Volume : 5 | Issue : 8 | August 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Clinical Study of Efficacy and Toxicity Profile of Antiretroviral Treatment Regimens in Resource Restricted Settings. –Original Article

Medical Science

KEYWORDS : Antiretroviral treatment, CD4 count, Virological count, success rate, toxicity

Dr. Umesh Bhoi	MD, Associate Prof. Dept of Dermatology, Govt Medical College, Miraj
*** Dr. Shekhar N Pradhan**	MD, Professor, Dept of Dermatology, Govt Medical College, Miraj * Corresponding Author
Dr Sudarshan Gaurkar	MD, Assistant Professor, Dept of Dermatology, R.C.S.M. G.M.C., Kolhapur
Dr. Amruta Kamble	MD , Assistant Professor, Dept of Dermatology, Govt Medical College, Miraj

ABSTRACT

Background: *When AIDS was first recognized in 1981, patients with the disease were unlikely to live longer than a year or two. Since the development of an effective arsenal of drugs that can help many people infected with HIV live longer and healthier lives.*

Aims: *The present study was conducted to compare efficacy of different antiretroviral regimens in form of immunological and virological success and drug toxicity of anti retroviral treatment.*

Materials and Methods: *Study was conducted in resource restricted setting on 230 HIV positive patients who are on antiretroviral treatment to compare efficacy and toxicity. Assessment was done with clinical, virological and immumnological criteria at baseline, 3 months interval and at 48 weeks.*

Results: *All of the five regimens studied had increased CD4 count at the 48 weeks of antiretroviral therapy. Success rate is higher in double PI regimen (86.7%) while lowest in 2NRTI regimen (56.6%). The Efavirenz, Nevirapine, single PI based regimen had almost same (>80%) success rate. Failure rate was highest in 2NRTI regimen (44.7%) while lowest in double PI regimen (13.3%) Most of the adverse effects are associated with Stavudine i.e. peripheral neuritis and lipoatropy. Serious adverse effects were seen with Nevirapine.*

Introduction:

Once inside the cell, HIV viruses use specific enzymes to survive. The first approved classes of antiretroviral drugs that worked by interfering with the virus ability to use these enzymes. They are either reverse transcriptase (RT) inhibitors or Protease inhibitors. RT inhibitors can be Nucleoside RT inhibitors or non-nucleoside inhibitors. The newest class of antiretroviral drugs works by changing the shape of gp41 envelope protein surrounding HIV. These molecules are called fusion inhibitors. Different studies have compared different HAART regimens in treatment-naive individuals, to evaluate data regarding the optimal choice in patients starting treatment with a low CD4 count by using prospectively collected data from a single centre; we have compared the treatment response to different ART regimens. Most of these patients commencing therapy with low CD4 count. Decisions regarding initiation or changes in antiretroviral therapy should be guided by monitoring the laboratory parameters of plasma HIV RNA viral load and CD4+ T cell count in addition to the patient's clinical condition. Results of these laboratory tests provide clinicians with key information regarding the virological and immunological status of the patient and the risk for disease progression to acquired immunodeficiency syndrome (AIDS).[1] Measurement of plasma HIV RNA levels by using quantitative methods should be performed at the time of diagnosis and every 3-4 months With optimal therapy viral levels in plasma at 24 weeks should be below the limit of detection.[2] Data from clinical trials demonstrate that lowering plasma HIV RNA to <50 copies/ml is associated with increased duration of viral suppression compared with reducing HIV RNA to levels of 50-500 copies/ml.[3]

Aims and Objectives:

1. To compare efficacy of different antiretroviral regimens in form of immunological and virological success.
2. To asses immunological and virological failure rate and causes of the failure.
3. To asses drug toxicities of different ART drugs.

Materials and Methods:

The study was conducted at tertiary hospital over a period of 48 weeks. Total 230 patients were included in the study.

Inclusion criteria

Those patients were started on anti retroviral in considering criteria

1) One of following test is positive for HIV

- One ELISA + one spot / One ELISA + WB- PCR/ One ELISA + One clinical marker.

2) CD4 counts less than 300 cells/cu.mm.

Patient's spouses are also tested for HIV infection if available. Pretest and post test counseling was done.

Exclusion criteria:

If baseline CD4 count or viral load is not available patient is not taken in the study.

Criteria for the success /failure of ART are determined by:

1. If viral load is above 400 copies / ml at the end of 48 weeks – considered as failure, < 400 copies / ml considered successful.
2. Increase 25 to 50 cells / cu. Mm above the base line CD4 + T cell count as the end of 48 week – successful.
3. If both the above criteria not available at the end of 48 weeks clinical improvement without any new opportunistic infection considered as successful.
4. If the drug toxicity is the cause of change in therapy it is considered as failure.
5. If the drug is changed due to the cost in the same class it is considered as successful or failure according to above criteria.
6. Any new opportunistic infection during antiretroviral treatment (AIDS defining opportunistic infection) considered as failure irrespective of viral / CD4 cell count.

Volume : 5 | Issue : 8 | August 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Results:
Most of the patients i.e. 129 (56.1%) were in the age group of 31 to 40 years and majority (90%) patients belongs to the age group between 21 to 50 years. (Table-1) Out of 230 patients 187 (81.3%) were males while 43 (18.7 %) patients were females with male to female ratio being 4.3:1. Amongst total of 230 patients 166 (72.2%) were married, 47 (20.4%) were unmarried and 16 belongs to other categories. On testing the spouses it was found that 70 (36.9%) spouses of the involved patients are HIV positive and 101 (53.1 %) are discordant couple. (Table-2)

Among the various patients majority 200 (86.9%) patients were tested for HIV as they were symptomatic for one or other reasons. Another large component of the patients 7.8% (n=18) were tested as they were suffering from STDs. Patients who were tested as part of preoperative check up were 1.7% (n=4) and for ANC checkup 1.3% (n=3).

Out of total 230 patients only 2 patients each had co infection with Hepatitis B and Hepatitis C while one patient showed VDRL positive.

Almost 95 % of the patients were having heterosexual exposure. Blood transfusion history was there in 8 patients and vertical transmission in 2 patients.

Most of the patient 37 % (n=83) were in Efavirenz group because of associated Tuberculosis in 53 patients out of 83. In Nevirapine group 62 (26%) patients were there as it was cheaper triple drug combination. (Table-3)

On comparing CD4 count of the patients amongst different group at the beginning of the ART and ant an interval of 48 weeks it was found that increase in CD4 count is much higher in 2NRTI + PI group i.e., 387.6 followed by 2NRTI + double PI with 383.5 and lowest in 2 NRTI group i.e. 109.32 though baseline CD4 count of 2 NRTI group was high. (Table- 4), Fig-1

Successful rate was high in double PI group (86.6%) followed equally by 2NRTI + single PI and 2NRTI +EFV (81%). While the success rate was lower in 2 NRTI groups (55.2%). (Table-5)

This success rate is determined by following criteria as in

Virological	- 45 pt
Immunological	-100 pt
Clinical	-75 pt

Highest failure rate (44.7%) was seen in 2 NRTI group followed by 2NRTI + NVP group while lower (13.3%) in double Pl group. (Table-6)

Failure data is based	Virological	-	7 pt
Immunological		-	16 pt
Clinical	-		9 pt
Drug toxicity	-		30 pt

Discussion
In the present work, 230 patient who had received ART for about 48 weeks were studied with view to study the success rate of ART and epidemiological aspect in Indian scenario.

Age Distribution: In our study most of the patients included were about 90% in the age group of 31-50 years i.e. affecting the working population impacting social and economical status. The youngest was the 4 yrs child and oldest was of 73 years. The group involving the most no. of patient was 31-40years of age group (56.08%) shows disease affecting sexually active.

Sex Distribution: 187 patient (81.30%) patient were male and 43 patients were females. This figures evaluate more prevalence of disease is among male than females, as well as approach towards ART is higher in males.

Marital Status: In our study 166 (72.1%) were married and 47 (20.4%) are unmarried. Another 11 patients (4.7%) were widow most probably husband died because of HIV/AIDS.

Testing Of Spouses: Total 190 spouses were included out of this 19 are not tested after counseling also because many patient are migrants from interiors of Maharashtra or Uttar Pradesh. Amongst all 70 spouses were detected positive for HIV i.e. 70 cordant couples (36.8%), 101 were discordant couple (53.1%)

Two patients out of 230 are detected positive during pre-employment and 2 patient during general checkup while one referred from infertility clinic. Rests of the patients are tested for symptoms like chronic fever, weight loss, chronic diarrhea etc. Patients tested for STD and 3 are positive during ANC clinic.

Viral co-Infection: Only two patients had Hepatitis B and two patients had Hepatitis C positive. One patient had admitted for secondary syphilis, which had VDRL titer positive in higher dilution.

Route of Transmission: Two patients had vertical transmission parents of both children were positive. In one patient we could not found exact cause of transmission on history, patient was 64 year old. History of blood transfusion was seen in 8 patients, in these patient no other risk factor. 201 patients (95.2%) were heterosexual intercourse; in this majority patients had history of sexual exposure to female sex worker. In our study no one had given h/o homosexual or bisexual behavior.

No. Of Patient in Different Regimen:

1. 15 patients were on 2 NRTI + double Pl in this group only 8.5% was included because of higher cost of regimen. Most of on boosted Pl i.e. addition of Retinovir.
2. 2NRTI+single Pl include 32 (14%) patients. Initially more patients were on this regimen that was shifted on Efavirenz because of cost. Out of 32 patients 28 were on Nelfinavir. One patient each on Retinovir, Saquinavir. 2 patients on Indinavir
3. 2 NRTI + Efavirenz: include 83 (37 %) patient, 63 patients in this group had tuberculosis typical/atypical (disseminated) in this patient Efavirenz given in 800 mg doses.
4. 2NRTI + Nevirapine included 62 (26%) patients from study. This is cheaper triple drug regimen. In this group 23 patients had tuberculosis but ART was started after intensive phase of ATT because of drug interaction. Rifampicin decreases level of Nevirapine 20 – 58% and increase chances of hepatotoxicity. Maintenance phase is started with INH and Ethambutol.
5. 2 NRTI: Patient who was not affording triple drug combination was started on 2 NRTI drugs by the practitioners 38 (16.5%) patients were included in this group.
6. Combination of 2NRTI for each group was backbone. Most of the patient was started on d4T + 3Tc Following NRTI drugs were used in patient: D4T–203, 3 TC – 217, AZT – 27, DDI – 10 patients respectively.

CD4 Count
Most of the increase in CD4 cell count is seen in double PI group while least in 2 NRTI group though the mean baseline CD4 count of 2NRTI group was higher.

Success of Antiretroviral Therapy
Success rate is highest in double PI group (86.6%) while lowest in 2NRTI group (55.2%). Groups with Efavirenz, single PI and Nevirapine has almost same success rate 81.9% and 80.6%. This success rate is on higher side than previous studies because we consider mostly the clinical criteria while other studies are concluded from virological base. We could not depend on the virological and immunological data because many patients were not affording the cost for laboratory investigations at the end of 48 weeks. We had included only 45 patients with virological data, 100 patients with immunological data and 75 patients on clinical improvement base. Success rate was considered at the initial 48 weeks of ART. Also we had switched over many drugs from higher cost to lower cost which also consider success / failure according to end result of regimen.

Failure Rate
1. 2NRTI Group: Most of the failure was seen with 2NRTI (44.7%) group.

Virological failure - 2 patients
Immunological failure - 5 patients
Opportunistic infection - 3 patients
(2 – develop PCP, 1-Abdominal TB)
Not Followed – 8 patients
Showing adherence was less in this group.

2. NEVIRAPINE Group: Failure rate was 19.3%. Out of total 60 patients 12 were failure.
Virological failure - 1 pt
Immunological failure - 3 pts
Clinical failure - 5 pts
2- Pulmonary tuberculosis
2- Abdominal tuberculosis relapses. 1PCP
Not followed - 2 patients

3. Efavirenz group: Failure rate was 18%
Virological failure – 1 pt
Immunological failure – 5 pts
Clinical failure – 2 {1-PCP, 1-Cryptococal meningitis.}
Not followed – 2

4. 2 NRTI+ double PI group: Failure rate was very low 13.3%. Out of 15 patients only 2 had failure of ART
Immunological failure - 1 pt
Drug toxicity - 1 pt

5. 2 NRTI + Single PI group: Failure rate was 18.7%
Virological failure - 3 pts
Immunological failure - 3 pts
Clinical failure -1 pt [progressive myeloleucoencephalopathy developed during therapy."
Not followed - 1
Drug toxicity - 1

Drug Toxicity: HIV infected patient's present complex immunological alterations which pose these patients at a higher risk of developing cutaneous adverse drug reactions due to drug hypersensitivity [4]

2NRTI + Single PI :1 – Patient had peripheral neuritis
2 – Patient had lipoatropy
3 – Patient develops nephrolethiasis because of Indinavir.

In 5 patients Nelfinavir stopped after 9 months of treatment because of cost and switched over to Efavirenz and Nevirapine.

2. NRTI + Double PI group: 1 – patient had peripheral neuritis
2 – Diarrhea and lipoatropy after 9 months.

3. 2 NRTI + Efavirenz: 5 - Patient had giddiness and drowsiness initially when regimen started
1 - Chest pain
5 - Peripheral neuritis - premature cataract
1– Patient was switched over to PI because of failure
5 – Patient were switched over to Nevirapine because of cost

It is mentioned by NACO that patients who initially were on NVP based ART and shifted to Efavirenz due to antitubercular treatment (ATT) should again be shifted to NVP without any lead in dose after completion of Rifampicin-based ATT.[5]

4. 2NRTI + Nevirapine

4 – Patients develop severe skin rash (Steven – Johnson's syndrome)

Nevirapine was suspected in 52 out of 90 (57.7%) cases of CADRs which included four cases of Stevens-Johnson syndrome [6]

2 – Develop hepatotoxicity

2 – Lipoatrophy at 12 months

A recent study by Lokhande et al., has shown that there is striking increase in the incidence of NVP-induced cutaneous rashes of all forms (4.64% patients treated before November 2011 vs 9.03% patients treated after November 2011) and considerable increase in frequency of severe kind of reactions with the revised guidelines.[7]

Number of previous studies has shown NVP to be the most common anti-retroviral agent associated with cutaneous adverse drug reactions including severe CADRs like Stevens-Johnson syndrome, Toxic epidermal necrolysis and Stevens-Johnson Syndrome-Toxic epidermal necrolysis overlap .[8, 9, 10, and 11]

5. 2 NRTI 1 – Peripheral neuritis

1 – Lipoatrophy at 12 month

All over 8 patients shows peripheral neuritis, 9 shows lipoatrophy, these were because of Stavudine side effect. Most dangerous side effects were with Nevirapine (Steven Johnson's Syndrome, hepatotoxicity). Out of 27 patients on Zidovudine, 3 patients had bone marrow suppression at 48 week of therapy and 5 patients had Zidovudine induced hyper pigmentation.

Conclusion
In present study 230 patients of HIV positive that were on ART studied was studied

1. Most of the patients were in the age group of 20 – 50 years (90%).
2. Male – 81.3% married (72.1%) were forming the majority of patients.
3. 53.1% were discordant couple while 36.8% were cordant couple.

Volume : 5 | Issue : 8 | August 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

4. Most of the patients were tested because they were symptomatic and 95.2% had h/o heterosexual exposure.
5. The entire five regimen studied had increased CD4 count at the 48 weeks of antiretroviral therapy.
6. 63% patients out of total patient were in the Efavirenz and Nevirapine based regimen.
7. Success rate was higher in double PI regimen (86.6%) while lowest in 2NRTI regimen (56.6%). Efavirenz, Nevirapine, single PI based regimen had almost same (>80%) success rate.
8. Failure rate was highest in 2NRTI regimen (44.7%) while lowest in double PI regimen (13.3%)
9. Most of the adverse effects are associated with Stavudine i.e. peripheral neuritis and lipoatropy. Dangerous adverse effects were seen with Nevirapine.

Thus it can be concluded from present study that Antiretroviral therapy in the HIV infected patient is beneficial to extend the life span, improve the quality of life on the basis of immunological, virological and clinical improvement. Out of studied ART combination regimen, Efavirenz based regimen had a high success rate, less adverse effect and affordable, can be used with anti- tuberculosis treatment. So it can be considered as favorable alternative in drug in Indian scenario.

Table 1: Age distribution of patients (n=230)

Age in the year	No. of patient	Percentage
1 – 10	2	0.9
11 – 20	2	0.8
21 – 30	51	22.2
31 – 40	129	56
41 – 50	30	13
51 – 60	12	5.2
61 – 70	3	1.3
71 – 80	1	0.43
Total	230	100

Table 2: Testing of spouses

Sex	No. of patients	%
Positive / cordant	70	36.9
Negative / discordant	101	53.1
Not Tested	19	10
Total	190	

Table 3: No of the patients in different group

Group	ART combinations	No. of patients	Percentage
A	2NRTI+Single PI	32	14
B	2NRTI + Double PI	15	6.5
C	2NRTI + EFV	83	37
D	2NRTI + NVP	62	26
E	2NRTI	38	16.5
Total		230	

Table-4: Comparison of CD4 count at baseline and at 48 weeks interval in different groups.

Group	ART combinations	Baseline CD4 cells/ cu mm	At 48 week CD 4 cells / cu.mm	Total increase
A	2NRTI+Single PI	185.5	572.6	387.6
B	2NRTI + Double PI	213.7	597.2	383.5
C	2NRTI + EFV	200.4	387	187
D	2NRTI + NVP	177.2	434	256.7
E	2NRTI	247.9	357.2	109.3

Fig-1

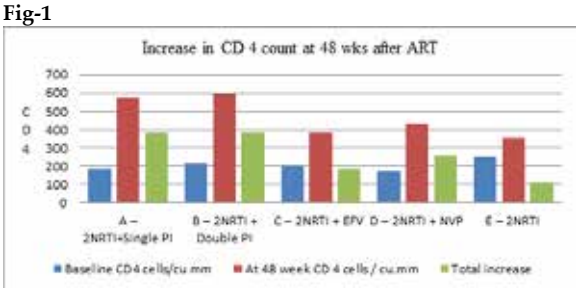

Table 5: Success rate of Anti-Retroviral therapy

Group	ART combinations	No. of Successful patient	No. of Total patient	Percentage
A	2NRTI+Single PI	26	32	81.2
B	2NRTI + Double PI	13	15	86.6
C	2NRTI + EFV	68	83	81.9
D	2NRTI + NVP	50	62	80.6
E	2NRTI	21	38	55.2
Total		178	230	77.3

Table 6: Failure rate among different groups taking Anti-Retroviral therapy

Group	ART combinations	No. of failure patient	No. of Total patient	Percentage
A	2NRTI+Single PI	6	32	18.7
B	2NRTI + Double PI	2	15	13.3
C	2NRTI + EFV	15	83	18.0
D	2NRTI + NVP	12	62	19.3
E	2NRTI	17	38	44.7
Total		52	230	22.6

References:

1. Mellors JW, Ronaldo CR, Gupta P et al.Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Scoence, 1996. 272 (5265): 1167-70.
2. Mellors JW, Munoz A, Giorgi JV et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997. 126 (12): 946-54.
3. Powderly WG, Saag MS, Chapman S et al. Predictors of optimal virological response to potent antiretroviral therapy. AIDS , 1999. 13 (14): 1873-80.
4. Yunihastuti E, Widhani A, Karjadi TH. Drug hypersensitivity in human immunodeficiency virus-infected patient: challenging diagnosis and management. Asia Pac Allergy. 2014;4(1):54-67.
5. National AIDS Control Organization. Antiretroviral Therapy Guide-

lines for HIV Infected Adults and Adolescents Including Post Exposure Prophylaxis. New Delhi: Ministry of Health and Family Welfare, Government of India; 2013 May

6. Journal of Clinical and Diagnostic Research. 2015 Nov, Vol-9(11): FC17-FC20 Nevirapine: Most Common Cause of Cutaneous Adverse Drug Reactions in an Outpatient Department of a Tertiary Care Hospital Mayur Popat Pawar1 , Shraddha Milind Pore
7. Lokhande AJ, Sutaria A, Shah BJ, Shah AN. Changing incidence of nevirapineinduced cutaneous drug reactions: After revised guideline Nov 2011. Indian J Sex Transm Dis. 2013;34(2):113-18.
8. Barvaliya M, Sanmukhani J, Patel T, Paliwal N, Shah H, Tripathi C. Druginduced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS-TEN overlap: a multicentric retrospective study. J Postgrad Med. 2011;57(2):115-19.
9. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The Euro SCARzstudy. J Invest Dermatol [Internet]. 2007 [cited 2015 Jul 16];128(1):35-44. Available from: http://www.nature.com/jid/journal/v128/n1/full/5701033a.html
10. Kondo W, Carraro EA, Prandel E, Dias JM, Perini J, Macedo RL, et al. Nevirapineinduced side effects in pregnant women: experience of a Brazilian university hospital. Braz J Infect Dis. 2007;11(6):544-48.
11. Sharma A, Vora R, Modi M, Sharma A, Marfatia Y. Adverse effects of antiretroviral treatment. Indian J Dermatol Venereol Leprol. 2008;74(3):234-37.