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Incidence of Switching To Second Line Treatment Among HIV Patients Receiving Anti-Retroviral Therapy

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ABSTRACT

Aim: The main aim of this study is to estimate the incidence of switching to second line Anti-Retroviral Therapy (ART) among HIV patients.

Objective: The primary objective of this study is to determine the reason for switching to second line ART. The secondary objective of the study is to estimate the rate of treatment failure among HIV patients receiving first line ART. To determine the factors responsible for first line treatment failure.

Methodology: A Retrospective Observational study is conducted at a tertiary care hospital, Ongole, Prakasam District, Andhra Pradesh. Incidence of switching to second line ART among 4,187 HIV patients is assessed.

Results: In our study, we have collected ART cards of 4,187 patients living with HIV/AIDS. Out of which 3,419 patients are excluded from the study. 768 patients are included for the study who met the inclusion criteria. Of these patients, 739 members are receiving first line regimen and 29 patients are switched to second line Anti-Retroviral Therapy (3.77%).

Conclusion: Our study concluded a low incidence of switching to second line ART with an incidence rate of 1.01 per 100 persons a year. Out of 29 patients, failure of first line treatment is majorly observed with AZT+3TC+NVP (Zidovudine+Lamivudine+Nevirapine) among 13 patients (44.82%). Reasons for failure are determined majorly as a result of immunological and virological failure (37.93%). These reasons are associated with decreased adherence of 80-90% among 21 patients (72.41%).

Key words:
Anti-Retroviral Therapy, Adherence, Transmission, World Health Organization, Tonsillitis.

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INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is caused by Human Immunodeficiency Virus (HIV) which was first discovered in 1980[1]. First cases of HIV/AIDS were reported among female sex workers in Chennai, Tamil Nadu in 1986 in India. By 1987, 135 cases were reported of which 14 cases are progressed to AIDS (stage IV condition)[2].

HIV/AIDS is a condition which exposes the people to infections and some types of cancers due to weakened immune system. HIV/AIDS, a major global public health issue resulted in 9, 40, 000 deaths in 2018 globally. Out of 36.9 million people affected with HIV, 1.8 million cases were reported newly in 2017[3]. According to 2016 statistical reports of India, there were 21, 00, 000 people living with HIV, of which 49% were accessing Anti-Retroviral Therapy (ART). 80,000 were newly diagnosed and 62,000 were AIDS related deaths [4]. India is third country in the world with 2.14 million people living with HIV, an estimated count of 87,000 new infections and 69,000 AIDS related deaths annually [2]. Transmission of HIV infection occurs majorly through three main routes:

1) Sexual intercourse
2) Parenteral route
3) Perinatal route

World Health Organization (WHO) classified HIV/AIDS into four clinical stages as follows:
(Adults)

Clinical Stage 1
Asymptomatic and Persistent Generalized Lymphadenopathy

Clinical Stage 2
Moderate unexplained weight loss of <10% of presumed body weight; Recurrent Respiratory tract infections like Sinusitis, Tonsillitis; Herpes Zoster, Angular cheilitis recurrent oral ulceration; fungal nail infections; seborrheic dermatitis; popular pruritic eruption.

Clinical Stage 3
Unexplained weight loss of >10% of presumed body weight; unexplained chronic diarrhea for more than one month; persistent oral candidiasis; pulmonary Tuberculosis; severe bacterial infections like meningitis, bacteremia; acute

necrotizing ulcerative stomatitis, gingivitis; unexplained anemia (<8gm/dl).

Clinical Stage 4

HIV wasting syndrome; recurrent severe bacterial pneumonia; Chronic herpes simplex virus; Esophageal candidiasis; extrapulmonary tuberculosis; Kaposi sarcoma; Cytomegalovirus infection; Central Nervous System toxoplasmosis; HIV Encephalopathy; Lymphoma; Symptomatic HIV associated nephropathy or cardiomyopathy; recurrent septicemia; invasive cervical carcinoma; Atypical disseminated leishmaniasis [6].

Life threatening opportunistic infections are caused due to underlying immunosuppression resulting in morbidity and mortality of HIV infected people [7]. Weakened immune system is seen in the patients living with HIV or patients receiving chemotherapy which might make it harder to fight off the opportunistic infections [8].

Human Immunodeficiency Virus (HIV) consists of an enzyme reverse transcriptase enclosed in a lipoid bilayer membrane enclosed by a capsid. The surface glycoprotein molecule (GP 120) has strong affinity for proteins of CD4 receptors which are found predominantly on T-helper cells. HIV entry is a complex process. In addition to the attachment to CD4 cells, subsequent binding to the co-receptors like CCR-5 or CXCR-4 also occur along with membrane fusion. The virus sheds its outer coat and releases its genetic material after entry into the host cell. The enzyme reverse transcriptase converts viral RNA into viral DNA which is then integrated into host genome where it undergoes transcription, translation resulting in the production of new viral proteins. These new virus particles assemble and bud out of the host cell, mature to form infectious virions with the help of protease enzyme. 10, 000 million new virions are produced each day.

The diagnosis of HIV infection is mainly made by detecting antibodies against HIV [9]. These antibodies are developed after 3-4 weeks of initial exposure [10]. Measurement of CD4 cell count also helps in diagnosis of HIV/AIDS by measuring the level of immunosuppression which is a major indicator for Anti-Retroviral Therapy. This included measuring CD4 positive T-lymphocytes in a peripheral blood sample. Normal range is 500-1500 cells/mm^3. Number of cells depletes with disease progression. Prophylactic treatment against P. jiroveci pneumonia should be offered for the patients with CD4 count <200cells/mm^3. Viral load measurement is done to estimate the amount of circulating HIV RNA virus in plasma. Viral load and CD4 cell count ensures the clinician to start and change Anti-Retroviral Therapies [11].

National AIDS Control Organization was established in 1992 for prevention and control of HIV infection and Anti-Retroviral Therapy was introduced in 2004. With the introduction of Anti-Retroviral Therapy, there is a rapid decline in HIV related morbidity and mortality over last two decades. ART aims at reducing plasma viral levels and restoring immunological functions [2]. With increased exposure to first line Anti-Retroviral Therapy, the risk of viral resistance and subsequent treatment failure has become more important resulting in switching to second line regimens [12]. 4 symptom tool including current cough, fever, night sweats and weight loss should be considered for screening of Tuberculosis in HIV patients and Isoniazid Preventive Therapy (IPT) should be added to the patients as a prophylactic therapy [2].

Tab No. 1: Anti-Retro Viral (ARV) drugs

S.No	Class	Drugs
1	Nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTIs)	Abacavir, Emtricitabine, Lamivudine, stavudine, Tenofovir, Zidovudine
2	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz, Nevirapine
3	Protease Inhibitors	Atazanavir, Ritonavir, Indinavir, Lopinavir, Nelfinavir, Saquinavir
4	Entry Inhibitors i. Fusion Inhibitors ii. CCR5 inhibitors	 Enfuvirtide Maraviroc
5	Integrase Inhibitors	Raltegravir

The first line regimen which is recommended by NACO consists of a triple drug combination from two different classes of Anti-retro viral. Due to the better efficacy and lower incidence of side effects, the patients with HIV-1 infection should be initiated with the fixed dose combination consisting of Tenofovir (TDF-300mg) + Lamivudine (3TC-300mg) + Efavirenz (EFV-600mg) in a single pill once daily. This drug should be taken 2-3 hours after dinner at bed time and fatty foods should be avoided while taking this pill.

The drugs prescribed are considered as second line agents and the current recommendations for prescribing second line Anti-retroviral agents are as follows:

i. New class of anti-retro viral agent and a Ritonavir boosted Protease Inhibitor (Atazanavir/Ritonavir or Lopinavir/Ritonavir)
ii. One new NRTI which is not used previously in the first line regimen (Tenofovir or Zidovudine) or an integrase inhibitor in an inevitable situation (Raltegravir)
iii. Continue Lamivudine for reduced viral fitness.

Replacement of single individual drug within the same class due to toxicity, drug-drug interactions or intolerance is called as Substitution. Alternative first line regimens for substitution therapy that can be prescribed other than TDF+3TC+NVP are:

1) TDF+3TC+NVP
2) AZT+3TC+EFV
3) ABC+3TC+EFV
4) ABC+3TC+NVP

The preferred first line regimen for patients with HIV-2 infection is the fixed dose combination of Tenofovir (300mg) + Lamivudine (300mg) + Lopinavir/ Ritonavir (800mg/200mg).

TYPES OF TREATMENT FAILURE

Loss of antiviral efficacy to the current regimen can be considered as treatment failure [2]. Failure of antiretroviral therapy results in persistent viral replication implying immunological deterioration and clinical disease progression [19]. Increased exposure to first line agents increases the risk of viral resistance leading to treatment failure [20, 21].

Treatment failure of first line Anti-retroviral agents results in Switching. With failure of first line regimen, viral load starts rising followed by decline in CD4 count and clinical stage 4 manifestations appear after few months. Hence, Switching is defined by clinical and immunological failure which is further confirmed by virological failure particularly in resource limited settings [2]. Switching improves immune reconstitution, increases life expectancy and decreases drug resistance [22]. Mutations in protease reverse transcriptase and integrase genes results in resistance to antiretroviral drugs. Higher resistance to NNRTIs is mainly due to single point mutations. Testing of drug resistance gives an indirect measure of drug susceptibility and this is done using Polymerase chain reaction (PCR) [19]. WHO estimates the average switch rate from first to second line ART as 2-3% in adults [12].

Clinical failure is defined as the development of WHO clinical stage 3 or 4 condition after 6 months of treatment initiation.

Immunological failure can be defined by any of the three criteria:

a) Return to or fall of CD4 count below pre therapy base line after six months of treatment initiation
b) 50% decline from on-therapy peak value
c) CD4 count of 100 cells/mm^3 after 12 months of treatment initiation.

Virological failure is defined by plasma viral load of 1,000 or more copies/ml after six months of treatment initiation in the patients with >95% of treatment adherence (National Technical Guidelines on Anti-retroviral Treatment, October 2018). Other predictors for treatment failure include older age, male sex, severe malnutrition, anaemia, advance baseline WHO clinical stage, longer duration of ART intake and a negative change in body weight [22].

Fixed dose combinations of Anti-Retro Viral agents are preferred because of their ease to prescribe and improved treatment adherence [2]. Missing a single dose can barely suppress viral replication and plasma levels of the drug fall dangerously low. The turnover rate of Human Immunodeficiency virus is rapid with 108 replications per day. This results in emergence of drug resistant variants which implies virological treatment failure. Factors responsible for lack of adherence are associated with medication, patient or provider. Medication associated factors are pill burden, inconvenience to regimen and drug complexity. Patient specific factors are level of motivation, psychological well-being, health beliefs and social support. Provider based factors include provision of counseling about adherence and implementation of adherence support techniques [19].

AIM

The main aim of this study is to estimate the incidence of switching to second line Anti-Retroviral Therapy (ART) among HIV patients.

OBJECTIVES

The primary objective of this study is to determine the reason for switching to second line ART. The secondary objective of the study is to estimate the rate of treatment failure among HIV patients receiving first line ART. To determine the factors responsible for first line treatment failure.

METHODOLOGY

A Retrospective Observational study is conducted at a tertiary care hospital, Ongole, Prakasam District, Andhra Pradesh. The study is conducted in 4,187 patients for a period of one year.

Inclusion criteria

Patients aged 18 years and above who are on ART for 6 months or more are included in this study. Patients with serial CD4 cell count having at least 4-5measurements are included. Patients who are alive and under follow- up are included.

Exclusion criteria

Patients whose CD4 count is not documented for at least once after 6 months of ART are excluded. Patients who are prescribed with third line ART regimen are also excluded from the study. Patients who are dead and those who are not under follow-up are excluded from the study.

Study procedure

This Retrospective observational study is carried out at an ART center in tertiary care hospital. The Anti-Retroviral Therapy data of the patients were collected at ART center from the ART cards of the patients living with HIV/AIDS. Patients are included in the study, if they met the inclusion criteria. Data was collected by using a specialized form, it included, demographic details of the patient like age, gender, marital status and social habits; clinical details included functional status, WHO clinical stage, CD4 count and Viral load; therapeutic details included medication adherence, first line Anti-Retroviral Regimen, second line Anti-Retroviral Regimen and reason for switching to second line therapy. All the details of the patients receiving both therapies are analyzed and incidence of switching is assessed. Reasons for estimating treatment failure of first line Anti-Retroviral Regimen is also assessed according to the National Technical Guidelines on Anti-retroviral Treatment, October 2018. Reasons for switching are clinical, immunological and virological failure. Other factors responsible for switching are also analyzed.

RESULTS

In our study, we have collected ART cards of 4, 187 patients living with HIV/AIDS. Out of which 768 patients are included for the study who met the inclusion criteria. Of these patients, 739 members are receiving first line regimen and 29 patients were switched to second line Anti-Retroviral Therapy (3.77%). Incidence rate of switching to second line regimen is 1.01 per 100 persons a year. Remaining 3, 419 patients are excluded from the study.

Considering the demographic parameters, switching to second line Anti-Retroviral Therapy is majorly observed mostly among the people with age group of 30-59 years (82.75%) followed by people with age group of <30 years (17.24%). Males (62.06%) experienced higher percentage of first line treatment failure compared to females (37.93). Among the patients switched to second line ART, majority are not having any social habits like alcohol consumption and smoking (75.86%). Alcohol consumption is seen among few switched patients (10.34%) and very few patients are having both habits like alcohol consumption and smoking (3.44%). Taking clinical parameters into consideration, among the patients subjected to switching,

majority of the patients are working (96.55%), followed by ambulatory patients (3.44%). There are high proportions of patients experiencing WHO clinical stage I (44.82%) followed by clinical stages III (34.48%) and clinical stage II (20.68%) among patients switched to second line ART. Percentage distribution of demographics among HIV patients are shown in **Table 2.**

Therapeutic parameters include Medication adherence and treatment. Switching is experienced majorly among the patients with adherence percentage of 80-90 (based on pill-count method) (72.41%), followed by 90-100 adherence (72.41%) and <80 adherence (3.44%).Majority of patients are switched to second line Anti-Retroviral Therapy after 80-99 months (37.93%) of using first line Anti-Retroviral agents followed by <80 months (31.03%) and 100-119 Months (24.13%).First line treatment failure is majorly seen with AZT+3TC+NVP (44.82%), Followed by TDF+3TC+EFV (20.68%), TDF+3TC+NVP (13.79%), d4t+3TC+NVP (13.79%) and d4t+3TC+EFV (3.44%), AZT+3TC+EFV (3.44%). And the percentage distribution is depicted in fig. no. 1.

Tab 2: Percentage distribution of demographics among HIV patients.

Demographic Details	FIRST LINE ART		SECOND LINE ART	
	No. of patients	%	No. of patients	%
Age (years)				
<30	229	30.99	5	17.24
30-59	495	66.98	24	82.75
60-89	14	1.89	0	0
≥90	1	0.14	0	0
Gender				
Male	348	47.09	18	62.06
Female	391	52.9	11	37.93
Social habits				
Smoker	59	7.98	3	10.34
Alcoholic	43	5.82	3	10.34
Both	48	6.5	1	3.44
None	589	79.7	22	75.86
Functional status				
Working	**704**	**95.26**	**28**	**96.55**
Ambulatory	**32**	**4.33**	**1**	**3.44**
Bed ridden	**3**	**0.41**	**0**	**0**
WHO clinical stage				
Stage -1	435	58.86	13	44.82
Stage -2	190	25.71	6	20.68
Stage -3	109	14.75	10	34.48
Stage -4	5	0.68	0	0
Medication adherence (%)				
<80	15	2.03	1	3.44
80-90	150	20.3	21	72.41
90-100	574	77.67	7	24.13
Duration on ART (months)				
<80	346	46.82	9	31.03
80-99	384	51.96	11	37.93
100-119	9	1.22	7	24.13
≥120	0	0	2	6.89

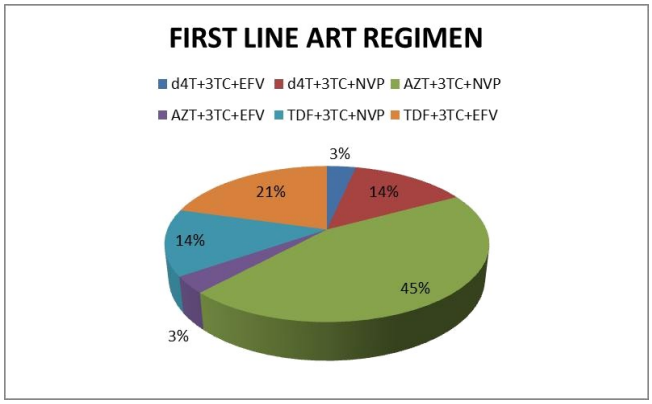

Fig. No. 1: Distribution of first-line regimen among patients switched to second line ART

Reason for switching

Reasons for switching are determined as follows:

(i) 8 patients are switched due to lack of adherence and increased viral load (HIV-1) that resulted in virological failure

(ii) 5 patients experienced advanced WHO clinical stage (III and IV), increased expression of viral load (HIV-1) in plasma determining clinical and virological failure.

(iii) 5 patients are with advanced WHO clinical stage (III and IV), decreased CD4 count and increased viral load (HIV-1) resulting in clinical, immunological and virological failure.

11 patients experienced decline in CD4 count and increased viral load (HIV-1) in plasma determining immunological and virological failure.

Tab 3: Percentage distribution of reasons for switching among patients switched to second line ART

Reason for switching	No. of patients	Percentage
Virological failure	8	27.58
Clinical and virological failure	5	17.24
Immunological and virological failure	11	37.93

Clinical, immunological and virological failure	5	17.24

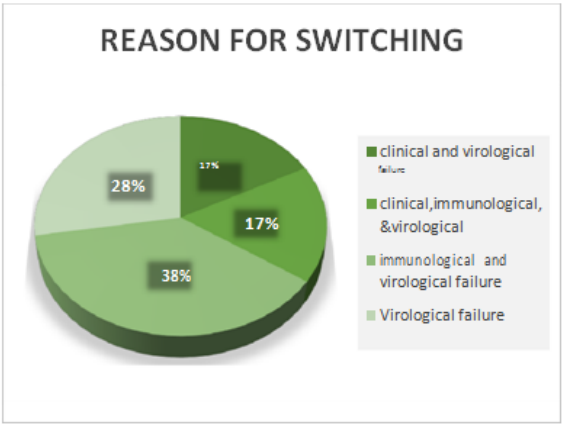

Fig. No. 2: Distribution of reasons for switching to second line ART regimen

Second line Anti-Retroviral Therapy with TL+ATV/r is given for all the patients who are introduced with switch therapy (100%).

Tab 4: Percentage distribution of second line regimen among patients switched to second line ART.

Second line treatment	No. of patients	Percentage
TL+ATV/r	29	100

DISCUSSION

Our study aimed to measure the incidence of the switching to second line ART among 4,187 HIV patients. Among these 768 patients, 29 patients were switched to second line ART. As per our study the incidence rate of switching to second line regimen is observed as 1.01 person-years in a 6 months period. The higher failure rate is noted in between 30-59 years of age among both switched (82.75%) and Non switched patients (66.98%). Of which 17.24% is observed among switched patients of 30years of age and 30% among non-switch patients, 1.89% in the patients of 60-89 years of age and 0.14% in the patients of ≥90 years of age.

Our results shows that majority of the patients are not having any social habits (75.86% in switched group,79.7%in non-switched group), 10.34% were alcoholic and smoker were 10.34%in switched group,5.8% of alcoholic, 7.9% were smoke, 6.5% were having both habits in non-switched groups, 3.4% of people having both habits in switched group.

Poor adherence of 72.4% is seen in switched group where as 77.67% is seen in non-switched. Adherences are calculated by pill count method in our study. Functional status of the patients are mostly working (96.5%), ambulatory (3.4%) in switched patients, where as 95.2% were working in non-switched patients.

Longer duration of ART can also effect the switching to second line ART. Our results show that among 29 patients switched to second line ART, patients who are on ART for 80-99 months were mostly switched to second line with (39.9%) among 29 patients. The risk of switching in first line ART patients was 51.96 %.

Clinical failure is one of the reliable factors in switching to second line ART regimen. Simultaneously only clinical failure alone shouldn't be consider. virological failure should also be considerd for switching.17.24% of clinical and virological failure was observed in our study. According to WHO, HIV is divided in to four clinical stages, stage -I, stage-II, stage-III, stage IV. Our results show that 44.82% are in Stage – I, 20.6% in stage II, 34.4% are in stage III among switched group, where as in non-switched group stage – I were 58.8%, stage II were 25.7%, stage III were 14.7%.

According to NACO guidelines for every 6 months CD4 Count should be tested. Under Immunological failure there are three criteria should be considered which are:1. Decrease of CD4 count to pre therapy baseline, 2. 50% decrease from the on treatment peak value, 3.persistent CD4 level below 100cells/mm^3.

In six months of study the serial CD4 count decreased based on above criteria when compared to non-switching group. It may vary due to various factors like drug resistance, poor adherence and other factors. Virological failure is most significant criteria for switching to second line ART. Even though the patient met the clinical failure or immunological failure they won't be switched to second line until they met virological criteria, According to NACO guidelines criteria for virological failure is plasma viral load of greater than 1000 copies/ml. In our study 27.58% were subjected to virological failure; 17.24% experienced clinical& virological, 37.9% were subjected to immunological & virological, and 17.2% were subjected to clinical, immunological &; virological. Only targeted viral load is carried out in HIV patients of RIMS. In ART center at RIMS fixed drug combinations were used which are

- Stavudine+Lamivudine+Nevirapine (d4T+3TC+NVP)
- Stavudine+Lamivudine+Efavirenz (d4T+3TC+EFV)
- Zidovidine+Lamivudine+Nevirapine (AZT+3TC+NVP)
- Zidovidine+Lamivudine+ Efavirinze (AZT+3TC+EFV)
- Tenofovir+Lamivudine+Nevirapine (TDF+3TC+NVP)
- Tenofovir+Lamivudine+Efavirinze (TDF+3TC+EFV)

Among these drugs, patients using Zidovidine+Lamivudine+Nevirapine (AZT+3TC+NVP) are mostly switched patients (44.82%).

CONCLUSION

Our study concluded a low incidence of switching to second line ART with an incidence rate of 1.01 per 100 persons a year. Out of 29 patients, failure of first line treatment is majorly observed with AZT+3TC+NVP among 13 patients (44.82%). Reasons for failure is determined majorly as a result of immunological and virological failure (37.93%). These reasons are associated with decreased adherence of 80-90% among 21 patients (72.41%).

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