modification of treatment regimens were toxicities (80.3%), pregnancy (6.3%), new TB (5.6%), drug unavailability/stock out (4.9%) and treatment failure (2.8%) (13).

From all toxicity reported, lipoatrophy accounted 58.8%, rash 12.3% and CNS toxicities (11.4%). D4T containing regimens accounted for 100% of lipoatrophy while NVP containing regimens accounted for 71.3% of rash and EFV containing regimens accounted for 100% of CNS disturbance (13).

Study conducted in Shashemene and Hawassa referral hospital showed that majority of patients (54.70%) were on D4T/3TC/NVP at the beginning of the ARV treatment and the rest were on D4T/3TC/EFV (20.88%), AZT/3TC/NVP (16.17%) and AZT/3TC/EFV (8.25%) (14).

The main reason reported for modification was toxicity among 230(67.65%) of the patients, Co morbidity in 65(19.11%), pregnancy in 36(10.59%) and treatment failure in nine (2.65%) (14).

From all toxicities reported, peripheral neuropathy accounted for (36.5%), followed by rash (17.90%) and anemia (17.40%). Peripheral neuropathy was due to D4T containing of D4T/3TC/NVP (77.38%) and D4T/3TC/EFV (22.62%) whereas rash was due to NVP containing regimens of D4T/3TC/NVP in (70.73%) of the patient and due to AZT/3TC/NVP (29.27%) of them. Anemia was reported due to AZT containing regimens of AZT/3TC/NVP (57.5%) and AZT/3TC/EFV (42.5%). The CNS toxicities observed were dizziness, nightmare, and sleep disturbance, which were all reported due to EFV containing regimens of AZT/3TC/EFV

(18.42%) and D4T/3TC/EFV (81.58%). Lipodystrophy was due to D4T containing regimens of D4T/3TC/NVP (75%) and D4T/3TC/EFV (25%) (14).

The other toxicities observed were nausea and vomiting (GI toxicities) due to AZT containing regimens of AZT/3TC/NVP (36.36%) and AZT/3TC/EFV (27.27%) and hepatotoxicity was due to NVP containing regimens of D4T/3TC/ and AZT/3TC/NVP (14).

3. OBJECTIVES

3.1. General objective

To assess reasons for initial regimen change among patients on Anti retro viral therapy (ART) in Asella hospital ART clinic.

3.2. Specific objectives

- To assess toxicity associated with ART that cause regimen change.
- To assess co morbid condition that contributes to ART regimen change.
- To assess treatment failure associated with ART regimen switch.
- To assess regimen type which are reasons for switching.

4. METHOD AND MATERIALS

4.1. Study setting

The study was conducted in Asella zonal Hospital, which is located at 175km from Addis Ababa and at 521 from Jimma town. Asella is found in east Arsi Zone of the Oromia region. This town has an estimated total population of 67,267 of which 33826 were males and 33443 were females. The hospital delivers outpatient and inpatient services and has five specialists (surgeon, gynecologist/obstetrician, internist, pediatrician and ophthalmologist), five general practitioners, 71 nurses, four health officers, six laboratory technicians and two lab technologists and two pharmacists and five pharmacy technicians. The study was conducted from January 24, 2014 - February 8, 2014.

4.2. Study design and period

A cross-sectional study on retrospective data was conducted by reviewing patient information sheet record cards with a period from Jan 01, 2011 –December 31, 2013.

4.3. Population

4.3.1. Source population

All adult patients' information sheet record cards of HIV/AIDS patients that under gone switching ART in Asella hospital during January 01, 2011 – December 31, 2013.

4.3.2. Sample population

All adult patient information sheet record cards of HIV/AIDS patient who had undergone switching.

4.4. Sample size and Sampling techniques

The study included all adult HIV/AIDS patients who had undergone switching, so that no sampling technique was used.

4.5 Eligibility Criteria

4.5.1 Inclusion criteria

All study population whose regimen were changed with in study period.

All study population with age ≥ 20 years.

4.5.2 Exclusion criteria

All study population whose regimen were not changed with in study period.

All study population with age < 20 years.

4.6. Variables

4.5.1. Dependent variables:-

Duration of initial therapy
Modification of HAART regimen

4.5.2. Independent variables:-

Age	Marital status
Religion	Educational status
Sex	Pregnancy
Co morbidity	Toxicity
Card number	

4.7. Data collection

Data was collected from patient information sheet record cards by using structured formats.

4.8. Data processing and Analysis

Data was processed and analyzed by using calculator for statistical analysis. The estimated prevalence of HAART modification was reported as percentage.

4.9. Ethical Consideration

Ethical consideration was strictly followed. Prior to data collection, a formal letter was written from Jimma University student research program.

4.10. Quality assurance

Before the starting of actual data collection, pilot study was undertaken to ensure patient information sheet and physician diagnosis card for their completeness and to evaluate the data collection format for its validity, reliability and consistency.

4.11. Limitation of the study

Lack of appropriately filled information sheet of some patients.

5. RESULT

One hundred forty five (145) patients record were reviewed in the study. Patients' demographic characteristic showed that, 89(61.39%) patients were females. Majority of the patients, 73(50.34%) were in the group of 20-34 years. Regarding patients' source, most of them 139 (96%) were out patient. Regarding patients address 137(94.5%) of them were from urban. Seventy-nine (54.48%) of patients were married and in case of educational status Seventy-six (54.14%) of patients were in primary school (Table 1).

Table 1: Socio demographic characteristics of HIV/AIDS patients who changed their Initial ART regimen in Asella hospital ART clinic, Jan 01, 2011-Dec 31, 2013.

Variables	Classification	Frequency (%)
Sex	Female	89(61.37%)
	Male	56(38.63%)
Age	20-34	73(50.34%)
	35-49	55(37.93%)
	50-64	16(11.03%)
	>64	1(0.69)
Educational status	No formal education	44(30.34%)
	Primary school	76(52.14%)
	Secondary school	20(13.79%)
	Higher institute	5(3.45%)
Marital status	Single	51(35.17%)
	Married	79(54.48%)
	Divorced	10(6.89%)
	Widowed	5(3.45%)

Based on the weight of patients during start and switch of ART, 53(36.55%) of the patient have reported of having weight between 41-40 and 51-60 and only 13(8.97%) of them had weight between 31-40 during start of ART. Similarly, 57(39.31%) have weight range between 41-50 at the switch of ART and only 19(13.10%) of them reported of having weight >60 (**Table 2**).

Table 2: Weight of HIV/AIDS patients on start and during switch of ART regimen in Asella hospital ART clinic, January 01, 2011-December 31, 2013.

Weight(kg)	On start		During switch	
	frequency	% age	frequency	% age
<_30	-	-	-	-
31-40	13	8.97	21	14.48
41-50	53	36.55	57	39.31
51-60	53	36.55	48	33.10
>60	26	17.93	19	13.10
Total	145	100	145	100

A majority of patients had their initiation of treatment at clinical WHO stage III 86(59.2%) , the remaining were at stage II 32(22.3%), stage IV 17(12.2%) and stage I 3(1.8%) . For 4.5% patients' clinical stage was not recorded (**figure 1**).

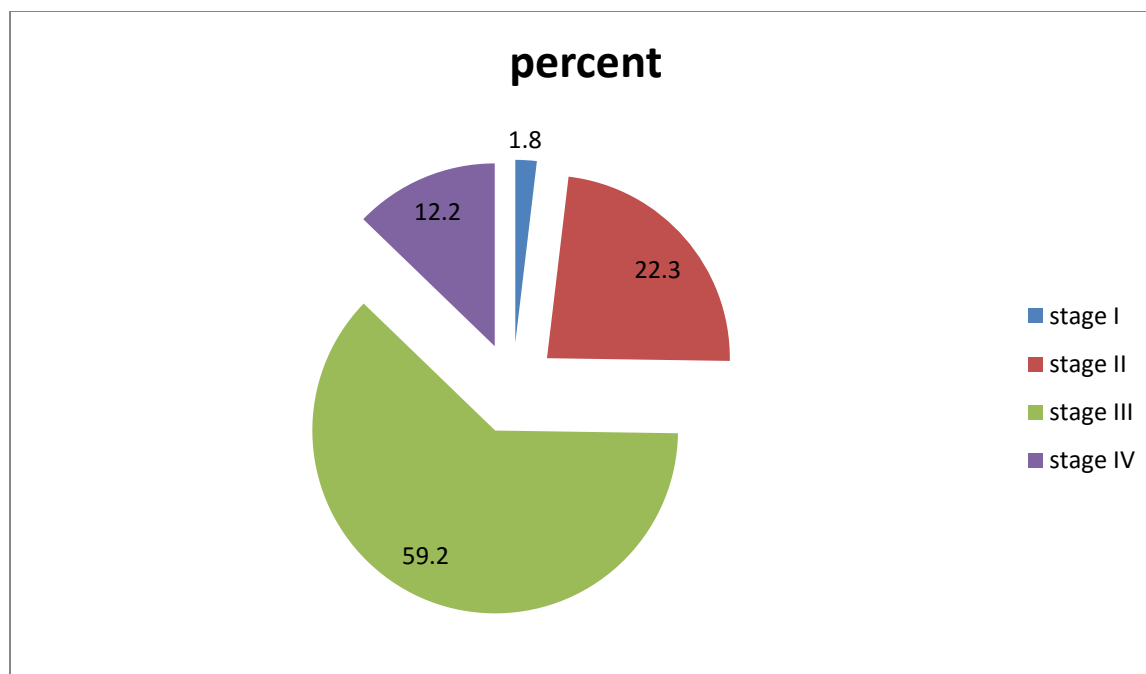


Figure 1: Initial WHO clinical stages of HIV/AIDS patients who changed their initial regimen in Asella hospital ART clinic Jan 1, 2011-Dec 31, 2013.

Regarding CD4 count, 48.26% of patient had their initial CD4 count in the range of 201-300. 27.59% and 6.89% of patients in the range of 301-350 and >350 respectively. About 2.76% of patients were in advanced HIV/AIDS (CD4 cell count <50copies/ml). For 4.5 patients initial CD4 cell count was not recorded (**Table 3**).

Table 3: Initial CD4 cell count at base line in Asella hospital ART clinic, Jan 01, 2011-Dec 31, 2013.

CD4	N (%)
<50	4(2.76)
51-100	6(4.14)
101-200	8(5.52)
201-300	70(48.26)
301-350	40(27.59)
>350	10(6.89)
Information missing	7(4.5)

Based on the results, 36.55% of patients were on AZT/3TC/NVP initially and the rest were on AZT/3TC/EFV (19.31%), D4T/3TC/NVP (13.79%), TDF/3TC/NVP (13.10%), D4T/3TC/EFV (10.34%) and TDF/3TC/EFV (6.89%) (**Figure 2**).

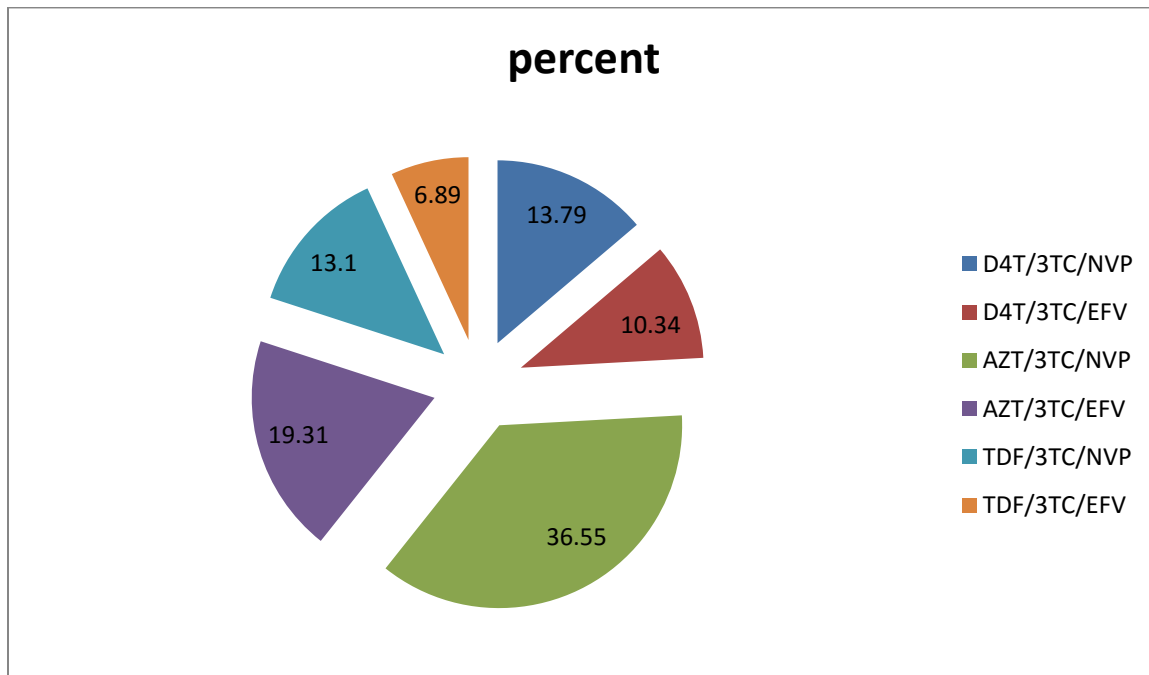


Figure 2: Types of initial first treatment regimens in Asella Hospital ART clinic Jan 01, 2011- Dec 31, 2013.

From the results, the main reasons reported for modification of treatment were toxicity (70.34%) followed by Co morbidity (16.55%), pregnancy (5.52%) and treatment failure (4.83%). The other reason observed was drug stock out (Unavailability) (2.76%) (**Figure 3**).

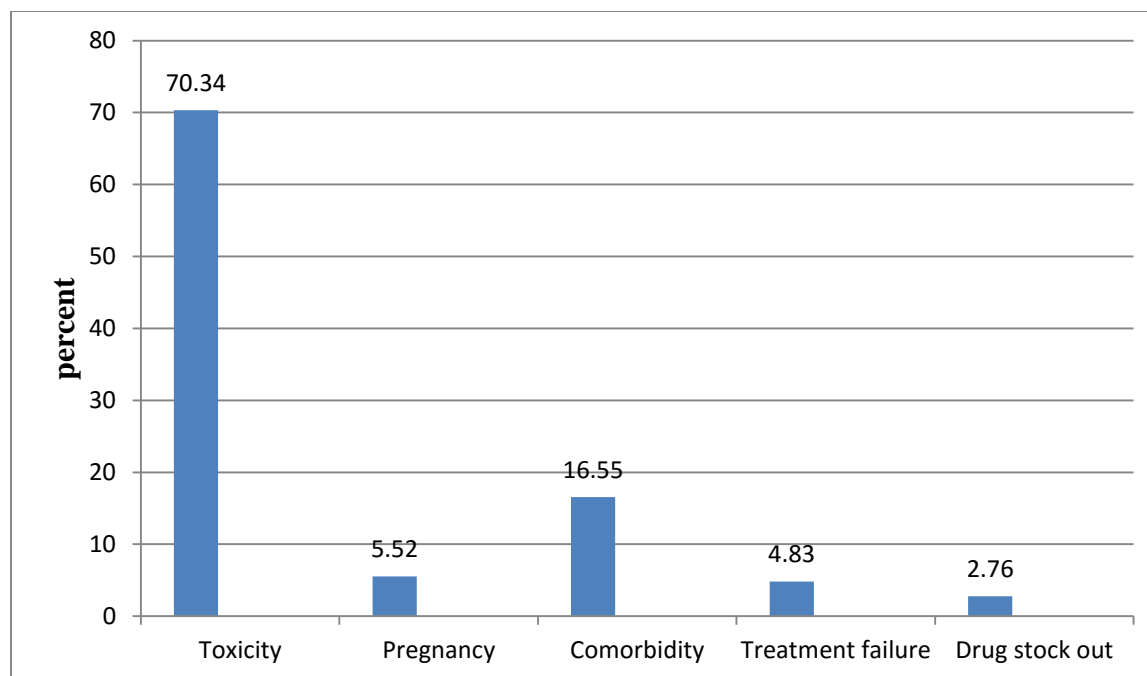


Figure 3: Common reasons for modification of first treatment regimen in Asella Hospital ART clinic, Jan 01, 2011-Dec, 31, 2013.

From 102 patients that modified their first regimen in case of toxicity, 40 (39.22%) were due to AZT/3TC/NVP and the remaining 22 (21.57%), 14 (13.73%), 12 (11.76%), 8 (7.84%) and 6 (5.88%) were due to AZT/3TC/EFV, D4T/3TC/NVP, D4T/3TC/EFV, TDF/3TC/NVP and TDF/3TC/EFV respectively. Twelve (50%) patients initially on AZT/3TC/NVP and the remaining 10 (41.67%) and 2 (8.33%) respectively on TDF/3TC/NVP and D4T/3TC/NVP modified due to co morbid condition. From eight patients that modified their first regimen in case of pregnancy, three patients were due to AZT/3TC/EFV, the remaining two were due to D4T/3TC/NVP, another two were due to D4T/3TC/EFV, and one patient was due to TDF/3TC/EFV. Similarly, two patients initially on D4T/3TC/NVP, another two on AZT/3TC/EFV and one patient on D4T/3TC/EFV, another one patient on TDF/3TC/EFV and also another one patient on AZT/3TC/NVP modified their first regimen due to treatment failure. On the other hand, two patients initially on TDF/3TC/EFV, one patient on AZT/3TC/EFV and another one patient on TDF/3TC/NVP switched first their regimen due to drug unavailability (**Table 4**).

Table 4: Common reasons for modification of first treatment regimen in Asella Hospital ART clinic, Jan 01, 2011-Dec, 31, and 2013.

Reason	Treatment regimen					
	D4T/3TC/NVP	D4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV	TDF/3TC/NVP	TDF/3TC/EFV
Toxicity	14(13.73%)	12(11.76%)	40(39.22%)	22(21.57%)	8(7.84%)	6(5.88%)
Co morbidity	2(8.33%)	-	12(50%)	-	10(41.67%)	-
Pregnancy	2(25%)	2(25%)	-	3(37.5%)-	-	1(12.5%)
Treatment failure	2(28.57%)	1(14.29%)	1(14.29%)	2(28.57%)	-	1(14.29%)
Drug stock out	-	-	-	1(25%)	1(25%)	2(50%)

From all toxicities reported rash accounted for 53 (51.96%) followed by peripheral neuropathy 29(28.43%) and anemia 12(11.76%). Rash was due to NVP containing regimens of AZT/3TC/NVP (64.52%) ,D4T/3TC/NVP(22.58%) and TDF/3TC/NVP(12.90%) whereas peripheral neuropathy was due to D4T containing regimens of D4T/3TC/NVP in (53.85%) of the patient and due to D4T/3TC/EFV (46.15%) of them. Anemia was reported due to AZT containing regimens of AZT/3TC/NVP (64.52%) and AZT/3TC/EFV (35.48%) (**Figure 4**).

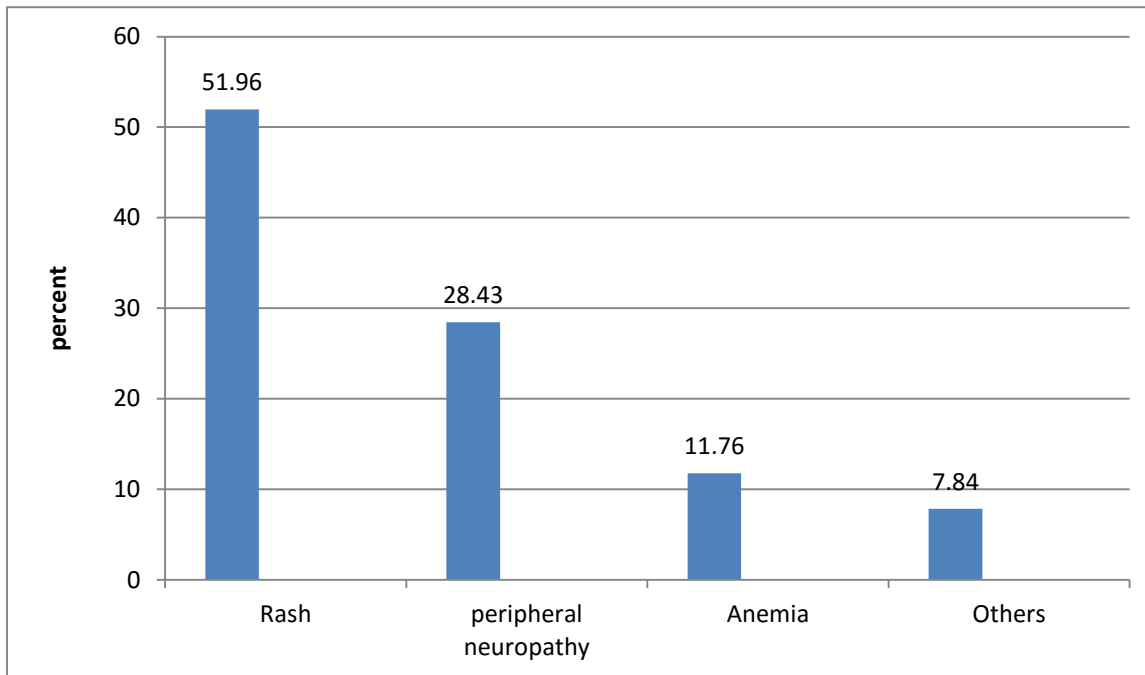


Figure 4: Toxicities reported as a reason for treatment change in Asella Hospital ART clinic Jan 01, 2011-Dec 31, 2013.

The majority of patients (42.07%) modified their initial treatment regimen with 3 months of the start of taking medications and only 4.83% of patients remained on the first regimens for more than 104 week before first switch (**Figure 5**).

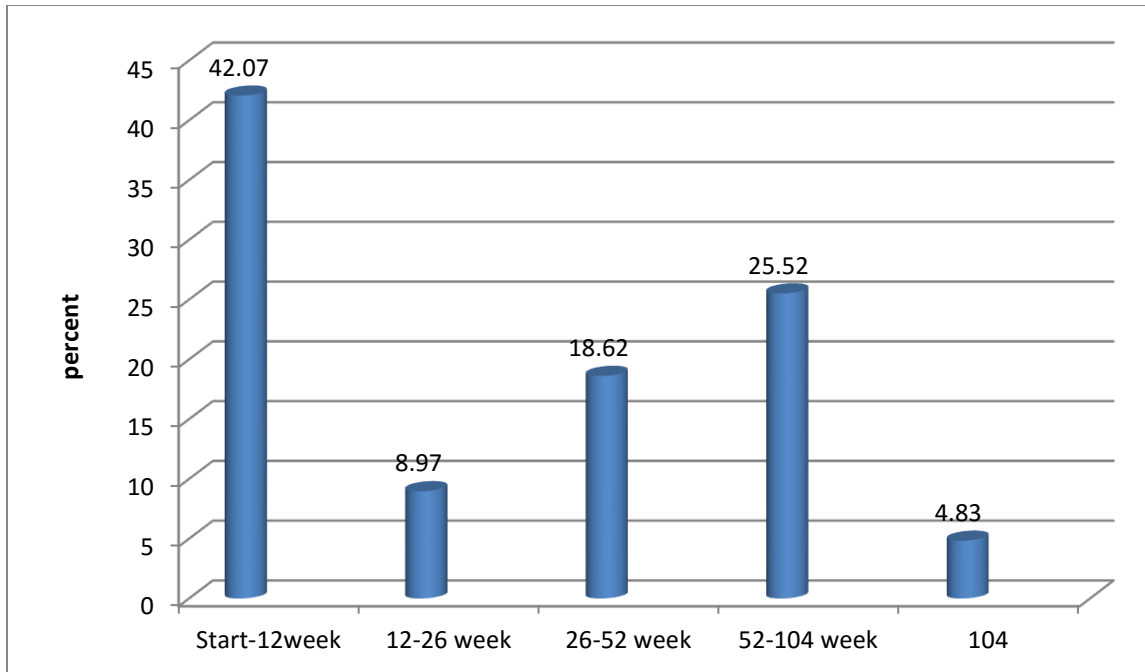


Figure 5: Weeks on initial anti retro viral (ARV) therapy before first switch in Asella Hospital ART clinic Jan 01, 2011-Dec 31, 2013.

From 102 patients who switched due to toxicity majority of them (48.03%) switched in the first 3 months (start-12 week) and only 2.94% of patients remained for more than 104 week before first switch. Similarly in case of patients with co morbid condition majority of them (33.33%) switched first regimen in the first 3 months (start-12 week) .Due to pregnancy, majority of patients(37.5%) switched first regimens in the first 3months(start-12 week and 26-52 week and only 12.5% switched in 12-26 and 52-104 week. In the case of treatment failure 28.57% of patients' switched first regimen in 12-26, 26-52 and 52-104 weeks and only 14.29% of patients remained for more than 104 week before first switch (**Table 5**).

Table 5: Common reason for modification by duration on first treatment regimen in Asella Hospital ART clinic Jan01, 2011-Dec 31, 2013.

Reason	Weeks on initial therapy				
	Start-12 weeks	12-26 weeks	26-52 weeks	52-104 weeks	>104 weeks
Toxicity	49(48.03%)	7(6.86%)	17(16.67%)	26(25.49%)	3(2.94%)
Co-morbidity	8(33.33%)	3(12.5%)	5(20.83%)	6(25%)	2(8.33%)
Pregnancy	3(37.5%)	1(12.5%)	3(37.5%)	1(12.5%)	-
Treatment failure	-	2(28.57%)	2(28.57%)	2(28.57%)	1(14.29%)
Drug stock out	1(25%)	-	-	2(50%)	1(25%)

6. DISCUSSION

The primary goals of antiretroviral therapy are to maintain maximum suppression of the viral load (i.e. fewer than fifty copies per micro gram) as much as possible for as long as possible, to restore and preserve immunologic function, to improve quality of life and reduce HIV related morbidity and mortality which is achieved through properly regulated antiretroviral therapy and rational treatment regimen switch (13).

The rationale for treatment switch can be due to risk of toxicity, poor adherence, treatment failure, or co morbidity (14).

A majority of the patients were on NVP based regimens of AZT/3TC/NVP (36.55%), the remaining were AZT/3TC/EFV (19.31%), D4T/3TC/NVP (13.79%), TDF/3TC/NVP (13.10%), D4T/3TC/EFV (10.34%) and TDF/3TC/EFV (6.89%). The result of this study was not consistent with other studies done in Southern India, Nekemte and Shashemene referral hospital (10,13 and 14) where D4T/3TC/NVP accounted for 63, 42.2% and 54.7%, respectively. Contraindications, Co morbid situations, Drug-drug interaction due to co morbidities and Stock status could be the possible factors that might have contributed to the variation.

Similar to other studies done in United Kingdom, Southern India, Swaziland, Dessie referral hospital, Nekemte referral hospital and Shashemene referral hospital (9, 10, 11, 12, 13, and 14), the most predictable cause for ARV switching, in the present study, was toxicity (102 patients). The patients with a more advanced disease at the base line could necessitate higher rates of regimen change/discontinuation due to adverse events.

From all the toxicities reported, rash (51.96%) was the most common reason for modification, similar to research done in Southern India (10) but contrary to other studies done in Swaziland, Nekemte hospital and Shashemene referral hospital (11, 13 and 14) where peripheral neuropathy was the most common reason for modification. This was most probably the reason why most of the patients in the study setting were on NVP-based regimens of AZT/3TC/NVP (64.52%), D4T/3TC/NVP (22.68%) and TDF/3TC/NVP (12.90%).

Peripheral neuropathy (28.43%) and Anemia (11.76%) were second and third most causes for modification. Peripheral neuropathy was due to D4T containing regimens of D4T/3TC/NVP (53.85%) and D4T/3TC/EFV (46.15%) whereas Anemia was due to AZT containing regimens of AZT/3TC/NVP (64.52%) and AZT/3TC/EFV (35.48%).

Unlike other study done in Dessie referral hospital (12) where 64 patients modified their first regimen due to anemia, the low rate of HAART change due to anemia, in this study (12 patients), could be due to the lack of adequate baseline anemia assessment.

Tuberculosis was the second cause of regimen switch in the study setting (24 patients). It was the only co morbid disease reported in this study, which is consistent with research done in Swaziland and Shashemene referral hospital (11 and 14) where 18 and 65 patients respectively switch their first regimen due to TB. Due to Tuberculosis, 50% switch D4T/3TC/NVP to D4T/3TC/EFV, (41.67%) patients switch from TDF/3TC/NVP to TDF/3TC/EFV and 8.33% switch from D4T/3TC/NVP to D4T/3TC/EFV in the study setting. The probable suggestion for NVP switch to EFV is overlapping drug toxicity of NVP with anti-TB, which is hepatotoxicity, and drug interaction since NVP is CYP3A4 enzyme inducer.

Pregnancy was the third major reason for modifying ART drugs in this study (8 patients). 37.5%, 25% and 12.5% of the patients on AZT/3TC/EFV, D4T/3TC/EFV and TDF/3TC/EFV were switched, consistent with studies done in Swaziland and Shashemene referral hospital (11 and 14) where 9 and 36 patients respectively switch due to pregnancy. This switch was due to the recommendation of the Ethiopian guideline to avoid teratogenic effect of EFV in pregnant women during the first trimester. Contrary to the recommendation of the guideline, current studies reveal no increased risk of overall birth defects in women exposed to EFV during the first trimester of pregnancy. Two patients switch from D4T/3TC/NVP which may be due to higher risk of nevirapine associated hepatic events and lactic acidosis associated with stavudine which is consistent with other studies done in United Kingdom (UK) and Dessie referral hospital (9 and 12) where one from each study area switched due to high risk of toxicity.

Treatment failure was given as a fourth reason for regimen change. Only seven patients face treatment failure from their first regimen in the study setting, (4 patients due to immunological failure and 3 patients due to development of opportunistic infection). According to the study in United Kingdom (10) virological failure alone accounted for 48% of the patients. Low rate of regimen switch due to treatment failure in the study setting could be due to lack of the viral load measuring device, lack of continuous monitoring of patients with a CD4 count, and on the occurrence of opportunistic infection.

Cost was one of the major reasons for discontinuation and modification of ARV drugs according to the study conducted in Southern India (10). However, it was not a reason for modification of ARV drugs in this study, due to the cost-free (fee-free) provision of ARV drugs for the patients in Ethiopia. Despite the cost free service, stock out problems accounted 2.76 % of the treatment regimen change which is a result of poor pharmaceutical stock management system either at the hospital or national level.

7. CONCLUSION AND RECOMMENDATION

7.1 CONCLUSION

In conclusion, the proportions of subjects who modify HAART in our resource constrained setting present a challenge to the limited treatment options that we currently have. Within this, Toxicity/side effect was the main reason for modification of initial antiretroviral drugs; while, tuberculosis, pregnancy, treatment failure and stock out were the rest reasons for initial antiretroviral regimen changes in this study.

From all recorded toxicity, rash was the leading one cause for modification of HAART. Furthermore, most of the toxicity and even most modification were incurred from NVP-based regimen especially AZT/3TC/NVP.

7.2 RECOMMENDATION

Since, most of modification of ARV regimen require laboratory result monitoring, there should be:

- ✓ enough, quality and effective laboratory equipment and trained professionals in Asella Referral Hospital
- ✓ Proper clinical recording,

Improvements in pharmaceutical procurement and stock management systems at hospital or national level are recommended.

Health providers working in the ART clinic should monitor patients both clinically and with laboratory for the occurrence of side effects.

The health system should develop ADR database so as to easily record and report adverse effect.

The hospital is recommended to have viral load measuring device.

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Data collection format.

Date of data collection _____

Name of data collector _____ sign _____

A. Patient Information

1. Card number _____
2. Sex: a) Male b) Female
3. Address a) Urban b) Rural
4. Marital status a) single b) married
 c) Divorced d) widowed
5. Educational status
 - a) No formal education c) Higher institute education
 - b) Primary school education d) Secondary school education
6. Date eligible _____
7. Age _____ years
8. Weight on start _____ kg
9. Weight during switch _____ kg
10. Patient source:
 - a. In patient b. Out patient c. PMTCT
 - d. General VCT

B. Clinical information

11. CD4 count on start (CD4cell/ul at base line n (%))
 - a. <50 b. 51-100 c. 101-200 d. 201-300 e. 301-350 f. > 350
12. WHO clinical stage on start of ART
 - a. Stage I b. stage II c. stage III d. stage IV
13. Starting regimen: -----
 - a. D4T/3TC/NVP e. TDF/3TC/NVP
 - b. D4T/3TC/EFV f. TDF/3TC/EFV
 - c. AZT/3TC/NVP
 - d. AZT/3TC/EFV

14. Duration of an initial ARV therapy before first switch
- a. Start – 12 weeks
 - b. 12-26 weeks
 - c. 52-104 weeks
 - d. .> 105 weeks
15. Regimen switched to _____
- a. AZT/3TC/NVP
 - b. AZT/3TC/EFV
 - c. D4T/3TC/EFV
 - d. TDF/3TC/NVP
 - e. TDF/3TC/EFV
 - f. D4T/3TC/NVP
16. Reasons for switching
- a. Toxicity
 - b. Treatment failure
 - c. Co morbidity
 - d. pregnancy
 - e. drug is not available
 - f. Drug is not available
17. If reason for modification is toxicity (adverse effect), type of adverse effect:
- a. Lipo atrophy
 - b. Rash
 - c. Anemia
 - d. Peripheral Neuropathy
 - e. Metabolic disturbance
18. If reason for change is treatment failure, type of treatment failure
- a. Clinical failure
 - b. Immunological failure
 - c. Virologic failure
19. If switch is due to co morbidity, co morbid condition of the patient:
- a. New TB
 - b. CNS disorder
 - c. Hepatitis

Research paper final endorsement form to be filled before final submission to the school of pharmacy.

Here with my signature, I declare that this paper is done under my advisor ship and I have approved that this draft is the final paper for submission to the school of pharmacy, SRP office of Jimma University.

Name _____

Signature

Here with my signature, I declare that this paper has been examined by me and I have checked that the student has corrected the comment that I forwarded during examination.

Name

Signature

Here with my signature, I declare that this paper is done by me as principal researcher and I assure that this paper is the final draft for submission to the school of pharmacy, SRP office of Jimma University.

Name

Signature

