

**Original article**

# GENERAL PROFILE AND SURVIVAL PROBABILITIES OF HIV PATIENTS REGISTERED AT ANTI RETROVIRAL THERAPY CENTRE, NEW CIVIL HOSPITAL, SURAT, GUJARAT

Sridhar P Ryavanki<sup>1</sup>, J K Kosambiya<sup>2</sup>, Alap Mehta<sup>3</sup>, Sonal O Dayama<sup>4</sup>, Nitin Solanki<sup>5</sup>, Shantilal L Kantharia<sup>6</sup>

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**Author's Affiliation:**

<sup>1</sup>State Health Consultant, Commissionerate of Health, Gandhinagar;  
<sup>2</sup>Professor (Addl.), Dept of Community Med., Govt. Medical College, Surat; <sup>3</sup>Senior Medical Officer, ART Centre, New Civil Hospital Surat; <sup>4</sup>Resident, Dept of Community Med., Govt. Medical College, Surat; <sup>5</sup>Assistant Professor, Dept. of Community Med, NHL Medical College, Ahmedabad; <sup>6</sup>Professor & Head, Dept. of Community Med., Govt. Medical College, Surat

**Correspondence:**

Dr Sridhar R. P  
Email: sridhar.ryavanki@gmail.com

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## ABSTRACT

**Introduction:** With advent of Anti Retroviral Therapy (ART) life of HIV positive patients has prolonged. In pre ART era survival probability of HIV patients was well studied but very few studies are documented on survival probability of HIV patients on ART. The current paper is an attempt to describe general profile of adult HIV patients and provide an estimate of survival probabilities following the time of diagnosis and initiation of antiretroviral therapy and its relation with WHO staging and CD4 count.

**Methodology:** Analysis of secondary data of ART centre, New Civil Hospital, Surat, Gujarat, India was carried in January 2011. Individuals with age >15 years and had required information for analysis were included. Death of HIV patient was considered as outcome. Descriptive statistics to describe general profile, Kaplan Meier Method for survival probability and Log rank test for significance was used. Cox's proportional hazards used to look for association between variables and survival.

**Results:** The proportions of males were 66%. Age group 25-45years contributes 77% of cases. Majority of patients were married (75%). Survival probability after 15 years of diagnosis of HIV was 83%. The 4 year survival probability was 88% after the start of ART. The crude mortality rate was 8.6%. The mortality density was 10.8 per 1000 person years. The marital status and gender were not associated with survival. WHO clinical staging 3 and 4, CD4 count <200, and age >55 yrs have poor survival. There was significant difference in survival among different WHO clinical stages but no significant difference in survival between CD4 count 200 to 250, 250 to 350, 350 to 500 and >500.

**Conclusion:** The new WHO guideline to start ART when CD4 count is <350 can cause financial burden to provide free ART without survival advantage.

**Key words:** HIV, Anti Retroviral Therapy, Survival, CD4 count, WHO staging

## INTRODUCTION

The "3 by 5" initiative, launched by United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) in 2003, was a global target to provide three million

people living with HIV/AIDS in low- and middle-income countries with life-prolonging antiretroviral treatment (ART) by the end of 2005. <sup>(1)</sup> Demographically the second largest country in the world, India has also the third largest num-

ber of people living with HIV/AIDS. As per the provisional HIV estimate of 2008-09, there are an estimated 22.7 lakh people living with HIV/AIDS in India. The HIV prevalence rate in the country is 0.29 percent (2008-09).<sup>(2)</sup> Gujarat State is estimated to have more than 1 lakh People Living with HIV/AIDS (PLHA).<sup>(3)</sup> The primary goal of ART is it prolongs lives, making HIV/AIDS a chronic disease, not a death sentence.<sup>(1)</sup> As of April 2011 in Gujarat 22 Anti Retroviral Therapy (ART) centers are functional. At the end of May '11, patients ever registered are 61847, out of which 21259 patients are alive and taking treatment on ART. In addition, 259 patients are taking second line ART at Centre of Excellence (COE), Ahmedabad & Surat. Alternate regime of ART is being provided to 372 patients.<sup>(3)</sup> There is little evidence regarding survival probabilities in HIV-infected patients in Gujarat particularly and India by large due to the lack of prospective studies. This study investigated survival probability both after initial HIV diagnosis and start of ART in HIV/AIDS patients on ART.

## OBJECTIVES

Objective of this study was to describe the general profile of adult HIV patients registered at ART centre, NCH, Surat and to provide an estimate of survival probabilities of adult HIV patients following the time of diagnosis and also following initiation of antiretroviral therapy.

## METHODOLOGY

**Study setting:** Surat city and district, with maximum migrant workers and floating population, has the highest number of AIDS patients in the Gujarat state. Currently, in National AIDS Control Programme (NACP) Phase III, Surat district belongs to the Category A of risk categories for HIV/AIDS.<sup>(4)</sup> The ART centre at New Civil Hospital Surat has been established in the year 2006 and 5,422 HIV-infected individuals are registered with the ART Centre since September 2006 until December 2010. It is the nodal center for providing ART and care to the PLHA and newly diagnosed HIV positive in the entire South Gujarat. Secondary data analysis of the data was done in January 2011.

**Selection Criteria:** For general profile the data of all the individuals with age >15 years were included for description. The data of individuals who had information regarding HIV diagnosis

date, baseline WHO staging and CD4 count, date when ART was started and ART centre, Surat as the first centre of registration were included for survival analysis.

**Sample size:** Out of the total 5,422 HIV-infected individuals registered with the ART Centre since September 2006 until December 2010, 5230 patients were with age  $\geq 15$  years and on ART, the secondary data of which was analyzed in the current study

**Outcome Measure:** Death of a HIV patient was taken as the primary end point.

**Statistical Analysis:** The use of descriptive statistics was done to describe general profile of the patients. The survival probability was calculated using Kaplan Meier Method for survival probability and Log rank test was used to define the significance of the survival analysis. The regression analysis using Cox's proportional hazards was done to look for association between variables and survival. **Software:** The analysis was performed using SPSS Version 16.

Ethical clearance was taken from Human Research Ethics Committee, Government Medical College, Surat.

## RESULTS

Out of the total 5,422 HIV-infected individuals registered with the ART Centre since September 2006 until December 2010, 5230 patients were with age  $\geq 15$  years and on ART (Table 1). The mortality density is 10.8 per 1,000 person years. The proportions of males (66%) were more but sex wise proportion of deaths was similar (males 8.7%, females 8.4%). The age groups between 25-45 years contribute to 77% of cases. The proportion of deaths is more as the age advances and maximum after 55 years. The marital status data of 4921 patients was available. Out of which majority of the patients were married (75%) and proportion of deaths among married was 7.9%, 9.7% among unmarried and 8.1% among conflict marital status.

The baseline CD4+ count of 4671 patients was available. Out of which the proportion of patients (66.5%) and the deaths (10.5%) is high in patients with CD4+ count <200. Only 2918 patients' baseline WHO staging was available. Majority of the patients are registered at ART center with WHO stage 2 (33%) and Stage 3 (30%). The proportion of deaths is more in Stage 4 patients (22%) and next to it is Stage 3 (14%).

**Table 1: Characteristics of study population**

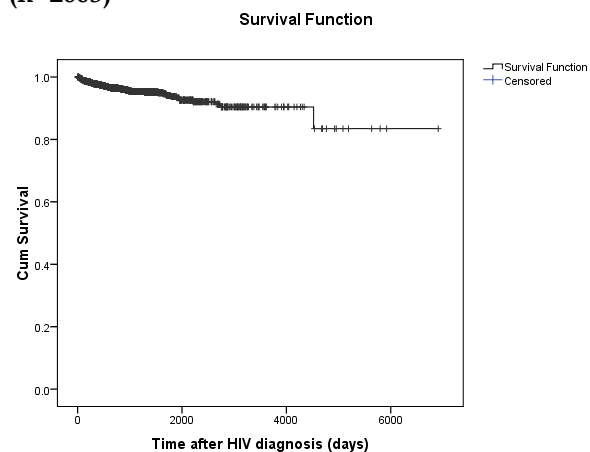
| Categories                               | All (%)     | Deaths (%) | Mortality density |        |              |  |
|--|-------------|------------|-------------------|--------|--------------|--|
|  |             |            | No.*              | Deaths | Person years | Mortality density (per 1,000 person yrs) |
| <b>Total Individuals (≥15 years age)</b> | 5230        | 448 (8.6)  | 3608              | 117    | 10830        | 10.8                                     |
| <b>Sex</b>                               |             |            |                   |        |              |  |
| Male                                     | 3445 (65.9) | 298 (8.7)  | 2348              | 75     | 7052         | 10.7                                     |
| Female                                   | 1785 (34.1) | 150 (8.4)  | 1260              | 42     | 3778         | 11.1                                     |
| <b>Age (years)</b>                       |             |            |                   |        |              |  |
| 15-24                                    | 292 (5.6)   | 18 (6.2)   | 190               | 4      | 492          | 8.1                                      |
| 25-34                                    | 1918 (36.7) | 123 (6.4)  | 1339              | 30     | 4079         | 7.4                                      |
| 35-44                                    | 2102 (40.2) | 186 (8.8)  | 1438              | 48     | 4492         | 10.7                                     |
| 45-54                                    | 689 (13.2)  | 85 (12.3)  | 497               | 25     | 1384         | 18.1                                     |
| >55                                      | 229 (4.4)   | 36 (15.7)  | 144               | 10     | 383          | 26.2                                     |
| <b>Marital Status (n=4921)**</b>         |             |            |                   |        |              |  |
| Married                                  | 3677 (74.7) | 290 (7.9)  | 2666              | 77     | 7950         | 9.7                                      |
| Unmarried                                | 350 (7.1)   | 34 (9.7)   | 249               | 12     | 678          | 17.7                                     |
| Conflict#                                | 894 (18.2)  | 72 (8.1)   | 640               | 25     | 2073         | 12.1                                     |
| <b>CD4+T-cell counts (n=4671)**</b>      |             |            |                   |        |              |  |
| <200                                     | 3104 (66.5) | 325 (10.5) | 2031              | 81     | 6011         | 13.5                                     |
| 200-250                                  | 641 (13.7)  | 29 (4.5)   | 467               | 10     | 1370         | 7.3                                      |
| 250-350                                  | 459 (9.8)   | 26 (5.7)   | 337               | 9      | 1180         | 7.6                                      |
| 350-500                                  | 267 (5.7)   | 16 (6.0)   | 188               | 4      | 852          | 4.7                                      |
| >500                                     | 200 (4.3)   | 4 (2.0)    | 141               | 2      | 714          | 2.8                                      |
| <b>WHO Staging (n=2918)**</b>            |             |            |                   |        |              |  |
| 1  | 687 (23.5)  | 30 (4.4)   | 438               | 6      | 2167         | 2.8                                      |
| 2  | 964 (33.0)  | 68 (7.1)   | 544               | 10     | 2321         | 4.3                                      |
| 3  | 885 (30.3)  | 122 (13.8) | 477               | 6      | 1787         | 3.4                                      |
| 4  | 382 (13.1)  | 84 (22.0)  | 175               | 6      | 665          | 9.0                                      |
| <b>Referral</b>                          |             |            |                   |        |              |  |
| Direct                                   | 3824 (73.1) | 377 (9.9)  | 2603              | 99     | 6382         | 15.5                                     |
| Transfer in                              | 1406 (26.9) | 71 (5.0)   | 1005              | 18     | 4448         | 4.1                                      |
| <b>ART Regimen (n=3090)**</b>            |             |            |                   |        |              |  |
| SLN@                                     | 801 (25.9)  | 96 (12.0)  | 454               | 7      | 2149         | 3.3                                      |
| ZLN                                      | 1719 (55.6) | 140 (8.1)  | 988               | 15     | 4167         | 3.6                                      |
| SLE                                      | 217 (7.0)   | 32 (14.7)  | 110               | 1      | 423          | 2.4                                      |
| ZLE                                      | 353 (11.4)  | 46 (13.0)  | 183               | 6      | 760          | 7.9                                      |

\*Includes only individuals whose date of diagnosis was available; \*\*Data of other individuals missing and does not include individuals on 2nd line ART; #Includes Divorce (Cases:113; Deaths:16) Separated (Cases:30; Deaths:2) Widow/er (Cases:739; Deaths:52), Live in (Cases:12;Deaths:2); @ S; Stavudine, L; Lamivudine, N; Nevirapine, E; Efavirenz

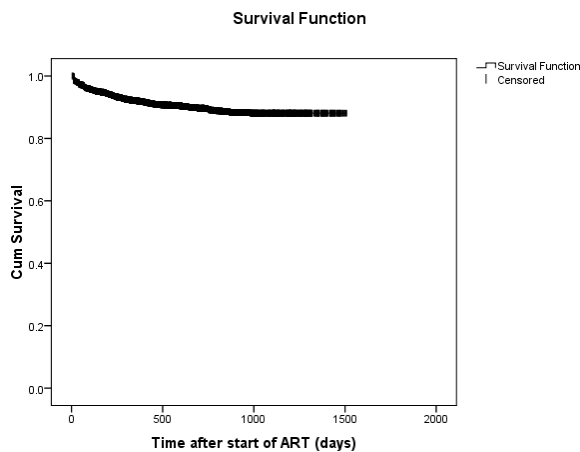
The patients with ART center Surat as the center of first contact were 73% and transfer in patients were 27%. Proportion of deaths was more among direct (10%) than transfer in (5%) patients. Out of the 3090 patients whose initial ART regimen was available majority of the patients were put on ZLN (56%) ART regimen.

Out of 5230 adult HIV patients registered at ART center Surat, 3824 patients were not referred from any center but ART center Surat was the first center of contact. Out of those 3824 patients, the date of HIV diagnosis was available for 2603 patients, whose survival probability after HIV diagnosis was estimated (Fig.1). The survival probability after 1 year of diagnosis of HIV and have taken ART at some point of time is 98% and

it is 93% after 5 years. The median follow up period was 2.46 years.

**Fig.1: Survival probability after HIV diagnosis (n=2603)**

**Fig.2: Survival probability after start of ART (n=3263)**



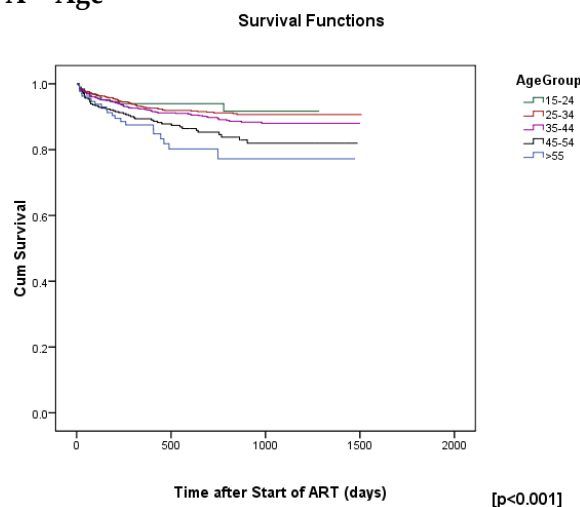
either no date of start of ART or they died on the day of start of ART and 411 had no data on baseline CD4+ count. So the survival probability after start of ART was estimated on remaining 3263 patients (Fig.2). The overall median follow-up was 16 months (interquartile range, 8-29 months). The survival probability after 6 months of start of ART is 92%, 91% after 1 year and 88% at third and fourth year.

The stratified Kaplan Meier survival analysis of 3263 patients showed that the survival probability was different among different age groups, patients with different CD4+ count and with different WHO staging (n=1902 patients data was available) and the difference was statistically significant ( $p < 0.001$ ). The difference in survival probability for male or female sex ( $p = 0.557$ ) and differential marital status ( $p = 0.136$ ) were statistically insignificant (Figure 3).

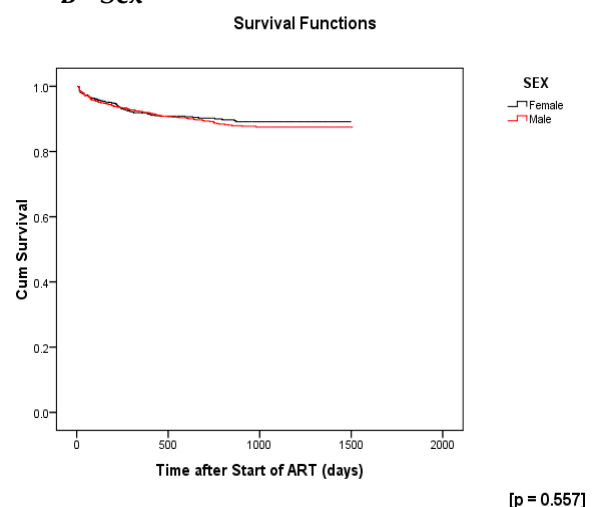
Out of 3824 adult patients with ART center Surat as the first center of contact 150 patients had

**Fig. 3: Survival after start of ART stratified by various characteristics A. Age; B. Sex; C. Marital Status; D. CD4+ count; E. WHO staging**

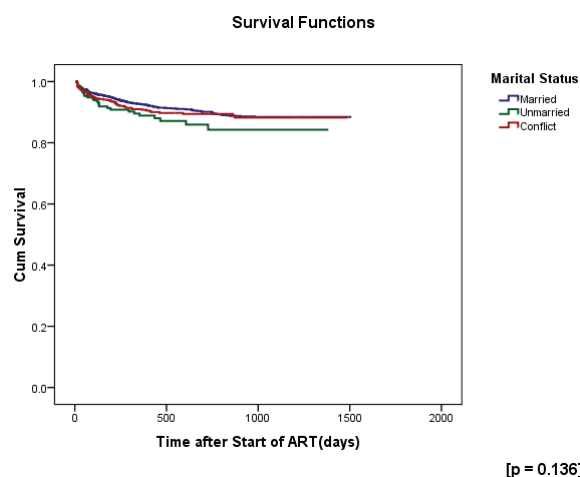
**A - Age**



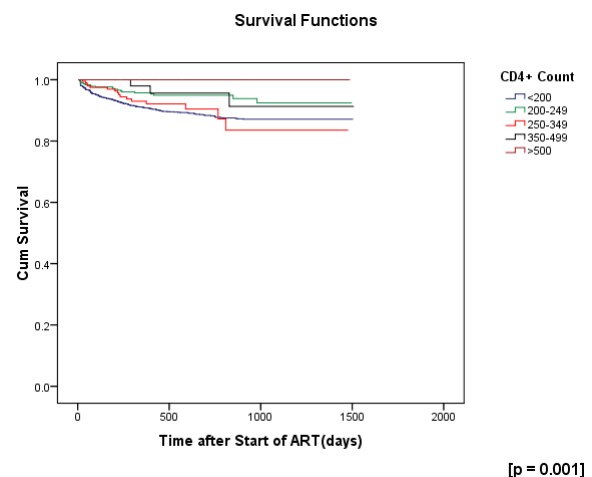
**B - Sex**



**C - Marital Status**

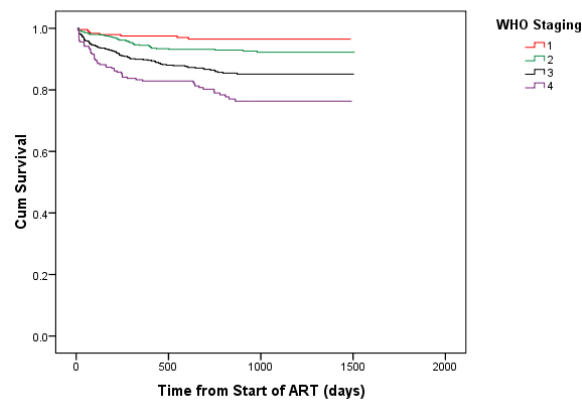


**D - CD4+ count**



### E - WHO Staging

Survival Functions



[p <0.001]

**Table 2: 4 yr survival probability following start of ART and estimated hazard ratios for variables**

| Variable             | Subgroup  | n    | % Survival | Hazard Ratio (95% CI)     | p-value |
|----------------------|-----------|------|------------|---------------------------|---------|
| Age (years)          | 15-25     | 199  | 91.7       | 0.3680 (0.1811 - 0.7480)  | 0.0057  |
|                      | 25-35     | 1227 | 90.7       | 0.4219 (0.2623 - 0.6786)  | 0.0004  |
|                      | 35-45     | 1282 | 88.0       | 0.5144 (0.3228 - 0.8197)  | 0.0052  |
|                      | 45-55     | 420  | 82.0       | 0.7654 (0.4623 - 1.2672)  | 0.2986  |
|                      | >55       | 135  | 77.2       | 1.0                       | -       |
| Marital Status       | Married   | 2362 | 84.2       | 0.8877 (0.6667 - 1.1821)  | 0.4151  |
|                      | Unmarried | 239  | 88.4       | 1.3164 (0.8367 - 2.0711)  | 0.2344  |
|                      | Conflict  | 662  | 88.3       | 1.0                       | -       |
| CD4+T-cell counts    | <200      | 2463 | 87.1       | 1.0                       | -       |
|                      | 200-250   | 481  | 92.5       | 0.4833 (0.3125 - 0.7477)  | 0.0011  |
|                      | 250-350   | 209  | 83.6       | 0.8435 (0.5085 - 1.3992)  | 0.5098  |
|                      | 350-500   | 64   | 91.3       | 0.4409 (0.1412 - 1.3763)  | 0.1585  |
|                      | >500      | 46   | 100.0      | 0.0                       | 0.9768  |
| WHO Staging (n=1902) | 1         | 225  | 96.5       | 1.0                       | -       |
|                      | 2         | 664  | 92.3       | 2.1170 (0.9966 - 4.4967)  | 0.051   |
|                      | 3         | 707  | 85.1       | 4.3144 (2.0942 - 8.8883)  | 0.0001  |
|                      | 4         | 276  | 76.0       | 7.0969 (3.3832 - 14.8874) | <0.0001 |

**Table 3: Comparison within WHO staging and CD+ Count (After start of ART)**

| Variable                     | Patients | Deaths | Kaplan-Meier Survival Analysis:<br>Comparison of groups using Log Rank test |           |            |           |
|------------------------------|----------|--------|---|-----------|------------|-----------|
| <b>WHO Staging (n=1902)</b>  |          |        |   |           |            |           |
| 1                            | 255      | 8      | P = <0.001  | P = 0.045 | P = <0.001 | P = 0.003 |
| 2                            | 664      | 44     |   |           |            |           |
| 3                            | 707      | 91     |   |           |            |           |
| 4                            | 276      | 56     |   |           |            |           |
| <b>CD4+ Count (n = 3263)</b> |          |        |   |           |            |           |
| <200                         | 2463     | 247    | P = 0.001   | P = 0.001 | P = 0.071  | P = 0.172 |
| 200-250                      | 481      | 22     |   |           |            |           |
| 250-350                      | 209      | 16     |   |           |            |           |
| 350-500                      | 64       | 3      |   |           |            |           |
| >500                         | 46       | 0      |   |           |            |           |
| <b>Age Group (n = 3263)</b>  |          |        |   |           |            |           |
| 15-25                        | 199      | 12     | P = <0.001  | P = 0.624 | P = 0.162  | P = 0.015 |
| 25-35                        | 1227     | 90     |   |           |            |           |
| 35-45                        | 1282     | 113    |   |           |            |           |
| 45-55                        | 420      | 54     |   |           |            |           |
| >55                          | 135      | 21     |   |           |            |           |

When calculated for different categories of age groups, the Cox proportional hazard was less among all age groups less than 45 years as compared with age group more than 55 years. The difference was statistically significant (Table 2). The hazard ratio of CD4+ count >200 is less as compared to CD4+ count <200. Among the WHO staging the hazard ratio is maximum for stage 4 (HR 7.0969,  $p < 0.001$ ).

Comparison within the WHO staging (Table 3) showed statistically significant difference in each group. The difference in survival probability between CD4+ count <200 and 200-250 is statistically significant ( $p = 0.001$ ) but there is no statistical significant difference between the groups 250-350, 350-500 and >500. ( $p = >0.05$ ) The difference in survival probability between age groups 15-25, 25-35 and 35-45 is insignificant. ( $p = >0.05$ ).

## DISCUSSION

The survival probability after 15 years of diagnosis of HIV is 83%. The 4 year survival probability

is 88% after the start of ART. The crude mortality rate is 8.6%. The Robert S. Hogg et al reported crude mortality of 33.1% in their study in 1998. <sup>(5)</sup> With time the awareness of HIV may be increased leading to early initiation of ART and good adherence and decline in mortality due to HIV. <sup>(5)</sup> The mortality density per 1000 person years in the current study and Mee-Kyung Kee et al <sup>(6)</sup> are 10.8 and 45.7 respectively. Mee-Kyung Kee et al <sup>(6)</sup> and Arif Alibhai et al <sup>(7)</sup> reported higher survival among women but the role of gender as predictor of survival could not be well established in the present study. The marital status as a social factor does not significantly contribute to survival. Mee-Kyung Kee et al and current study have the same opinion that the age >55 years, CD4+ count <200 and WHO stage 3 and 4 have poor survival. As the age more than 55 years has come out as an independent risk for poor survival. It may be due to the delayed diagnosis or due to the aging itself. The study suggests considering old age as one of the criteria in deciding start of ART in HIV individuals.

**Table 4: Initiation of ART based on CD4 count and WHO clinical staging\* <sup>(8)</sup>**

| Classification of HIV associated clinical disease | WHO Clinical stage | According to CD4 count (NACO and WHO 2006 guidelines)                      | According to CD4 count (WHO 2010 guidelines) |
|---|--------------------|--|--|
| Asymptomatic                                      | 1                  | Treat if CD4 <200  | Treat if CD4 <350                            |
| Mild symptoms                                     | 2                  |  |  |
| Advanced symptoms                                 | 3                  | Consider treatment if CD4 <350 and initiate ART before CD4 drops below 200 | Treat irrespective of CD4 count              |
| Severe/Advanced sympt.                            | 4                  | Treat irrespective of CD4 count  |  |

\*Antiretroviral Therapy Guidelines for HIV-infected Adults and Adolescents Including Post-exposure Prophylaxis, NACO, May 2007

NACO guidelines as when to start is based on 2006 WHO guidelines on ART. The 2010 WHO has recommended new guidelines for ART with different CD4 cut off to start ART. The NACO is trying to adopt the new guidelines. ART According to the NACO guidelines (which is based on 2006 WHO guidelines) ART is initiated depending upon the WHO stage of infection. PLHA with less than 200 CD4 (while blood cells/  $\text{mm}^3$ ) require treatment irrespective of the clinical stage. For PLHA with 200-350 CD4, ART is offered to symptomatic patients. Among those with CD4 of more than 350, treatment is deferred for asymptomatic persons. In the 2010 WHO guidelines the cut off for asymptomatic persons has been raised from 200 to 350. <sup>(9)</sup>

## CONCLUSIONS

The current survival analysis shows that at CD4 count less than 200 there is significant difference

in survival in comparison with the higher CD4 counts. Above the CD4 count 200 there is no statistical significance in survival between various cut off. So it doesn't matter when survival is considered, whether CD4 count is 350 or 250 unless it is less than 200 to start ART. But the survival is statistically significant within the WHO clinical staging. So to start ART it matters whether the patient is in Stage 1, 2, 3 or 4 for survival. The current study therefore supports that when CD4 count testing facility is not available WHO staging is to be the deciding factor to start ART. But when facility is available then for asymptomatic patients cut off of 200 is still preferred rather than 350 of new WHO guidelines. The cut off 200 can deprive ART for patients on borderline risk i.e. with CD4 count between 200 and 250. The cut off 350 is too high so that many patients need to be put on ART. It will not have any survival advantage rather will be financial overburden to the state.

## RECOMMENDATIONS

The study recommends for asymptomatic patients and symptomatic stage 1 and 2 patients the ART should be considered when CD4 count is below 250 and irrespective of CD4 count for Stage 3 and 4 patients. The data should be further analysed using regression model to identify the most important predictor of survival.

## Limitations

The analysis does not take into consideration the associated opportunistic infection neither at the time of diagnosis nor at the time of start of ART.

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