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.

INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is caused by Human Immunodeficiency Virus (HIV) which was first discovered in 1980. 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).

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. 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. 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. 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:

(Abdom)

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 puritic 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; Kaposis sarcoma; Cytomegalovirus infection; Central Nervous System toxoplasmosis; HIV Encephalopathy; Lymphoma; Symptomatic HIV associated nephropathy or cardiomyopathy; recurrent septicemia; invasive cervical carcinoma; Atypical disseminated leishmaniasis  

Life threatening opportunistic infections are caused due to underlying immunosuppression resulting in morbidity and mortality of HIV infected people. 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.

Human Immunodeficiency Virus (HIV) consists of an enzyme reverse transcriptase enclosed in a lipid 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. These antibodies are developed after 3-4 weeks of initial exposure. 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/mm³. Number of cells depletes with disease progression. Prophylactic treatment against P. jiroveci pneumonia should be offered for the patients with CD4 count <200cells/mm³. 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.

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. 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. A 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.

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 | Enfuvirtide |
| 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-retro viral 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).
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 measurements 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 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 (62.6%) 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, the 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,
The 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               |

Table 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 |

Fig. No. 1: Distribution of first-line regimen among patients switched to second line ART.
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 30 years 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 alcohol, 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 considered 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/mm³.

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)
- Zidovudine+Lamivudine+Nevirapine (AZT+3TC+NVP)
- Zidovudine+Lamivudine+Efavirenze (AZT+3TC+EFV)
- Tenofovir+Lamivudine+Nevirapine (TDF+3TC+NVP)
- Tenofovir+Lamivudine+Efavirinze (TDF+3TC+EFV)

Among these drugs, patients using Zidovudine+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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REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). AIDS Epidemic Update [internet]. Geneva: UNAIDS/AIDS; cited on: 01 December, 2003. Available from: http://data.unaids.org/pub/report/2003/2003_epiupdate_en.pdf

2. National AIDS Control Organization (NACO). National Technical Guidelines on Antiretroviral Treatment [internet]. India: NACO; cited on: 25 October, 2018. Available from: https://lms.naco.gov.in/frontend/pdf-

3. World Health Organization report. HIV/AIDS. 19 July, 2018, World Health Organization (WHO). HIV/AIDS fact sheets [internet]. Geneva: WHO; cited on: 19 July, 2018. Available from: https://www.who.int/news-room/factsheets/detail/hiv-aids

4. Joseph T. Dipiro, Robert L Talbert, Gary C. Yee, Gary R. Wells, L. Michael Posey. Pharmacotherapy, a Pathophysiologic Approach. 7th edition. Mc Graw Hill Medical; 2008: 2066-2067.

5. World Health Organization (WHO). WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: WHO; cited on: 07 August, 2006. Available on: https://www.who.int/hiv/pub/vct/hivstaging/en/

6. V Nissapatorn, C.K.C.Lee, Y.A.L.Lim, K.S.Tan, I.Jamaiah, M.Rohana et al., Toxoplasmosis: A Silent Opportunistic Disease in HIV/AIDS patients. Research Journal of Parasitology. 2007; 2(1):23-31.

7. U. S. Department of Health and Human Services. HIV and Opportunistic Infections, Coinfections, and Conditions [internet]. U. S. National Library of Medicine; cited on: 15 June, 2018.

8. Roger Walker and Cate Whittlesea. Clinical Pharmacy and Therapeutics. 5th edition. Edinburgh. Churchill Livingstone; 2012: 624-625.

9. Joseph T. Dipiro, Robert L Talbert, Gary C. Yee, Gary R. Wells, L. Michael Posey. Pharmacotherapy, A Pathophysiologic Approach. 7th edition. Mc Graw Hill Medical; 2008: 2067.

10. Roger Walker and Cate Whittlesea. Clinical Pharmacy and Therapeutics. 5th edition. Edinburgh. Churchill Livingstone; 2012: 627-637.

11. Jigarp.Modi, Amitalubavat, shaileshmundhava, UshaLalwani. A prospective study to evaluate prescription pattern of second line anti-retroviral therapy given to HIV patients. Journal of Young Pharmacists. 2018; 10(1): 117-122.

12. Grace Mc Comsey and J Lonergan. Mitochondrial Dysfunction: Patient Monitoring and Toxicity Management. Journal of Acquired Immune Deficiency Syndromes. September 2004; 37: S30-S35.

13. Andrew Carr. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. PlumX Metrics. March 2003; 361(9359):726-735.

14. Lichtenstein KA. Redefining lipodystrophy syndrome: risks and impavct on clinical decision making. Journal of Acquired Immune Deficiency Syndromes. August 2005; 39(4):395-400.

15. Schambelan M, Benson CA, Carr A, Currier JS, Dube MP, Gerber JG et al., Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society- USA panel. Journal of Acquired Immune Deficiency Syndromes. November 2002; 31(3): 257-275.

16. Sabin, C.A., Worn, S.W., Weber, R., et al., 2008. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet 371, 1417–1426.

17. Worn, S.W., Sabin, C., Weber, R., et al., 2010. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti HIV drugs (D:A:D) study. The Journal of Infectious Diseases. 201, 318–330.

18. Parveen Kumar and Michael Clark. Clinical Medicine. 8th edition. Edinburgh. Saunders; 2012: 184-185.

19. Olivia Keiser, Catherine Orrell, Matthias Egger, Robin Wood, Martin W. G Brinkhof, Hansjakob Furrer et al., Public- Health and individual approaches to antiretroviral therapy: Township South Africa and Switzerland compared. Public Library of Science. September 2008; 5(9):e195.

20. Mar Pujades-Rodriguez, Daniel O’Brein, Pierre Humblet, Alexandra Calmy. Second-line antiretroviral therapy in resource-limited settings: the experience of Medicines Sans Frontieres. Acquired Immuno Deficiency Syndrome (AIDS)" July 2008; 22(11): 1305-1312.

21. Thomas Gaponera, Maya Petersenb, Matthias Egger,c Sam Phirid, Marloes H. Maathuis. The Causal Effect of Switching to Second-line ART in Programmes without Access to Routine Viral Load Monitoring. National institute of health science. 2012; 26(1): 57–65.

22. Habib O. Ramadhani, John A. Bartlett, Nathan M. Thielman, Brian W. Pence, Stephen M. Kimani, Venance P. Maro et al., The Effect of Switching to Second-Line Antiretroviral Therapy on the Risk of Opportunistic Infections Among Patients Infected with Human Immunodeficiency Virus in Northern Tanzania. Infection Disease Society of America. 2016; 1-7.