Case Report

Performance profile of HIV seropositives on Antiretroviral therapy over 7 years. An experience at Centre of Excellence & ART Centre, Bowring & Lady Curzon Hospital, Karnataka, India.

Sree Ranga, Pramod K., Assistant Professors, Department of Medicine, Shrinath Shetty, Postgraduate, Department of General Medicine, Vidyashankar, Medical Office, Basavarajaiah D.M., Statistician, Prabhakar B., Professor & Head of Department, Department of Medicine, Nodal Officer, Centre of Excellence Bowring and Lady Curzon Hospital, Bangalore Medical College and Research Institute, Bangalore, India. Email: sreerangapallaki@gmail.com


Key Words: HIV seropositive, ART, Opportunistic Infections, adverse effects.

Abstract

Objectives: To study the spectrum of opportunistic infections and adverse effect profile in HIV seropositive patients on antiretroviral therapy.

Methods: Retrospective analysis from data of available records of HIV seropositives enrolled for ART from 2004-2010 and alive till 2010, who were on routine follow-up at ART Centre of Bowring and Lady Curzon Hospital was compiled. Laboratory monitoring for CD4 counts, Serum Lipid profiles, Serum lactate levels, haematological and relevant microbiological investigations were done according to standard recommended procedures. Occurrence of opportunistic infections, adverse effects of ART and other co-morbidities were noted for these patients from the records.

Results: 2101 records of adult HIV seropositives were scrutinized. Total number of males was 1248 (59.48%), females were 852 (40.55%) and one (0.47%) was transgender. The commonest opportunistic infection noted was tuberculosis 1079 (51.35%), of which 708(33.69%) had pulmonary tuberculosis, 366 (17.46%) had extrapulmonary tuberculosis and 5 (0.24%) had disseminated tuberculosis. The most common adverse effect noted was dyslipidemia occurred in 545 (25.94%) patients. Hyperlactatemia was observed in 119 (5.66%), peripheral neuropathy in 94 (4.47%), Zidovudine induced anaemia in 272 (12.94. IRIS was noticed in 28 (1.33%).
Conclusion: The commonest opportunistic infection noted was tuberculosis in 52% of patients. The most common adverse effect noted was dyslipidemia in 26% of patients. Hyperlactatemia, peripheral neuropathy and Zidovudine induced anaemia were also seen in significant number of patients. Constant vigilance and high index of suspicion is needed in early diagnoses of silent though fatal adverse effects. Our study also gives an incite of adverse effect seen in Indian population on antiretroviral therapy and likely success of large-scale treatment programmes.

Introduction

The first-line ART regimen consists of two nucleoside reverse transcriptase inhibitors (NRTIs) Zidovudine(ZDV) or Stavudine(d4T) and Lamivudine(3TC) and one nonnucleoside reverse transcriptase inhibitors (NNRTI) Nevirapine (NVP) or Efavirenz(EFV). Use of EFV in the place of NVP is largely limited to concomitant administration of Rifampicin, an anti-TB drug given to patients who also have tuberculosis. Patients are monitored monthly for clinical status, drug adherence and psychological motivation. Majority of initial highly active antiretroviral therapy (HAART) regimen in resource-limited settings include stavudine (d4T) or to a lesser extent zidovudine (ZDV), largely due to cost and availability considerations. Information about how well the regimen is tolerated and sustained in clinical practice is essential for evaluating the likely success of large-scale treatment programmes, and for understanding the magnitude of the need for second-line therapy or alternative drugs. Some studies have addressed the issue of adverse drug reactions with non-protease inhibitor (PI)-based antiretroviral therapy (ART) in resource-constrained settings.

d4T is associated with high rates of toxicity and side effects. This toxicity not only adversely affects patient quality of life, but may lead to treatment changes, discontinuation of therapy, and even death. The toxicities observed most frequently with d4T include peripheral neuropathy, lactic acidosis, and lipodystrophy. ZDV is also associated with a significant degree of treatment-limiting toxicity (mainly anemia and neutropenia), particularly in patients who are already at risk for cytopenias as a consequence of advanced AIDS. Estimation of CD4 cell count remains the primary monitoring tool in assessing efficacy or failure of Anti Retroviral Therapy (ART) under national program conditions in India. Primary mechanism of ART is plasma HIV reduction which allows increase in CD4 cell count. Some studies have shown that a plateau in CD4 cell gains after the second year of therapy. Kaufmann et al reported that a higher nadir CD4 cell count and younger age were independently associated with greater increases in CD4 cell counts at 48 months. Some studies from India have delineated CD4 progression over time. Keeping this background in view the experience of ART of five years at this tertiary care centre is presented.

Materials and Methods:

A Retrospective observational analysis was done from the records of patients enrolled for ART in 2004 and alive till 2010. A total of 117 patients were alive and on ART from 2004 to 2010. Laboratory monitoring for CD4 counts, Serum Lipid profiles,
Serum lactate levels, haematological and relevant microbiological investigations were done according to standard recommended procedures. Serial CD4 counts, occurrence of opportunistic infections, adverse effects of ART were noted for these patients from the records. ART regimen change was defined as treatment change in ART excluding dosage change. Analysis of the data compiled is described.

**Results:**
261 HIV seropositives were enrolled for antiretroviral therapy in the year 2004. Of these 60 (22.98%) were transferred to other centers, 43 (16.47%) died and 41 (15.70%) were lost to follow-up. Retrospective analysis of the records of 117 HIV seropositives alive and on ART from 2004 to 2010 revealed the following. Total number of males and females in the study population were 71 (60.68%) and 46 (39.32%) respectively (Figure 1). The age wise distribution of males and females in the respective age-intervals is shown (Figure 2). Maximum number of seropositives were observed in the 30-39 years age group.

![Figure 1](image_url)

**Figure 1**
- Males: 60.68%
- Females: 39.32%
Commonest mode of transmission observed was heterosexual (97.44%). In the study population 11 (9.4%) were in WHO clinical stage I, 69 (58.97%) in stage II, 27 (23.07%) in stage III and 10 (8.55%) were in stage IV at the time of enrolment for antiretroviral therapy. Analysis of baseline CD4 counts of the study populations at enrolment revealed 114 (97.43%) with CD4 count less than 200 of which 33 (28.2%) had CD4 counts less than 50 as depicted in figure 3.
Amongst the spectrum of opportunistic infections (OIs) observed, tuberculosis was the commonest seen in 43 (36.75%). Thirty-seven (31.62%) had pulmonary tuberculosis while 6 (5.13%) had extra pulmonary tuberculosis. In the extra pulmonary group tubercular lymphadenitis occurred in 3, tubercular meningitis 2 and pleural effusion in 1. Two patients developed pulmonary tuberculosis while on antiretroviral therapy. Opportunistic infections were seen in 45 (38.46%) patients in all. Table 1 enumerates the spectrum of OIs.

### Table 1

<table>
<thead>
<tr>
<th>Opportunistic Infections</th>
<th>Number</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB</td>
<td>37</td>
<td>31.62</td>
</tr>
<tr>
<td>Extra pulmonary TB</td>
<td>6</td>
<td>5.13</td>
</tr>
<tr>
<td>TB Lymph Node</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>TB Meningitis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>CMV Retinitis</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>Total Number</td>
<td>45</td>
<td>38.46</td>
</tr>
</tbody>
</table>
The adverse effects to antiretroviral therapy observed in the study population over 5 years is shown in Table 2

<table>
<thead>
<tr>
<th>Adverse Effects to ART</th>
<th>Number</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia (abnormal serum lipid profiles)</td>
<td>49</td>
<td>41.88</td>
</tr>
<tr>
<td>Lipodystrophy with normal serum lipid profile</td>
<td>32</td>
<td>27.35</td>
</tr>
<tr>
<td>Dyslipidemia with Lipodystrophy</td>
<td>20</td>
<td>17.09</td>
</tr>
<tr>
<td>Hyperlactatemia</td>
<td>14</td>
<td>11.97</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>3</td>
<td>2.56</td>
</tr>
<tr>
<td>Zidovudine induced anaemia</td>
<td>4</td>
<td>3.42</td>
</tr>
</tbody>
</table>

Details of Antiretroviral Regimen initiated for the seropositives is shown in Table 3.

<table>
<thead>
<tr>
<th>Antiretroviral Regimen</th>
<th>Number of Patients</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T+3TC+NVP</td>
<td>102</td>
<td>87.17</td>
</tr>
<tr>
<td>ZDV+3TC+NVP</td>
<td>15</td>
<td>12.82</td>
</tr>
</tbody>
</table>

Majority(87.17%) were started on Stavudine–based regimen. 27(23.08%) patients still continue to be on Stavudine–based regimen, while 75(64.10%) required changes in regimen due to related drug-toxicities. It was observed that 67 patients underwent a single change in regimen, 7 required change of regimen twice and one patient required change of regimen thrice.13(11.11%) patients continue to be on Zidovudine-based regimen, with only two patients(1.71%) requiring a single change in regimen. Thus, patients on stavudine-based regimen required more changes in regimen. Only one patient required change to second line antiretroviral therapy as a result of immunovirological failure.

46 (45.1%) patients on stavudine-based regimen developed dyslipidemia over 5 years and 26 (25.5%) had evidence of lipodystrophy on stavudine based therapy. In addition, 3(0.2%) patients on Zidovudine-based regimen also had dyslipedemia.

Immunological response to antiretroviral therapy was charted for the duration of 5 years in both males and females of the study population. As shown in figure 4 both males and females demonstrated a good CD4 progression in response to antiretroviral therapy. Female patients had higher CD4 counts than the male counterparts.
Discussion
This study is an attempt to describe the performance profile of 117 HIV seropositives alive and on ART over a seven year period from 2004-2010. Similar to many other studies this study also had more number of male HIV seropositives. Majority of the seropositives were in the sexually active age group of 30-39 years. Heterosexual transmission was the commonest mode of transmission as described in various other Indian studies. Maximum number of seropositives were in WHO Clinical Stage II, fewer patients were in WHO Clinical Stage IV. Other studies have reported more seropositives in WHO clinical stage III (45.2%) followed by Clinical stage II (26.5%)16. CD4 cell counts at enrolment were <50 cells/µL in 33(28.2%) patients especially in the 30-39 year age group followed by 30(25.64%) patients with CD4 counts between 50-100 cells/µL in the same age group.

In this study the commonest opportunistic infection observed was tuberculosis in 43(36.75%) seropositives, pulmonary tuberculosis in 37(31.62%) and extra pulmonary in 6(5.13%). An Indian study has reported an alarming rising trend of HIV infection in Thanjavur rural area tuberculosis patients from a mere 0.59% in 1996 to 8.89% in 199917. HIV-seropositivity in tuberculosis patients as reported in various studies published from India ranges from 0.4% to 20.1%18. In a study on the prevalence of co-infection of TB with HIV, among 230 seropositives enrolled, 38 (16.52%) patients had TB at some stage of HIV/AIDS infection19. In a study from Jammu, out of 60 patients with HIV and TB, pulmonary tuberculosis was seen in 46 (76.67%)20. A Jamaican study found that 11.6% (47/406) of the patients who met the inclusion criteria and were diagnosed as having pulmonary tuberculosis were HIV-1 seropositive. Most HIV-positive patients with tuberculosis were males, and prevalence of HIV co infection among patients with tuberculosis was highest in patients aged 30-39 years. The mortality rate in patients with tuberculosis and HIV
infection was 23.4% (11/47) compared to 3.9% (14/359; \( P = 0.001 \)) in HIV negative patients\(^{21} \).

Dyslipidemia was the commonest side-effect observed in 49 (41.88%) and 46 (45.1%) patients on stavudine-based regimen developed dyslipidemia over 5 years. A study by Sharma et al from Gujarat has observed 71% incidence of side effects in their patients who were on HAART, although their study included all adverse drug reactions irrespective to the fact whether the treatment required any change of therapy or lead to noncompliance in patient. The commonest adverse drug reaction reported by them was rash due to Nevirapine. Others in their study were peripheral neuropathy in 22.2% and anemia in 20%\(^{22} \). Another study from South India by Kumarasamy et al reported a 15.2% incidence of rash, 9% incidence of peripheral neuropathy, 5.4% anemia and 3.5% hepatitis\(^{23} \).

75(64.10%) required changes in regimen due to related drug-toxicities over a period of 5 years in this study. In a study from Vellore South India, the cumulative incidence of treatment change was 39.6% (91 patients). Drug toxicity (WHO grade 3 or 4) was the reason for treatment change among 62 (27%) (incidence rate 35.9/100 person-years). The most common toxicities were attributable to the thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs), d4T and AZT \([\text{lactic acidosis (8.7%), anemia (7%) and peripheral neuropathy (5.2%)}]\). The other toxicities were rash (3.9%) and hepatitis (1.3%) due to NVP\(^{16} \).

Despite adverse reactions to antiretroviral regimen, this study demonstrated a steady improvement in the CD4 counts of the seropositives, with female patients showing a better CD4 progression. In a study from Chennai South India it was documented that CD4 progression continues two years after therapy in patients who had base-line CD4 counts less <100\(^{14} \). Valdez et al reported that CD4 raises during the second and third year were not significant. Kaufmann et al reported that a higher nadir CD4 cell counts and younger age were independently associated with greater increases in CD4 cell counts at 48 months\(^{15} \). In a study from Chennai, where CD4 counts were serially monitored for seropositives on ART, female patients with CD4 cell counts <100 cells/µL had significantly lower gain in CD4 cell count as compared to patients whose CD4 cell counts 200 or more. The female patients whose age was 30-44 had significantly lower CD4 counts as compared to those whose age was 15-29 years\(^{14} \). In conclusion, the five year performance profile on ART of the study population revealed an encouraging CD4 cell count progression on therapy, although adverse effects to therapy occurred.

**Conclusion**

The commonest opportunistic infection noted was tuberculosis in 52% of patients. The most common adverse effect noted was dyslipidemia in 26% of patients. Hyperlactatemia, peripheral neuropathy and Zidovudine induced anaemia were also seen in significant number of patients. constant vigilance and high index of suspicion is needed in early diagnoses of silent though fatal adverse effects. our study also gives an incite of adverse effect seen in Indian population on antiretroviral therapy and likely success of large-scale treatment programmes.
References:


