

## Original Research Article

# Clinical profiles and trends in CD4+ counts to first-line antiretroviral therapy among HIV/AIDS patients in western part of Odisha state of India

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### ABSTRACT

**Background:** HIV infection is globally pandemic and about 36.7 million people living with HIV/ AIDS (PLHA) in 2016. At present CD4+ count is the gold standard of immunological marker of disease severity. Highly active antiretroviral therapy (HAART) is the first line of treatment to improve CD4 count. AIMS AND OBJECTIVES of study was to observe the clinical profiles and response in CD4+ counts to first-line HAART in PLHA and their adverse reactions.

**Methods:** Total 153 PLHA with CD4+ counts <250/ $\mu$ l was consecutively taken in the study and detail clinical examinations, baseline CD4+ counts and body weights were noted. HAART was started in 26 (16.99%), 37 (24.18%), 78 (50.98%) and 12 (7.84%) cases in WHO clinical stages of I, II, III, and V respectively and CD4+ counts, body weight and any adverse drug reactions were noted at 15 days, 3, 6, 18 and 24 months intervals and data were collected and analyzed.

**Results:** Out of 153 cases 89 were male and 64 were female. Mean age was 35.4 $\pm$ 9.08 years for male and 30.2 $\pm$ 5.75 years for female. Mean baseline CD4+ count was 202 $\pm$ 75/ $\mu$ l and mean body weight was 47.44kg. Mean CD4+ count was increased to 314.22 $\pm$ 166.53, 343 $\pm$ 194.02, 378 $\pm$ 221.30 and 299.6 $\pm$ 146.55/ $\mu$ l at 6, 12, 18 and 24 months respectively. Commonest adverse drug reaction was headache and GIT side effects.

**Conclusions:** HAART improves clinical and immunological parameter CD4+ count in PLHA, irrespective of their clinical stages. Headache and GIT manifestations are commonest adverse drug reactions.

**Keywords:** Antiretroviral therapy, CD4+ Cell count, HIV

### INTRODUCTION

HIV infection is a global pandemic involving about 76.1 million and killing 35 million people since the reporting of first case in 1981. The recent 2017 UN report says that, world wide about 36.7 million people were living with HIV/AIDS (PLHA) in 2016 and about 1.8 million people becoming newly infected globally. In India the total number of PLHA was estimated to be around 21.17

lakhs compared to 22.26 lakhs in 2007. There were total 43,000 HIV positive patients have been identified in Odisha state India.

The etiologic agent of HIV/AIDS is a Human Immunodeficiency Virus (HIV) belongs to the family of human retrovirus (Retroviridae) and subfamily of Lentivirus. There are two types of HIV viruses i.e. HIV-1 and HIV-2. The most common cause of HIV throughout the world and India is due to HIV-1 and only 1.7-4.6% is

due to HIV-2 and 3.3-20% are due to mixed cases mostly among intravenous drug users from Manipur state of India.<sup>1</sup> HIV is a chronic infection with progressive destruction of immune system as a result, the HIV infected individuals become immune compromised and suffer from variety of life threatening opportunistic infections and malignancies.<sup>2</sup> The CD4+ cells are the primary target of HIV infection and destruction of CD4+ cell occurs and CD4+ cell counts decreases as disease progresses. Thus CD4+ counts represent as a marker of disease progression. The causes of decrease in CD4+ counts may be due to (1) Direct virologic cytopathic effect on CD4+ cell and (2) Non-viral autoimmune mechanisms, energy, apoptosis and virus specific immune response.<sup>3</sup>

There are three types of progression of HIV infection has been described i.e.;

- Typical progression in which 80-90% of HIV infected persons have slow progression of disease with a median survival time of approximately 10 years.
- Rapid progression which consist of about 5-10% and patients have rapidly progressive course with median survival of 3-4 years.
- Non-progressor constitutes about 5% patients and survives for an extended period of time.<sup>4</sup>

WHO described four clinical stages of HIV/AIDS infection in adults and adolescents in 2006.<sup>5</sup> Clinical Stages-I: Asymptomatic and persistent generalized lymphadenopathy. Stage-II: Having unexplained moderate weight loss (<10% of presumed or measured body weight). Recurrent respiratory tract infections (Sinusitis, Tonsillitis, Otitis media, pharyngitis). Herpes zoster, Angular cheilitis, recurrent oral ulcer, papular purpuric eruptions, Seborrhoeic dermatis, fungal nail infections. Clinical Stage-III: Unexplained severe weight loss (>10% presumed or measured body weight). Unexplained chronic diarrhoea for longer than one month. Unexplained persistent fever (>37.5°C) intermittent or constant for >1 month. Persistent oral candidiasis. Oral hairy leukoplakia. Pulmonary tuberculosis, sever bacterial infections (e.g. Pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis.

Unexplained anaemia (Hb <8gm %), neutropenia (<0.5x10<sup>9</sup>/L) and or chronic thrombocytopenia (<50x10<sup>9</sup>/L). Clinical Stage IV: HIV wasting syndrome, pneumocystitis pneumonia, recurrent bacterial pneumonia, chronic herpes simplex infection (orolabial, genital, or anorectal of >1month duration or visceral at any sites. Oesophageal candidiasis (or Candidiasis of trachea, bronchial or lungs). Central nervous system toxoplasmosis, HIV encephalopathy. Extrapulmonary cryptococcosis including meningitis. Disseminated non-

tubercular mycobacterial infection. Progressive multifocal leukoencephalopathy.

Chronic cryptosporidiosis. Chronic isosporiasis. Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis). Recurrent septicemia (including non-typhoidal salmonella) lymphoma (cerebral or B-cell non-Hodgkin's). Invasive cervical carcinoma. Atypical disseminated leishmaniasis. Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy.

Normally CD4+ count is approximately 400-1200 cells/ $\mu$ l in male and 500-1600 cells/ $\mu$ l in female. CD4+ cells constitute about 40% of total lymphocytes and the normal ratio of CD4+/CD8 cells is between 1 and 4. As HIV disease progressed the CD4+ cell counts decline and the CD8 count is increased so that the ratio may 'invert' and the ratio become <1. Thus, the CD4+ count commonly used as a marker of HIV disease progression and for initiating and monitoring of antiretroviral drug therapy.<sup>6,7</sup> CD4+ cell count is an important tool in determining treatment failure when CD4+ count decline below baseline or 50% reduction from baseline during treatment or persistent of CD4+ count below 100 cells/ $\mu$ l.<sup>8</sup> Introduction of HAART for HIV/AIDS resulted in dramatic decrease in AIDS related morbidity and mortality with increase in CD4+ count.<sup>9,10</sup> There is paucity of study report on monitoring of response to HAART and its adverse effect in India. Aims and objective of this study was to observe the clinical profile and response in CD4+ counts to first-line HAART in HIV/AIDS patients and their adverse effects.

## METHODS

Adults and adolescent patients aged >15 years diagnosed as HIV/AIDS patients with CD4+ cell count <350/ $\mu$ l and specific indications for HAART according to NACO guideline 2015 were taken into the study from the OPD and IPD and ART centre of VISSIMSAR, Burla, Odisha (India) from October 2015 to October 2017. Total 176 cases were recruited consecutively for the study. Detail clinical history and physical examinations and measurement of body weight were done, and relevant investigations were done to identify any associated opportunistic infections and comorbid conditions. Baseline CD4+ cell count was done by PARTEC Cyflo counter at ART centre. After approval of institutional ethical committee HAART was given to all patients, in two type of regimen, i.e. 123 patients received TDF+3TC+RFV (Tenofovir+Lamivudine+Rifavirenz) and 30 patients received AZT+3TC+NVP (Zidovudine+Lamivudine+Nevirapine). Clinical profile, CD4+ counts, body weight and any adverse drug reactions were evaluated at 15 days, 1, 3, 6, 18 and 24 months intervals. Underlying opportunistic infections and other co- morbid conditions were treated according to standard medical care. Total 153 cases were remained in the study after drop out of 23 cases (11 died and 12 lost

to follow up). Data were collected and analyzed by ANOVA version 25 and paired 't' test.

## RESULTS

Total 153 cases were remained in the study after drop out of 23 cases. There were 89 (58.2%) and 64 (41.80%) male and female respectively. Mean age was 35.4±9.08 and 30.2±5.75 years for male and female respectively. Majority were between 25-34 years (43.13%). Baseline mean body weight was 47.44kg (55.4kg for male and 54.2kg for female). Mean baseline CD4+ counts in the

study was 202±75/μl (Mean of 119.15±78.57cells/μl in male and 208.24±78.5cells/μl in female). Commonest opportunistic infections at presentation was mucocutaneous candidiasis in 28 (18.30%), pulmonary TB in 12 (7.84%), extra pulmonary TB in 7 (4.47%), Herpes zoster in 6 (3.92%) and P. jirovecii in 2 (1.3%). Commonest physical findings were pallor in 73 (47.7%), pyrexia of unknown origin in 90 (58.82%), chronic diarrhoea 60 (39.21%), persistent generalized lymphadenopathy in 29 (16.33%), seborrhoeic dermatitis in 11 (7.18%), folliculitis, scabies and photosensitive light eruption in 9 (5.66%).

**Table 1: Changes in CD4 cell count and their significance in male.**

	Paired Difference					t	df	'p' value
	Mean	STD	SEM	95% confidence interval, the inference				
				Upper	Lower			
Paired 1 CD4 (Baseline) CD4 6M	101.666	124.78	16.527	134.775	68.557	6.151	65	0.0001
Paired 2 CD4 (Baseline) CD4 12M	157.634	195.17	30.481	219.239	96.028	5.171	40	0.0001
Paired 3 CD4 (Baseline) CD4 18M	175.818	185.61	32.311	241.634	110.00	5.441	32	0.0001
Paired 4 CD4 (Baseline) CD4 24M	79.857	151.88	40.592	167.552	17.838	1.967	13	0.071

**Table 2: Changes in CD4 cell counts and their significance in female.**

	Paired Difference					t	df	'p' value
	Mean	STD	SEM	95% confidence interval, the inference				
				Upper	Lower			
Paired 1 CD4 (Baseline) CD4 6M	126.416	192.320	27.759	182.260	70.572	4.554	47	0.0001
Paired 2 CD4 (Baseline) CD4 12M	129.904	172.532	37.649	208.440	51.368	3.450	20	0.003
Paired 3 CD4 (Baseline) CD4 18M	173.206	251.712	46.741	268.953	77.460	3.706	28	0.001
Paired 4 CD4 (Baseline) CD4 24M	4.500	173.254	70.730	186.319	117.319	0.064	05	0.952

**Table 3: Shows changes in CD4 counts in male vs female.**

	Baseline CD 4/μl	SD	6M	SD	P	12M	SD	P	18M	SD	P	24M	SD	P
Male	119.159	78.57	297.11	146.315	0.0001	35.014	207.884	0.0001	370.55	192.144	0.0001	302.93	146.558	0.071
Female	208.246	78.55	384.54	187.3	0.0001	328.57	167.510	0.003	388.55	252.923	0.001	219.83	165.772	0.952

Baseline WHO clinical stages before initiation of HAART were Stage-I-26 (16.99%), Stage-II-37 (24.18%), Stage-III-78 (50.98%), Stage-IV- 12 (7.84%) patients. Significant mean rise in CD4+ count of 314.22±166.53, 343±194.02, 378±221.30 and 299.6±146.55/μl was occurred at 6, 12, 18 and 24 months

respectively in both male and female. (Table 1, 2). Significant mean rise of CD4+ cell count of 96.92, 46.35 and 11.55/μl occurred at 6, 12, and 18 months respectively (P 0.0014). The mean rise in CD4+ count at 6 and 12 months was 332/μl observed in 18 cases up to 24 months (P 0.001), but it was 21.56/μl at 24 months in

other ( $P=0.126$ ). The mean rise in CD4+ cells count was better in female than male patients. (Table 3 and Figure 1). Mean body weight gain at 6, 12, 18 and 24 months was 0.438, 0.582, 1.11 and 1.954kg respectively. ( $P=0.0001$ ). Commonest adverse drug reaction was headache in 84 (54.90%), GIT side effects i.e. nausea, vomiting, diarrhoea in 43 (28.10%), nevirapine induced skin rash in 11 (7.18%), zidovudine induced anemia in 9 (5.88%). There was no correlation with baseline CD4+ count and/or the degree of rise in CD4+ count and stages of disease with adverse drug reactions.

## DISCUSSION

In this study majority of cases were between ages of 20-45 years. Asfaw A et al also reported majority of their cases were < aged 45 years and were sexually active.<sup>11</sup> In this study 89(58.2%) and 64(41.80%) were male and female respectively with ratio of 1.4:1. Ghate M et al, from Pune (India) reported 1.5:1 and Omati CE et al from Nigeria reported 1.8:1 and Glynn JR et al and baseline mean CD4 + count at which they started ART was at lower level of 96 cells/ $\mu$ l.<sup>12,13</sup> In our study mean baseline CD4+ count was 202 cells/ $\mu$ l. Incidence of opportunistic infections In this study was Mucocutaneous Candidiasis was 15 (18.5%), followed by extra pulmonary tuberculosis 14 (17.3%), pulmonary TB 6 (7.4%). P. jirovery 8 (9.9%), Herpes zoster 2 (2.5%). In a South Indian study by Kumarasamy N et al, reported pulmonary TB in 73% and extrapulmonary TB in 18% and P. jirovery in 8%, CMV retinitis of 7% cryptomeningitis of 5%.<sup>14</sup> In this study baseline CD4 cell count had no correlation with the adverse drug reaction. The mean CD4+ cells count was 166  $\pm$  85 cells/ $\mu$ l with adverse drug reaction which was comparable to no drug reaction with CD4+ count of 164  $\pm$  97 cells/ $\mu$ l. Zidovudine induced anaemia was associated with mean CD4+ count of 168  $\pm$  57 cells/ $\mu$  and GIT side effects with 159  $\pm$  87 cells/ $\mu$ l and 166  $\pm$  44 cells/ $\mu$ l with Nevirapine induced anaemia and hepatitis. Kamaya MR. et al also failed to draw a relationship between CD4 + cells count and adverse drug reactions.<sup>15</sup>

The CD4 cell count increased after 6 months of HAART to a mean of 314.22  $\pm$  166.53 from baseline and at 12 months to 343  $\pm$  194.02 and 378  $\pm$  221.30 cells/ $\mu$ l after 18 months. But at 24 months it was 299.6 cells/ $\mu$ l is insignificant. Kitahata M et al, reported increase in CD4+ count at all levels of baseline CD4+ count at 6 months.<sup>16</sup> Akinbami O et al, found higher CD4+ count in female than male at 6 months.<sup>17</sup> In this study maximum CD4+ cell count increased to 102 cells/ $\mu$ l at 6 months, but other study reported <50 cells/ $\mu$ l.<sup>18</sup> Kamaya MR. et al. reported 152,224, and 274 cells/ $\mu$ l.<sup>15</sup> In this study there was no correlation between baseline CD4+ cell count and degree of rise in CD4+ count. Kamaya MR et al, related to the baseline CD4+ cells count, but not by Badri M. et al and Martinez E. et al reported mean rise of 100 cells/ $\mu$ l at 1 year.<sup>18,19</sup> Highleyman L et al, reported poor response in

few patients.<sup>20</sup> Adherence to therapy is most important factor affecting the outcome.<sup>15</sup>

In this study, 11 patients died within 6 months due to extra pulmonary tuberculosis after starting of therapy and their baseline mean CD4+ count was 64  $\pm$  29 cells/ $\mu$ l. Kamaya et al, found mortality was related to low CD4 + cells counts of <200 cells/ $\mu$ l.<sup>15</sup> Gastrointestinal manifestations and headache were the most common side effect of HAART in this study. Zidovudine induced anaemia in 9 (8.88%) required switching to EFZ regimen. Nevirapine induced anaemia in 11 (7.18%) required switching to EFV and Nevirapine induced hepatitis in 5(3.26%) switched to EFZ regimen. Kumarasamy N et al, reported peripheral neuropathy in 21.8%, anaemia in 16.4%, blue coloration of nail in 10.9%, nausea and vomiting in 9.1% and hepatitis in 7.3%. Skin rash in 5.5% and diarrhoea in 1.8%.<sup>19</sup> Kamaya et al, most commonly reported gastrointestinal manifestations in 70.75%.<sup>15</sup>

In this study significant body weight gain was noted from 6 months onwards and mean increased in body weight at 6, 12, 18 and 24 months was 0.438, 0.582, 1.11 and 1.954kg respectively.

## CONCLUSION

HAART improves clinical and immunological parameters and rise in CD4+ cells count is a good immunological marker of response to HAART in all stages of PLHA and associated with decreases incidence of opportunistic infections, increases body weight and improves quality of life. Most common adverse drug reactions in this study were headache and gastrointestinal manifestations which were self limited or easily manageable.

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