**J Young Pharm, 2018; 10(1): 74-77**
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

*Original Article*

# Gender-based Early Immunological Response to Antiretroviral Therapy in HIV Patients at a Tertiary Care Hospital in Coastal Karnataka

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## ABSTRACT

**Background and Objective:** To compare the immunological response to antiretroviral therapy between genders and to identify other factors that could affect the immunological response. **Methods:** This was a prospective, observational study of 171 HIV patients with a follow-up at six months. The exposure to be measured was gender and the outcome of interest included CD4 count (immunological response) which was classified as adequate, suboptimal and immunological failure. **Results:** A total of 171 patients completed the study out of which 88 (51.5%) were males and 83 (48.5%) were females. Overall, 130 patients out of 171 (76.0%) showed an adequate response at the end of the first six months of ART. The response was comparable in both men and women, and no significant difference was seen (p = 0.216). Though not statistically significant, more than 80% of the patients with a baseline CD4 cell count less than 300 cells/mm$^3$ showed an adequate response. Also, the baseline BMI (classified as underweight, normal, overweight, obese) did not affect the immunological response significantly. **Conclusion:** Gender did not play a role in the immunological response following the initiation of antiretroviral therapy in treatment naïve patients. The baseline CD4 count and the baseline BMI did not significantly affect the immunological response.

**Key words**: Antiretroviral therapy, Immunological response, Response to antiretroviral therapy, Gender and HIV.

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**DOI:** 10.5530/jyp.2018.10.17

## INTRODUCTION

HIV-AIDS was first recognized in the United States in 1981; and until drugs were available to treat this condition, the management of this condition was a challenge. Development of anti-retrovirals, and , their use as combination therapy has significantly improved outcomes in patients infected with HIV.[1] Today, nearly half of the people living with HIV globally are women. Over the years it has been observed that the response to treatment, the adverse events to the drugs used and the outcomes of treatment are not the same in men and women. Several studies have evaluated potential differences between men and women during HIV infection, response to treatment, and drug pharmacokinetics.[2,3]

Many of these studies have been conducted in Western and African population. Such studies to assess the effect of gender on HIV therapeutics, on the response to therapy, and the occurrence of adverse drug reactions to antiretroviral drugs are scanty in the Indian population with limited documentation regarding this. In addition, there have been conflicting results from studies done, with some showing significant results. Response to therapy can be studied with the help of various markers, and immunological response is one of them.[4]

To optimize treatment in HIV-infected people with available resources, there is a need to conduct further research on gender differences in HIV therapeutics. This study was designed to compare the immunological response to antiretroviral therapy between male and female patients, and to identify any factors that could influence the differences in immunological response to antiretroviral therapy (ART).[5]

## MATERIAL AND METHODS

### *Study Setting*

It was conducted at a tertiary care teaching hospital in Coastal Karnataka which is frequented by many HIV patients from all over the region. The study was conducted during the period between October 2012 to March 2014. The study population comprised of HIV positive subjects of either gender who were on ART. It was an observational longitudinal study, with each patient being followed up for 6 months. The sample size was calculated to be 171 HIV positive patients who were on ART.

HIV positive patients aged more than 18 years on ART or those who were to be initiated on ART, whose baseline CD4 cell counts were available, were included in the study. Severely ill patients whose life expectancy was less than one week at recruitment, patients on anti-tubercular treatment/other drugs known to cause renal or hepatic toxicity at the time of recruitment, patients with history of alcohol abuse at the time of recruitment and patients who were not compliant with ART were excluded from the study.

Data was collected from the patient case sheet, the prescription and by personally interviewing the patient after each clinic visit. The patients' demographic details were recorded at the baseline visit on the proforma. Demographic data collected included age, gender, height, weight, and socio-economic status. Any other new symptoms and/-or any other new diagnoses were also recorded.

CD4 cell count was recorded at baseline and at six months. Other laboratory investigations that were collected at baseline included blood counts, liver function tests, renal function tests, blood sugar, fasting lipid profile

(whatever available). Any clinically indicated additional investigations and results were also recorded.

Details regarding HIV infection were also collected with respect to mode of infection, duration of illness, clinical signs and symptoms, WHO staging of the disease and the presence of any opportunistic infections. Details of antiretroviral treatment collected included the type of regimen that was initiated, the date on which it was started, switch over to any other regimen, and the reason for switch over. ART regimen was categorized according to the National AIDS Control Organisation (NACO) guidelines.[4] Details of other concomitant medications received by the patients were also collected with the dose, duration and indication.

The exposure to be measured was gender and the outcomes of interest included CD4 count (immunologic response). There is no clear consensus on what is defined as an adequate CD4 response to therapy at the end of six months and varying definitions have been used in prior studies. Immunological response has been commonly accepted as an absolute increase in CD4 cell count by 50 cells/mm$^3$ at six months or an absolute rise by 100 cells/ mm$^3$ at one year. It has also been defined based on the baseline count (before the initiation of ART) as a rise in CD4 count by 50% from the baseline value. A sub-optimal CD4 response at 6 months has been defined as a failure of the CD4 T-lymphocyte count to rise from baseline by more than 50 cells/ mm$^3$. Further, immunological failure, according to the NACO guidelines has also been defined as:[4, 6, 7, 8]

- Fall of CD4 count to pre-therapy level or below
- 50% fall of CD4 count from on-therapy peak value
- Persistent CD4 count below 100cells/mm$^3$

*Based on these definitions, the following definitions were used in this study*

- An absolute rise in CD4 cell count by 50 cells/mm$^3$ or more at six months was considered as an *adequate response*.
- A rise in CD4 cell count by less than 50 cells/mm$^3$ was considered as a *suboptimal response*.
- A fall in CD4 cell count from the baseline or a persistent count of less than 100 cells/mm$^3$ was considered as *failure*.

### *Statistical analysis*

The collected data was entered in MS-Excel and analysis was done using SPSS, version 16.0. For qualitative data, statistical test Chi square was done, and wherever appropriate, Fisher Exact test was done. p-value <0.05 was taken as statistically significant. Pearson's correlation test was applied to test for correlation between various parameters and the immunological response. Baseline characteristics were compared by applying the Student t test and the Levene's test for equality of variances.

The study was conducted after approval from the institutional ethics committee was obtained and informed consent was obtained from the study subjects.

## RESULTS

### *Demographic and Baseline Characteristics*

A total of 171 patients completed the study of 6 months duration and data from these patients was available for analysis. The study subjects included HIV positive, treatment naïve patients who were started on ART regimens recommended by the NACO guidelines. The CD4 cell counts were assessed at baseline and at 6 months. Routine blood investigations were done at baseline, and thereafter whenever warranted.

Table 1 shows the age distribution, baseline CD4 cell counts, baseline haemoglobin and baseline BMI classified according to gender. All the mentioned baseline characteristics were matched by gender, except for haemoglobin. On applying Levene's test for equality of variances, the difference in haemoglobin between genders was found to be statistically significant (equal variances assumed, F = 26.535, p < 0.001). A positive correlation was seen between baseline haemoglobin and the baseline CD4 cell count (r = 0.308, p < 0.001). A positive correlation was also observed between the baseline body mass index (BMI) and baseline haemoglobin (r = 0.281, p < 0.001).

**Table 1: Demographic Characteristics at Baseline.**

| Parameter | Female | Male | Total |
|---|---|---|---|
| **Number (%)** | 83 (48.5) | 88 (51.5) | 171 (100) |
| **Age** | 42.16 ± 9.50 | 43.79 ± 9.43 | 43.00 ± 9.47 |
| **BMI** | 19.95 ± 3.33 | 20.42 ± 3.34 | 20.19 ± 3.33 |
| **Haemoglobin** | 11.25 ± 1.49 | 12.43 ± 2.46* | 11.86 ± 2.12 |
| **CD4 count** | 245.04 ± 96.81 | 232.86 ± 94.79 | 238.77 ± 95.69 |

Figures expressed as mean ± SD; Student t-test: -* = highly significant, p<0.001

**Table 2: Immunological response among males and females.**

| Gender | | CD4 Cell Response | | |
|---|---|---|---|---|
| | | Failure | Suboptimal | Adequate |
| Female (n=83) | Number (Percentage) | 6 (7.2) | 14 (16.9) | 63 (75.9) |
| | Response (%) | 33.3 | 60.9 | 48.5 |
| Male (n=88) | Number (Percentage) | 12 (13.6) | 9 (10.2) | 67 (76.1) |
| | Response (%) | 66.7 | 39.1 | 51.5 |
| Total (n=171) | Number (Percentage) | 18 (10.5) | 23 (13.5) | 130 (76.0) |
| | Response (%) | 100.0 | 100.0 | 100.0 |

Chi-Square test

### *Role of gender in immunological response*

The objective of the study was to compare the immunological response to ART among male and female patients. Overall, 130 patients out of 171 (76.0%) showed an adequate immunological response at the end of first six months of ART. A suboptimal response was seen in 23 patients out of 171 (13.5%), and 18 patients out of 171 (10.5%) showed an immunological failure. This response was comparable in both men and women, and no significant difference was seen (p = 0.216). Out of 83 female patients, 63 (75.9%) of them showed an adequate response, as compared to 67 out of 88 (76.1%) male patients; this difference was not statistically significant. Out of 83 female patients, 14 (16.9%) of them showed a suboptimal response, whereas only 9 out of 88 (10.2%) male patients showed a suboptimal response; however, this difference was also not statistically significant. Immunological failure was seen in 6 out of 83 (7.2%) female patients and 12 out of 88 (13.6%) male patients. Table 2.

### *Effect of baseline BMI on immunological response*

The effect of baseline body mass index (BMI) on the immunological response was assessed. BMI was calculated as weight in kilograms divided by the square of height in meters. The various categories defined based on BMI are, underweight (<18.5), normal range (18.5 to 24.9), overweight (25 – 29.9), obese (30 to 39.9) and extreme obesity (>40), (adapted from the guidelines given by the National Institutes of Health, Lung and Blood Institute).[9]

Out of 171 patients, 68 (39.8%) were underweight with a BMI < 18.5, 84 patients out of 171 (49.8%) had a BMI ranging from 18.5 to 24.9 that was considered healthy, and 19 patients out of 171 (11.1%) were overweight

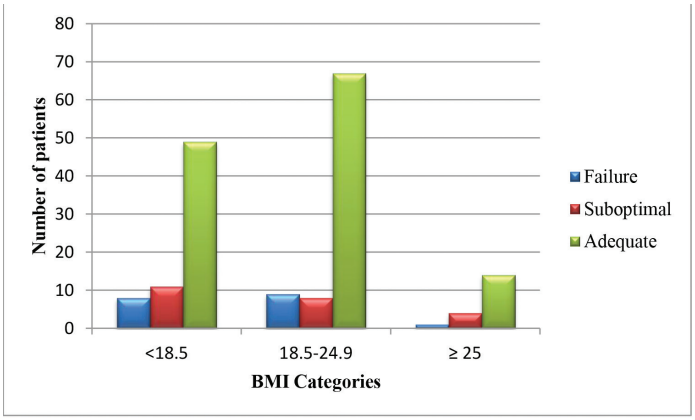


**Figure 1:** Baseline BMI and Immunological Response.
Chi square test; <18.5 – Underweight, 18.5-24.9 – Normal Range, ≥25 - Overweight

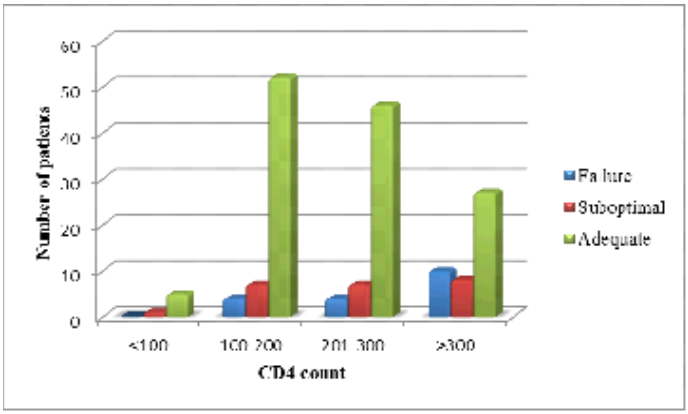


**Figure 2:** Baseline CD4 Cell Count and the Immunological Response.
Chi square test; CD4 count in *per mm3*

with a BMI ranging from 25 to 29.9. Among the three categories, the highest percentage of an adequate response was seen in the BMI category of 18.5 to 24.9 (67 out of 84 patients, 79.8%), followed by the overweight category and the least in the underweight category. The highest percentage of immunological failure was seen in the underweight category (8 out of 68 patients, 11.8%), and the least in the overweight category. However, these differences in immunological response between the groups were not statistically significant. Figure 1.

### *Effect of baseline CD4 counts on immunological response*

The baseline CD4 count was divided into four categories, them being: < 100 cells/mm$^3$, 100-200 cells/mm$^3$, 201-300 cells/mm$^3$ and >300 cells/mm$^3$. More than 80% of patients with a baseline CD4 cell count less than 300 cells/mm$^3$ showed an adequate response. Twenty-seven patients out of 45 (60%) with a baseline CD4 count of more than 300 cells/mm$^3$ showed an adequate immunological response. The maximum number of patients who had an immunological failure was seen in the group with baseline CD4 counts more than 300 cells/mm$^3$. However, this difference between the groups was not statistically significant (p = 0.081). Figure 2.

## DISCUSSION

Over the years, an increased access of HIV positive patients to antiretroviral medications has significantly decreased the mortality and morbidity among them. Based on clinical observations and previous studies, it has been suggested that the course of the disease and the response to treatment is not the same in men and women. To optimise treatment, gender differences in HIV therapeutics need to be studied.[3]

We started this study with the aim of testing this hypothesis- to try and assess any gender based difference in the patients' response to antiretroviral therapy, at a tertiary care hospital that catered to a large subset of population from the Western coastal belt of Karnataka and Northern Kerala. The immunological response was chosen as the indicator for the same, and was assessed by measuring the CD4 count at baseline and at the end of six months.[4] All baseline characteristics between genders were matched and no significant difference was seen, except in haemoglobin. As already known, haemoglobin was found to be significantly lower in female patients in comparison to males.[10] However, this difference in Hb between male and female patients did not affect the final response to therapy in terms of immunological response.[11]

Over 3/4ths of the patients recruited in the study showed an adequate immunological response to treatment. Immunological failure was seen in only 10.5% of patients. No significant differences were found between males and females about the CD4 cell response at the end of six months. This is like findings reported from a prior study done to assess the role of gender in long-term clinical, immunological and virological outcomes among patients on highly active antiretroviral therapy. It was observed that there was no significant difference between genders in terms of virological and immunological outcomes. However, the risk of clinical progression was seen to be lower in female patients with an intermediate baseline viral load than male patients.[12]

Another study conducted to look for the gender differences in HIV disease progression and treatment outcomes among HIV patients one year after starting antiretroviral treatment (ART), showed that a higher proportion of females survived after one year of standard ART, but this difference between genders was not significant statistically.[13] The median CD4 count at baseline was higher in women than in men, but at the end of one year, it was comparable in both genders. This signified a worse CD4 cell increase in female patients when compared to male patients, and the difference was also statistically significant. Also, this outcome was observed despite female patients having a higher BMI at baseline.[13] However, our study did not demonstrate any such difference in the disease course between genders, nor on the effect of the baseline BMI on the immunological response. This difference could probably be demonstrated in studies with larger sample size.

In an earlier study conducted to look at the long term response and pattern of CD4 cell response to highly active antiretroviral therapy, the factors associated with a higher CD4 cell count gain were a lower pre-therapy CD4 cell count, female sex, younger age, and a low-level viremia; the conclusion drawn thence was that a lower pre-therapy CD4 cell count did not adversely affect the CD4 cell count restoration in response to highly active antiretroviral therapy.[14] Our study showed a similar trend in CD4 cell response to antiretroviral therapy with respect to the baseline CD4 cell count, but not with gender. Our finding was also consistent with a nationwide cohort study done in Denmark to assess the role of gender in response to highly active antiretroviral therapy in patients with HIV-1 infection, which showed that gender did not significantly affect the immunological or virological outcomes and therapy modification.[15]

Baseline BMI also did not seem to play a role in the immunological response to ART in our study. Prior studies done to look at the relationship between BMI and CD4 cell recovery in HIV disease have had varying conclusions; with one concluding that the baseline BMI can predict CD4 T lymphocyte gains in men started on ART,[16] and another concluding that the immune reconstitution at the end of one year of ART was the highest among patients commonly classified as overweight. These

findings suggest that there could be an optimal BMI range for immune recovery in patients on ART.[17] Also, in another earlier study, the relationship between periodic weight measurements and the corresponding CD4 counts was investigated to assess the effect of obesity on CD4 counts. It was observed that obese patients had a smaller increase in CD4 counts, which might be an adverse consequence of obesity itself.[18]

In our study the highest percentage of an adequate response (79.8%) was seen in patients with a BMI ranging from 18.5 to 24.9, the highest percentage of immunological failure (11.8%) was seen in the underweight category, and the least in the overweight category. However, this difference in immunological response was not statistically significant. This finding differed from another earlier study, which had concluded that BMI could be an independent marker of survival, and could even be a marker to decide on the point of initiation of ART, when other more reliable laboratory facilities were not available.[19] It has also been suggested earlier that weight management is as important an issue in HIV as ART is, as BMI itself could independently affect the response to therapy in a patient.[20]

The major strengths of our study were the inclusion of a comparable number of female and male patients. Also, the inclusion of only treatment naïve patients, along with a prospective study design with a follow-up at six months, enabled us to study the early response to therapy, which is a very important predictor of long term prognosis and disease progression.[6]

Our study had certain limitations too; the baseline and sixth month virological loads were not done routinely unless indicated, and hence correlation between genders and the virological response was not possible. Also, the follow-up period was for six months only; to draw a valid conclusion, longer follow-ups would be required. Since the patients recruited were treatment naïve, the study did not include patients who were on protease inhibitors, and hence the response to these drugs could not be assessed. To study variations in immunological response based on factors such as BMI, Hemoglobin, type of regimen used, etc., a larger sample in each of these subgroups would be needed.

## CONCLUSION

Gender did not play a role in the immunological response following the initiation of antiretroviral therapy. Further studies in this area would help decision makers in framing strategic policies for the optimal use of currently available resources.

## ACKNOWLEDGEMENT

I would like to acknowledge the research grant received from the Honourable Indian Council of Medical Research for the conduct of this study. I would like to acknowledge the help extended by Dr. Srikanth N., Associate Professor, Department of Oral Pathology and Microbiology, Manipal College of Dental Sciences, Mangalore Manipal Academy of Higher Education in the statistical analysis of the study.

## CONFLICT OF INTEREST

None.

## ABBREVIATION USED

**HIV:** Human Immunodeficiency Virus; **ART:** Antiretroviral Therapy; **NACO:** National AIDS Control Organisation; **BMI:** Body Mass Index.

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**Article History:** Submission Date : 18-07-2017 ; Revised Date : 29-09-2017; Acceptance Date : 04-11-2017.
**Cite this article:** Priyanka K, Mukta CN, John RT, Ashok SK, Sanjay H. Gender-based Early Immunological Response to Antiretroviral Therapy in HIV Patients at a Tertiary Care Hospital in Coastal Karnataka. J Young Pharm. 2018;10(1):74-7.