Treatment Outcomes of Patients Receiving Combination Antiretroviral Therapy under the National Acquired Immunodeficiency Syndrome Control Programme

Abstract

Introduction: The free antiretroviral therapy (ART) initiative of the Government of India was launched on April 1, 2004, since then it is being scaled up in a phased manner. The aim of this study was to analyze the treatment outcome of patients receiving first-line ART through the National Acquired Immunodeficiency Syndrome Control Programme of India. Materials and Methods: This was a record-based retrospective analysis of data of patients who were put on ART from January 2009 to December 2009. Results: Of the 548 patients (63.87% males; median age of 37 years), 55% of patients were employed and majority of them have low monthly income. Patients showed a significant improvement in clinical and functional status after starting ART therapy, as percentage of patients in clinical Stage 1 increased significantly (from 35.5% to 90.3%) and that of Stage 3 and 4 decreased drastically. Ninety percent of patients were working, and none was bedridden after 2 years of ART. Patients with >95% adherence to ART showed more improvement than those with <95% adherence (40% patients). The median increase in cluster of differentiation 4 (CD4) count was 134 cells/mm³ at 6 months, 185 cells/mm³ at 12 months, and 255 cells/mm³ at 24 months. Majority of patients died in clinical staging 4 with CD4 cell count <50 cells/mm³. Over 2 year’s period, 20% patients died and 9.31% were lost to follow-ups (LFUs). Conclusion: Early detection, timely treatment, and long-term adherence are the keys for the success of ART programme in India; it is of utmost importance to do intense Information Education Communication/Behavioral Change Communication, regular monitoring, up-to-date record keeping, tracking of LFUs, and triangulation and data analysis for timely action and for consolidation of success made so far.

Keywords: Adherence, antiretroviral therapy, clinical staging, cluster of differentiation 4

Introduction

India has an estimation of 2.14 million people living with human immunodeficiency virus (HIV) infection.[1] The free antiretroviral therapy (ART) initiative of the Government of India was launched on April 1, 2004, at eight institutions in six high prevalent states and National Capital Territory of Delhi. Since then, it is being scaled up in a phased manner. India is committed to achieve the sustainable development goals (SDGs) of ending Acquired Immunodeficiency Syndrome (AIDS) as a public health threat by the year 2030. Currently, HIV care services are being delivered through a network of 541 ART centers, 1108 link centers with 310 care and support centers in India.[2] At present, 11, 81, 129 people are receiving free antiretroviral (ART) drugs.[3] In Punjab, currently, there are eight ART centers functional (Jalandhar, Patiala, Ludhiana, Pathankot, Bathinda, Ferozepur, Taran Taran, and Hoshiarpur), one ART plus center in Amritsar, providing ART to 36,851 patients.[4] According to the latest National AIDS Control Organization (NACO) Technical report 2017, overall, a total of 36,794 HIV/AIDS cases were estimated across Punjab in 2015. There was a steady increase in the total burden of the epidemic in the state since 2007 – a 58% increase in total HIV/AIDS cases during the past 8 years. It is estimated that there were 2225 new HIV infections in the state during 2014–2015, indicating a 19% decline in new HIV infections during 2007–2015. The estimated adult HIV prevalence increased from 0.15% in 2007 to 0.19% in 2015. During the same time, AIDS-related deaths declined by 47%, from a total of 978 in 2007 to 523 in 2015.[5]

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on epidemiological profile of HIV patients in Punjab are available at Punjab State AIDS Control Society (PSACS) and NACO sites, but there is a paucity of data on the treatment outcome of patients receiving ART in the state; taking this prospective into consideration, the current study was conducted to evaluate the effectiveness of combination ART regimes in the management of HIV-positive patients and to determine the treatment outcomes in terms of survival, adherence, functional status, clinical staging, and improvement in cluster of differentiation 4 (CD4) counts of the patients enrolled at ART center, Patiala. This information will be useful for PSACS and NACO to implement the program more effectively in Punjab and to achieve SDG by the year 2030.

Aims and objective

The aim of this study is to study the ART adherence and HIV care outcome of patients on ART.

Materials and Methods

This was a record-based retrospective analysis of 548 patients, who were put on ART, at ART Center of Rajindra Hospital, Patiala, India, between January 1, 2009 and December 31, 2009. We took all the patients who were put on ART therapy during the year 2009. The objective was to observe the treatment outcome of the patients who were put on ART, and their treatment records were studied for a period of 2 years after their initiation of ART in the ART center that is up to December 2011, and their data were analyzed based on their records related to sociodemographic profile, risk factors, antiretroviral drugs (ARV) adherence, and their HIV care outcome. Eligible patients were those aged 0 to 60 years and above and those who were diagnosed HIV positive by the standard COMBAIDS diagnostics kit as per the NACO guidelines. Initiation of ART was done in Clinical Stage I and II if CD4 <200 cells/mm³ and in Clinical Stage III if CD4 count is <350 and in Stage IV irrespective of CD4 counts. CD4 count is done by the flow cytometric technique, and the patient was put on combined ART regimens as per the following principles.[6]

Principles for selecting the first-line regimen

1. Choose 3TC (lamivudine) in all regimens
2. Choose one nucleoside analog reverse-transcriptase inhibitor (NRTI) to combine with 3TC (zidovudine [AZT] or stavudine [d4T])
3. Choose one nonnucleoside reverse-transcriptase inhibitor (NNRTI).

First choice: AZT + 3TC + Nevirapine (NVP) (for patients with hemoglobin (HB) >8 g/dl).

Second choice: d4T + 3TC + NVP.

(Substitute NVP with Efavirenz (EFV) for patients with tuberculosis (TB) or toxicity to NVP in above regimens).

Special considerations

Tenofovir (TDF) +3TC + (NVP or EFV): This combination is only for special situations, when there is toxicity or other contraindications to AZT or d4T substituted with TDF.[6]

Results

Out of 548 patients, males constitute 63.87%. Majority of patients were married (72.45%) and fall in the age group of 30–50 years (65%), with a median age of 37 years. Nearly 40.15% of patients were illiterate, and 90% patients have monthly income below 10,000 rupees. Nearly 55.11% patients were employed; out of them, 16.42% were farmers followed by construction workers/laborers (13.87%), drivers (11.31%), and police/homeguard (2.74%).

Table 1 shows the World Health Organization clinical staging of the patients at the start of their ART therapy, and then, their subsequent clinical staging when they were on ART therapy for a period of 2 years. From the table, it is clear that patients improved significantly after starting ART therapy, as percentage of patients in Clinical Stage 1 increased significantly and that of Stage 3 and 4 decreased drastically. With the improvement in clinical staging, there is a marked improvement seen in the functional status of the patients. At the start of ART, 55.2% of patients were working, 32.85% ambulatory, and 11.86% bed ridden, and at the end of 24 months, 98.63% of surviving patients on ART were functional and none was bedridden.

Table 2 shows the CD4 cell count of the patients over 2 years. At the start of ART therapy, almost 20% patients had very low CD4 cell count of ≤50 count/mm³, 70% had CD4 cell count within a range of 51–250, and only 7.5% had a CD4 cell count of ≥350. After 2 years of ART therapy, noticeable less percentage of patients (2.47%) had a CD4 cell count of ≤50 and those with CD4 cell count ≥350 significantly increased to 56%. This showed that there has been a statistically significant increase in the CD4 cell count of patients after receiving ART therapy. The mean CD4 cell count at ART initiation was 144.79 (95% confidence interval [CI], 131.4–149.4) cells/mm³ which increased to 266.09 (95% CI 254.7–277.15) cells/mm³ (84% increase from the mean baseline value) at 6 months, at 12 months of ART therapy 312.53 (95% CI, 302.26–323.52) cells/mm³ (116% increase from mean baseline value), and at 24 months 322.7 (95% CI 311–335) cells/mm³ (123% increase from mean baseline value). The median CD4 cell count was 127.6/mm³ at the start of ART, which it increased to 261.84 cells/mm³ at 6 months and further increased to 357.8 cells/mm³ and 382.13 at 12 and 24 months, respectively, with ART. Majority of patients died in clinical staging 4 with CD4 cell count of <50 cells/mm³ followed by those with CD4 cell count between 50 and 150 cells/mm³. Nearly 41.6% died in clinical staging 4 and 28.7% patients died in clinical staging 3. Almost 70% of patients died in clinical staging 3 and 4.

Table 3 shows the HIV care outcome of patients in 2 years follow-up. Out of 548 patients, 108 patients died who
constitute almost 20% of the total patients. Among them, 53% died during the first 6 months of receiving ART, 17.34% patients were transferred out from the ART center of Rajindra hospital, Patiala, to other ART centers, 9.31% patients were lost to follow-up (LFU) (44% were LFUs during the first 6 months of start of ART), and almost 3% patients stopped treatment on their own.

Discussion

Majority of patients were in the productive age group, with a median age of 37 years and belonged to economically weaker section of society. Studies done in other parts of India have reported similar findings. It is clear from the data, that Punjab being agriculture state with almost 70% population residing in rural areas, farming is the most common occupation that is reflected in patient’s occupation classification. Truckers constitute almost 42% of the total drivers in the study, followed by car/taxi drivers (35.48%), combine harvester, and bus drivers make 11.29% each. Studies done in West Bengal and Karnataka reported a similar prevalence of HIV among drivers.

Table 1: Effect of antiretroviral therapy on clinical and functional status of immunodeficiency virus infected positive patients

| Clinical staging | At start of ART (n=548) | At 24 months (n=291) | $\chi^2$ | $P$ |
|------------------|-------------------------|----------------------|---------|-----|
| Stage 1          | 195                     | 263                  | 104.55  | 0   |
| Stage 2          | 192                     | 19                   | 61.41   | 0   |
| Stage 3          | 121                     | 6                    | 50.32   | 0   |
| Stage 4          | 40                      | 3                    | 14.95   | 0.0001 |

| Functional status | At start of ART (n=548) | At 24 months (n=291) | $\chi^2$ | $P$ |
|-------------------|-------------------------|----------------------|---------|-----|
| Working           | 303                     | 287                  | 360.14  | 0   |
| Ambulatory        | 180                     | 4                    | 85.85   | 0   |
| Bedridden         | 65                      | 0                    | 11.98   | 0.0005 |

Table 2: Effect of antiretroviral therapy on CD4 cell count of patients on antiretroviral therapy

| CD4 cell count/mm$^3$ | At start of ART (n=548) | Mean and median CD4 cell count at start (95% CI) | At 6 months (n=446) | Mean and median CD4 cell count at 6 months |
|-----------------------|-------------------------|--------------------------------------------------|---------------------|---------------------------------------------|
| ≤50                   | 106                     | Mean=144.79                                     | 11                  | Mean=266.09                                 |
| 51-150                | 217                     | 131.5 ≤ X ≤ 149.4                               | 81                  | 254.8 ≤ X ≤ 277                             |
| 151-250               | 166                     | 117                                              |                     |                                             |
| 251-350               | 18                      | Median=127.63                                   | 79                  | Median=261.84                               |
| ≥350                  | 41                      |                                                   | 158                 |                                             |

| CD4 cell count/mm$^3$ | At 12 months (n=371) | Mean and median CD4 cell count at 12 months (95% CI) | At 24 months (n=291) | Mean and median CD4 cell count at 24 months |
|-----------------------|---------------------|------------------------------------------------------|----------------------|---------------------------------------------|
| ≤50                   | 2                   | Mean=312.53                                         | 1                    | Mean=322.77                                 |
| 51-150                | 30                  | 302.3 ≤ X ≤ 323.5                                  | 26                   | 311.4 ≤ X ≤ 335                             |
| 151-250               | 79                  | 43                                                  |                      |                                             |
| 251-350               | 69                  | Median=357.89                                      | 57                   | Median=382.13                               |
| ≥350                  | 191                 | 164                                                 |                      |                                             |

| CD4 cell count/mm$^3$ | At start of ART | At 24 months | $\chi^2$ | $P$ |
|-----------------------|----------------|--------------|---------|-----|
| ≤50                   | 106            | 1            | 53.79   | 0   |
| 51-150                | 217            | 26           | 61.7    | 0   |
| 151-250               | 166            | 43           | 18.37   | 0.0001 |
| 251-350               | 18             | 57           | 56.53   | 0   |
| ≥350                  | 41             | 164          | 185.83  | 0   |

| CD4 cell count/mm$^3$ | Stage 1 | Stage 2 | Stage 3 | Stage 4 |
|-----------------------|---------|---------|---------|---------|
| ≤50                   | 0       | 4       | 19      | 21      |
| 51-150                | 4       | 11      | 9       | 19      |
| 151-250               | 5       | 5       | 2       | 4       |
| 251-350               | 2       | 1       | 1       | 1       |

ART: Antiretroviral therapy, CI: Confidence interval
patients where most of them become working and ambulatory after 24 months of ART therapy. A study done in Karnataka by Ramesh and Deepti had reported similar improvements where percentage of patients in Clinical Stage 1 doubles and that of Stage 2 decreased to 64.1%, Stage 3 decreased to half (5.4%) and Stage 4 decreased to 1.3% after 2 years of ART and 99% patients were working after 2 years of ART therapy.\[8,12\]

At the start of ART therapy, almost 20% of patients had very low CD4 cell count of ≤50 count/mm\(^3\), and just 7.5% have CD4 cell count of ≥350. After 2 years of ART therapy, only 2.47% of patients have CD4 cell count of ≤50 and those with CD4 cell count ≥350 increased significantly to 56%. There was also increased in mean CD4 cell counts from 144 to 322 CD4 cells/mm\(^3\). Comparable results were reported by the study done in Karnataka where mean CD4 count of 156.9 ± 7.6 increased to 433 ± 19.7 after 2 years of ART therapy.\[12\]

Studies done in other parts of India have also corroborated the above findings.\[13-15\] In the current study, it was seen that patients who were in clinical staging 3/4 or who have baseline CD4 cell count of 50 or less are more likely to die than those who have >50 cells/mm\(^3\) at the start of ART, a similar finding was reported by treatment outcome studies done in India and Nigeria.\[14,15\] Hence, it has prognostic significance to detect the patients with HIV at the earliest in Clinical Staging 1 and 2, this will not only increase their life but will also help in preventing the spread of HIV to others.

In the current 2 years follow-up study, almost 20% patients died, and 9.31% were LFUs with majority of them in first 6 months, in comparison to Bachani et al. which reported 13% mortality and 16% LFUs in 2 years.\[14\] Another similar study in same time period done in the Banaras Hindu University (BHU) by Chakravarty et al. reported (16.10%) mortality, (12.13%) LFUs with majority in the first 6 months similar to current study, and 31.14% were transferred out to other facilities in 2 years follow-up.\[16\] Contrasting results were reported by Bachani et al., which reported 2.3% transferred out rate. Two years follow-up study done by Sharma et al. in the All India Institute of Medical Sciences (AIIMS) reported 22% LFUs, 12% died, and 11% had been transferred out.\[17\] In our study, 17.5% of patients were transferred out. One of the reasons for higher transferred rates in our study is that ART center in Patiala was established in 2008, with the rapid scaling of ART centers in other districts of the state, patients were transferred to their respective districts, but decentralization of HIV services to the primary health-care level was at very incipient stage, and there was a lack of institutional linkage between ART centers and other HIV testing centers, which might be one of the reasons for higher LFUs in our study. Similar reasons for higher transferred out rates were reported by the study conducted in the BHU.\[16\] In the current study, almost 3% patients stop treatment on their own. A study in North Malawi reported that 50% of the LFUs were dead and 15% stopped treatment on their own.\[18\]

Another important determinant of treatment outcome is the adherence to ART, which seems to be poor in the current study with 40% patients have <95% adherence to ART, which was more than a study in Western India, which reported 27% adherence.\[19\] Some of the reasons for poor adherence were financial constraints, lack of transport, poor family support, adverse drug reactions, and migrant populations who migrated to places of work after taking ART for few months. Since the treatment is life long, ART should be available as close as possible to where the people live. The results of the new estimates by the NACO show that there remains a number of challenges ahead. The pace of reductions in new HIV infections has decreased, indicating that greater prevention efforts will be required to change the epidemic trajectory further.\[20\]

**Limitations**

First, the patient’s records were incomplete or not available, particularly with regard to patients who were transferred out and LFUs, which make 26.6% of the patients. Lack of tracking of treatment outcomes of patients can led to underestimate of mortality in patients, as many patients who are considered LFUs and transferred out might be dead. Second, since the study was done in one ART center only, the results cannot be generalized at national level, which needs further analysis.
**Recommendations**

Records must be complete, updated, and computerized database must be developed for each patient at ART centers. Tracking of the patients who are LFUs and transferred out must be done and their treatment outcome records must be updated at ART center from where they are transferred out to improve the quality of data. Operational research must be done to find out the cause of LFUs and poor treatment adherence; further, triangulation and analysis of data from different sources at district and state levels will provide valuable instincts and feedback to consolidate the success of ART in India.

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**Conflicts of interest**

There are no conflicts of interest.

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