Trends in Clinical Characteristics and Short-Term Outcome of HIV-Infected Patients at a Tertiary Care Hospital in South India

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Abstract

Background: Limited information is available on changing trends in HIV positive patients treated with first-line antiretroviral therapy from India. Methods: The clinical characteristics and short-term outcome were compared between a retrospective group enrolled between January 2006 and March 2007 (06-07 group—100 patients) and a prospective group enrolled between February 2011 and March 2012 (10-12 group—85 patients). Results: Median age was 36 and 38 years in 06-07 and 10-12 groups, respectively. Median baseline CD4 count was 146 cells/mL³ in the 10-12 group, and it was not significantly different from that of 06-07 group. Tuberculosis was diagnosed 3 times more commonly in the 10-12 group. The retention proportion at the end of 10 months was 68% in the 10-12 group when compared to that of 59% in the 06-07 group. Conclusion: There was a trend toward improved outcome over the period of time, but the attrition rate remained high.

Keywords

antiretroviral therapy, short-term outcome, time trends, resource limited setting, HIV

Introduction

The National AIDS Control Organisation (NACO) started the rollout of free antiretroviral therapy (ART) in India in 2004.¹ Since then the NACO policy has evolved, and ART is being started at higher CD4 cutoffs; stavudine (d4T) has been phased out of first-line ART, and tenofovir (TDF) has been introduced as a first-line agent. The short-term outcome from 3 ART centers following the initial introduction of first-line ART has been published.² But the centers which have reported these initial data have not reported on the trend of the disease later. Information on trends in disease at presentation and outcome are required to measure the impact of the NACO policies. The trend of median CD4 count at presentation is available from Karnataka, India.² It had increased from 125 in 2004 to 235 in 2011. Overall information on Asia is available from the TREAT Asia HIV Observational Database (TAHOD).³ The median CD4 count at ART initiation had increased from 115 in 2008 to 302 in 2011.³ The proportion of patients with late ART initiation significantly decreased over time from 79.1% before 2007 to 36.3% after 2011.³ But, comprehensive information is lacking and it prompted us to study it at our center. Patient data had been

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gathered during 2 periods, 2006 to 2007 and 2010 to 2012. The patient characteristics (CD4 count at the start of ART, initial opportunistic infections [OIs] and outcomes (response to first-line therapy, drug side effects, survival rate) between these 2 groups have been compared in this study.

Methods

Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) has been providing ART with the support of Pondicherry State AIDS Control Society since January 2006 and has recently been designated as a LINK PLUS ART Center. The objective was to describe the time trends of clinical characteristics at initial presentation and short-term outcome at JIPMER. Two observational studies done at JIPMER approximately 4 years apart were selected for the same. First was a retrospective study of first 100 ART-naive patients enrolled for first-line ART between January 2006 and March 2007. One hundred forty patients in total had been registered in the clinic during that period. The data had been compiled in February 2012. The long-term outcome of this group has been published previously. This group of patients will be addressed as 06-07 group. The second was a prospective study of 85 ART-naive patients enrolled for first-line ART between February 2011 and March 2012. One hundred sixty-six patients in total had been registered in the clinic during the period. The study had been approved by the institute ethics committee (IEC No. SEC/2011/1/1 Approved on January 13, 2011) and written informed consent had been obtained from all the participants. The patients had been followed up for a median period of 10 months, and the data had been compiled in September 2012. This group of patients will be addressed as 10 to 12 group.

Antiretroviral therapy was started in patients if they were symptomatic or if the CD4 count was below 250 cells/mL (10-12 group), after ruling out or treating an OI. Opportunistic infections were diagnosed based on the World Health Organization definitions for diagnosis of clinical events. This could be supplemented by microbiological diagnosis, as available. The CD4 count threshold for starting ART was 200 in the 06-07 group as per the then NACO guidelines. Patients were initially monitored once in 2 weeks and later once monthly. Adherence, side effects and clinical status were recorded at follow-up visits. CD4 count was done once in 6 months. Patients had been followed up for a minimum of 6 months.

The demographics, baseline CD4 counts, clinical presentation, and initial ART-related trends have been presented. Initiation of first-line ART in patients with a CD4 count of less than 200 was considered as late initiation of ART. Outcome data that include retention proportion after a median follow-up of 10 months, lost to follow-up (LFU) and deaths within 6 months of initiation of ART, outcome of patients with concomitant tuberculosis (TB), and improvement in CD4 counts in patients who had received more than 6 months of ART have been compared between the 2 groups of patients. A patient was considered LFU if he was absent from the hospital for a minimum period of 3 months, unless the patient had died, stopped ART, or had been transferred. The date of the last visit to the hospital was recorded as the date of LFU. Adherence to ART was estimated by measuring timeliness of patient visits to scheduled medicine pickup appointments at the hospital.

Statistical Analysis

Microsoft Excel and StatsDirect (version 2.8.0) software were used in statistical analysis. The data were summarized using appropriate descriptive statistics. The baseline CD4 counts between the 2 groups were compared by Student t test. The CD4 counts at baseline and later were compared by paired Student t test. Survival analysis was done using the Kaplan-Meier method. Death and LFU were considered as events. The short-term survival was compared between the 2 groups by the log-rank method. The retention proportion was obtained from the life table at the end of 10 months. The statistical test used for the association between poor adherence, LFU, and various patient characteristics was the Fisher exact test.

Results

The baseline clinical characteristics of both the patient groups are provided in Table 1. They were middle-aged adults. Majority (84%) of patients were from Tamil Nadu in the 10-12 group, whereas in the 06-07 group, the patients from Tamil Nadu and Pondicherry were in equal proportion. The median CD4 count was 146 cells/mm³ in the 10-12 group when compared to 117 cells/mm³ in the 06-07 group, but this was not statistically significant (P = .661). The proportion of patients with late ART initiation was higher in the 06-07 group (88% vs 64%).

First-line ART contained d4T in 54% of patients in the 06-07 group, which reduced to 27% in the the 10-12 group. Zidovudine (ZDV)-based ART became the preferred treatment, except for patients with anemia. Proportion of patients receiving efavirenz (EFV) when compared to nevirapine (NVP) were more in the 10-12 group as greater proportion of patients were receiving anti-TB treatment simultaneously.

Opportunistic infections were diagnosed in much higher proportion of patients in the 10-12 group. Tuberculosis was the main OI. It was diagnosed 1.5 times more commonly in the 10-12 group (11% and 39% of patients in 06-07 group and 10-12 group, respectively). The average CD4 count was less than 150 and similar in the 2 groups. Definitive diagnosis had been achieved in 27% (9/33) of the patients in the 10-12 group (a positive Ziehl-Neelsen stain on sputum smear, on a sample obtained by fine needle aspiration, or biopsy in 9 patients). Disseminated and extrapulmonary TB was more common than pulmonary TB alone (Table 2).

Treatment Outcomes

Twenty-five percent of the 10-12 group had drug-induced adverse effects in the short term when compared to 20% of patients in the 06-07 group. Details are provided in the Table 3. The differences in the side effects appear to reflect the changes
in the antiretroviral drug usage during those periods. One patient in each group had Steven-Johnson syndrome. One due to NVP and the other due to EFV. Drug-induced hepatitis was uncommon.

Thirty-three patients were diagnosed to have TB in the 10-12 group. Of them, 3 had died and 5 patients were LFU. Twenty-five (76\%) patients had improved with anti-TB drugs. Clinically discernable immune reconstitution inflammatory syndrome was not noted in any of the patients. In the 06-07 group, 11 patients had TB. Of them, 9 (81\%) had improved with Antituberculous treatment (ATT) and 2 patients had been LFU. (Table 2)

In the 10-12 group, of the 85 patients, 53 (62\%) patients had completed 6 months of ART in the clinic (12 patients had been transferred out, 16 patients were LFU, 4 had died within 6 months). Of all, 98\% of the patients had improved to clinical stage 1. The CD4 count improved from a baseline mean of 153 cells/\text{mL} to a mean of 307 cells/\text{mL} after 6 months of ART (\text{P} < .0001). Sixty-seven percent of the patients were more than 95\% adherent to treatment. In the 06-07 group, 55\% of the patients had completed 6 months of ART. Repeat CD4 count was available in 32 of the 55 patients after a median period of 9 months from baseline. In them, the mean CD4 count had improved from 160 cells/\text{mL} at baseline to 361 cells/\text{mL}.

The 10-12 group had been followed up for a median period of 10 months. Lost to follow-up, deaths, and retention proportion were compared between the 06-07 and the 10-12 groups. The proportions of patients dead or LFU within 6 months of starting ART were compared between the 2 groups (Table 4).

Nineteen percent of patients had been LFU and 4.7\% had died

### Table 1. Baseline Clinical Profile of the Patients.

| Characteristic                  | 06-07 Group (n = 100), n (% | 10-12 Group (n = 85), n (% | P Value |
|--------------------------------|---------------------------|----------------------------|--------|
| Median age, years              | 36 (31\text{-}41)         | 38 (33\text{-}45)          | -      |
| Proportion of females, %       | 32                         | 39                         | .35    |
| Proportion of patients from Puducherry, % | 52                     | 16                         | -      |
| Median CD4 count, cells/mm\(^3\) | 117 (76\text{-}193)       | 146 (73\text{-}207)        | .661   |
| % of patients with CD4 count of less than 200 | 88                     | 64                         | -      |
| Number of patients with an opportunistic infection | 20 (20\%)            | 43 (51\%)              | .0001  |
| Opportunistic infections       |                           |                            |        |
| Oral candidiasis: 20 (20\%)    |                           |                            |        |
| Tuberculosis: 11 (11\%)         |                           |                            |        |
| Chronic diarrhea: 2             |                           |                            |        |
| Pneumocystis jiroveci pneumonia: -1 |                   |                            |        |
| Cryptococcal meningitis-1       |                           |                            |        |
| Cerebral toxoplasmosis-1        |                           |                            |        |
| Coinfection                    |                           |                            |        |
| Malignancy                     |                           |                            |        |
| Initial antiretroviral drugs    |                           |                            |        |
| d4T/3TC/NVP 52\%               |                           | AZT/3TC/NVP 46\%           | -      |
| AZT/3TC/NVP 29\%               |                           | AZT/3TC/EFV 27\%           | -      |
| AZT/3TC/EFV 17\%               |                           | d4T/3TC/EFV 12\%           | -      |
| d4T/3TC/EFV 2\%                |                           | d4T/3TC/NVP 15\%           | -      |

### Table 2. Tuberculosis in the 2 Groups.

| Characteristic                  | 06-07 Group (n = 100), n (%) | 10-12 Group (n = 85), n (%) |
|--------------------------------|-----------------------------|-----------------------------|
| Total no. of cases (%)         | 11 (11\%)                   | 33 (39\%)                   |
| Extrapulmonary tuberculosis   | 6                           | 14                          |
| - LN TB                        | 4                           | 9                           |
| - Pleural TB                   | 1                           | 2                           |
| - TBM                          | 0                           | 2                           |
| - CNS tuberculoma              | 0                           | 1                           |
| - Pericardial TB               | 1                           | 0                           |
| Disseminated TB                | 2                           | 13                          |
| Pulmonary tuberculosis         | 3                           | 6                           |
| Average CD4 count (cells/mm\(^3\)) | 145                 | 135                         |
| Outcome                        |                             |                             |
| Death/LFU                      | 2                           | 8                           |
| Improved                       | 9 (81\%)                    | 25 (76\%)                   |

### Table 3. Drug-Induced Side Effects and Adherence to Antiretroviral Therapy.

| Side Effect                  | No. of Patients (\%), 06-07 Group | No. of Patients (\%), 10-12 Group | Drug Responsible |
|------------------------------|-----------------------------------|-----------------------------------|------------------|
| Anemia                       | 2 (2\%)                           | 8 (9\%)                           | AZT              |
| Rash                         | 15 (15\%)                         | 5 (5.9\%)                         | NVP EFV          |
| Hyperpigmentation            | 0                                 | 4 (4.7\%)                         | AZT              |
| Hepatitis                    | 0 (1\%)                           | 1 (1.1\%)                         | ATT NVP          |
| Drowsiness                   | 2 (2\%)                           | 0                                 | EFV              |
| Dizziness                    | 0                                 | 2 (2.3\%)                         | -                |
| More than 95% adherence to ART | 48\%                            | 67\%                             | -                |

### Table 4. TB outcome in the 06-07 and 10-12 groups.

| Characteristic                  | 06-07 Group (n = 100), n (%) | 10-12 Group (n = 85), n (%) | P Value |
|--------------------------------|-----------------------------|-----------------------------|--------|
| Median age, years              | 36 (31\text{-}41)         | 38 (33\text{-}45)          | -      |
| Proportion of females, %       | 32                         | 39                         | .35    |
| Proportion of patients from Puducherry, % | 52                     | 16                         | -      |
| Median CD4 count, cells/mm\(^3\) | 117 (76\text{-}193)       | 146 (73\text{-}207)        | .661   |
| % of patients with CD4 count of less than 200 | 88                     | 64                         | -      |
| Number of patients with an opportunistic infection | 20 (20\%)            | 43 (51\%)              | .0001  |
| Opportunistic infections       |                           |                            |        |
| Oral candidiasis: 20 (20\%)    |                           |                            |        |
| Tuberculosis: 11 (11\%)         |                           |                            |        |
| Chronic diarrhea: 2             |                           |                            |        |
| Pneumocystis jiroveci pneumonia: -1 |                   |                            |        |
| Cryptococcal meningitis-1       |                           |                            |        |
| Cerebral toxoplasmosis-1        |                           |                            |        |
| Coinfection                    |                           |                            |        |
| Malignancy                     |                           |                            |        |
| Initial antiretroviral drugs    |                           |                            |        |
| d4T/3TC/NVP 52\%               |                           | AZT/3TC/NVP 46\%           | -      |
| AZT/3TC/NVP 29\%               |                           | AZT/3TC/EFV 27\%           | -      |
| AZT/3TC/EFV 17\%               |                           | d4T/3TC/EFV 12\%           | -      |
| d4T/3TC/EFV 2\%                |                           | d4T/3TC/NVP 15\%           | -      |

### Abbreviations:

- AZT, zidovudine; d4T, stavudine; EFV, efavirenz; IQR, interquartile range; NVP, nevirapine; 3TC, lamivudine.
Table 4. Comparison of LFU and Deaths of Patients Within 6 Months of Initiation of ART in the 2 Groups.

| Characteristic          | 06-07 Group (n = 100), n (%) | 10-12 Group (n = 85), n (%) |
|-------------------------|------------------------------|----------------------------|
| Lost to follow-up (%)   | 30 (30%)                     | 16 (19%)                   |
| Died (%)                | 9 (9%)                       | 4 (4.7%)                   |

in the 10-12 group, whereas 30% of the patients had been LFU and 9% patients had died in the 06-07 group. Kaplan-Meier curves were plotted for both the groups and are shown in Figure 1 (LFU or death was counted as an event, transferred out patients and those patients on follow up for more than or equal to 10 months were censored). The retention proportion of the 10-12 group at 10 months was 68%. The same for the 06-07 group was 59.4%. This was not statistically significant (P = .10; log-rank test).

Twenty-one percent (18/85) of the patients were LFU in the 10-12 group after a median follow-up of 10 months. Majority of them were males (78%), alcohol consumers (67%), had a low socioeconomic status (89%), and had a baseline CD4 count of ≤200 cells/µL (67%). The above associations were not statistically significant.

Discussion

The time trends of clinical characteristics and short-term outcome of HIV-infected patients initiated on first-line ART at a single center have been presented here. The median CD4 count at presentation was higher in the 10-12 group when compared to that of the 06-07 group, but this was not a statistically significant difference. In the Asian countries, according to the TAHOD database (which includes 2 centers from India), the median CD4 at ART initiation has improved from a median of 115 cells/mm³ in 2008 to 302 cells/mm³ after 2011. In a study involving 12 ART centers in Karnataka, spanning from 2004 to 2011, median CD4 count at presentation had risen from 125 in 2004 to 235 in 2011. Such a change has not been noted here. In a retrospective study from Postgraduate Institute Of Medical Education and Research (PGIMER), Chandigarh, the median CD4 count at presentation in year 2003 was 197/µL, while in year 2007, it was 186.5/µL. It appears that the change in CD4 count at ART initiation is not uniform across India, and the improvement has lagged behind Asian counterparts. Similarly, the proportion of patients with late initiation of ART reduced to 64% in the 10-12 group here, but it was less than 36.3% noted in the TAHOD database after 2011. This suggests that the cases are still being diagnosed late during the course of the illness. Sogarwal and Bachani, while assessing the proportion of patients being registered at ART centers in India with an initial CD4 count of less than 250, found that it was 85% and it did not change significantly over 3 years from 2005 to 2008. Hence even though the latest NACO guideline advises to initiate ART below a CD4 count of 350 cells/µL, it may not impact outcome.

Tuberculosis was the commonest OI in the 10-12 group. The proportion of patients being diagnosed with TB had increased over the years. Thirty-nine percent of the 10-12 group of patients were diagnosed to have TB (64% extrapulmonary TB), similar to a retrospective analysis of 1754 patients by Sharma et al wherein 33.2% of patients were found to have active TB at diagnosis. Favorable outcome (cure and completion of treatment) had been noted in 77% in the same study, which again is similar to both the groups here (76% and 81% in 10-12 group and 06-07 group, respectively).

There was a shift in the use of ART from d4T-based ART to ZDV-based ART as per the NACO policy to reduce the long-term side effects. Anemia was commoner in the 10-12 group as more patients received ZDV-based ART. More number of patients received EFV in the 10-12 group as they were simultaneously receiving anti-TB drugs. Hence, the NVP-related side effects were lower in the 10-12 group. In general, side effects can now be expected to reduce as NACO has introduced TDF, lamivudine (3TC), EFV/NVP combination as first-line ART along with ZDV, 3TC, and NVP/EFV.

Among patients initiated on first-line ART, 65% to 88% remain alive and on treatment at 12 months in the Asia-Pacific region. The retention proportion of the 10-12 group at 10 months was 68% when compared to 59.4% in 06 to 07 group, which is similar to those observed in the region (survival rate is expected to be greater than retention proportion, if transferred out patients remain on ART). More number of OIs were diagnosed and treated and less number of patients had died in the 10-12 group when compared to the 06-07 group and there was a trend toward better short-term outcome in the 10-12 group. But, the LFU rates that were 30% and 20% in the 06-07 and 10-12 groups, respectively, affected outcome. The LFU rates are high in Asia. In the TAHOD database, 20% of the patients were LFU in a given year. A study from Delhi
over a decade showed that LFU happened at each level of HIV care, with maximum LFU happening before the initiation of ART.\textsuperscript{13} Lost to follow-up rates reduced after institution of strategies adopted in the National AIDS Control Programme Phase (NACP)-III. These methods should be incorporated here to reduce the rate of LFU, which in turn will automatically improve the overall outcome.

The study has the following limitations. It has been reported from a single center, and the sample size was small. It was underpowered to demonstrate the difference in the attrition rates (post hoc power analysis; power = 75%). The time series design has an inherent weakness in internal validity. The adherence to ART was measured only by the timeliness to pick up drugs; hence, this underestimates nonadherence to therapy.

Moving forward, NACO needs to adopt new strategies to improve early case detection and implement measures already advocated in NACP-III to reduce LFU rates. The expanded voluntary HIV testing as advocated by Venkatesh et al is worth considering.\textsuperscript{14} According to their model, the CD4 count at diagnosis would improve from the current 201 to 290 cells/mm\textsuperscript{3} with the introduction of a single-time national screening.\textsuperscript{14}

In conclusion, a trend toward better survival could be noted in the 10-12 group of patients, but to improve outcomes further, patients need to be diagnosed earlier and they need to be retained on therapy.

\section*{Author's Note}
S.B.S. contributed to the conception, design, acquisition of data, analysis, and preparation of manuscript. A.H. contributed to analysis and preparation of manuscript. K.K.M. was involved in acquisition of data and preparation of manuscript.

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\section*{References}
1. Bachani D, Garg R, Rewari BB, et al. Two-year treatment outcomes of patients enrolled in India’s national first-line antiretroviral therapy programme. \textit{Natl Med J India}. 2010;23(1):7–12.
2. Shastri S, Boregowda PH, Rewari BB, Tanwar S, Shet A, Kumar AM. Scaling up antiretroviral treatment services in Karnataka, India: impact on CD4 counts of HIV-infected people. \textit{PloS One}. 2013;8(8):e72188. doi:10.1371/journal.pone.0072188.
3. Zhou J, Sirisanthana T, Kiertiburanakul S, et al. Trends in CD4 counts in HIV-infected patients with HIV viral load monitoring while on combination antiretroviral treatment: results from The TREAT Asia HIV Observational Database. \textit{BMC Infect Dis}. 2010;10(1):361. doi:10.1186/1471-2334-10-361
4. Hamide A, Shamanna SB, Subbian M, Balaguru S. Long term outcome of a group of first hundred HIV infected patients treated at a tertiary care hospital in South India. \textit{Natl Med J India}. 2014;27(3):134–137.
5. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach: 2010 revision. http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf?ua=1 Accessed August 14, 2018.
6. National AIDS control organization of India. Antiretroviral therapy guidelines for HIV infected adults and adolescents including post-exposure prophylaxis. 2007. http://apps.who.int/medicine/docs/documents/s18021en/s18021en.pdf Accessed August 14, 2018.
7. Kumar S, Wanchu A, Abeygunasekera N, Sharma A, Singh S, Varma S. Profile of presentation of human immunodeficiency virus infection in north India, 2003-2007. \textit{Indian J Community Med}. 2012;37(3):158–64.
8. Sogarwal R, Bachani D. Are persons living with HIV timely accessing ART services in India? \textit{J Indian Med Assoc}. 2009;107(5):288–290.
9. National AIDS Control Organization of India. Antiretroviral therapy guidelines for HIV infected adults and adolescents including post-exposure prophylaxis. 2013. http://naco.gov.in/sites/default/files/Antiretroviral%20Therapy%20Guidelines%20for%20HIV-Infected%20Adults%20and%20Adolescents%20May%202013%28%20%282%29%29_0.pdf Accessed August 14, 2018.
10. Sharma SK, Soneja M, Prasad KT, Ranjan S. Clinical profile & predictors of poor outcome of adult HIV-tuberculosis patients in a tertiary care centre in north India. \textit{Indian J Med Res}. 2014;139(1):154–160.
11. Srikantiah P, Ghidinelli M, Bachani D, et al. Scale-up of national antiretroviral therapy programs: progress and challenges in the Asia Pacific region. \textit{AIDS}. 2010;24(suppl 3):S62–S71.
12. Zhou J, Tanuma J, Chaiwarith R, et al. Loss to followup in HIV-infected patients from Asia-Pacific region: results from TAHOD. \textit{AIDS Res Treat}. 2012;2012:375217. doi:10.1155/2012/375217.
13. Gupta AK, Dabla V, Joshi BC, Chakraborty S, Baishya JJ, Gupta AM. Challenges in retention of patients in continuum of HIV-care in Delhi—experience of a decade & way ahead. \textit{World J AIDS}. 2014;4(4):387.
14. Venkatesh KK, Becker JE, KumaraSamy N, et al. Clinical impact and cost-effectiveness of expanded voluntary HIV testing in India. \textit{Plos One}. 2013;8(5):e64604.